UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

HELSINN HEALTHCARE S.A.,
Patent Owner.

IPR2025-00945,
8,623,826
IPR2025-00946,
9,186,357
IPR2025-00947,
9,186,357
IPR2025-00948
9,943,515
IPR2025-00949
10,828,297

CONFIDENTIAL DEPOSITION OF STEPHEN J. PEROUTKA

Palo Alto, California

Tuesday, January 13, 2026

REPORTED BY: Derek L. Hoagland

CSR No. 13445

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Deposition of STEPHEN J. PEROUTKA, taken before Derek L. Hoagland, a Certified Shorthand Reporter for the State of California, commencing at 9:20 a.m., Tuesday, January 13, 2026, at Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, California 94304.

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ALSO PRESENT
Luisa Barorelli

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E X H I B I T S

EXHIBIT	DESCRIPTION	MARKED
1009	Declaration	8
2036	Review Article Titled "Pharmacology Management of Chemotherapy-Induced Nausea and Vomiting Focus on Recent Developments."	49
1010	Herrstedt	52
1030	Review	54
1013	MASCC Reference	70
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1023	Campos	145
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9:20 p.m. P R O C E E D I N G S

(Whereupon, the deponent is duly sworn by the court reporter.)

STEPHEN J. PEROUTKA,
having first been duly sworn,
was examined and testified as follows:

EXAMINATION

BY MR. ASHKENAZI:

Q. Dr. Peroutka, how are you today?

A. I'm good.

Q. Just for the record, can you please state your full name for the record?

A. Sure. Stephen Joseph Peroutka.

Q. And what's your current address?

A. 3665 Via Mar Monte, three words, Carmel, California 93923.

Q. Have you been deposed before?

A. Yes.

Q. About how many times?

A. Five to ten.

Q. Okay. And, generally, were those related to patent cases?

A. Yes.
Q. Would you say all of them are?
A. Possibly, one 30 years ago, it was a clinical case, but the rest were patents.
Q. And were you on which side of -- in the cases, the patentee side or the challenger side?
A. Both.
Q. Both. Okay. Just so we're on the same page, I just want to go over some basics.
You understand you are testifying under oath today, correct?
A. Correct.
Q. Is there any reason you cannot provide full and truthful and accurate testimony today?
A. No.
Q. Okay. If you don't understand a question that I ask, I -- could you let me know?
A. Yes.
Q. All right. And just so we're on the same page, you have to give verbal answers. Head nods aren't going to suffice because we don't have a videographer here today.
A. Yes.
Q. All right. Great. I am going to do my best not to speak over you. I will -- I'll ask that you do the

same. Let me finish my question before you start answering. It's really mainly for the court reporter and for your counsel to be able to object.

Is that fair?

A. Yes.

Q. Okay. If we need to take -- we will try to take breaks about every hour. The only thing I will ask is that if we have a question pending, you answer the question before we take a break. Is that fair?

A. Yes.

Q. Okay. And we will try to take lunch before 12 o'clock. So if that works for you.

A. Okay. That's fine.

Q. All right. Great.

Generally, when did you start working on this matter?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: I believe late 2024.

BY MR. ASHKENAZI:

Q. Okay. And how much time would you say you have spent on this matter since late 2024?

MR. TORCZON: Same objection.

THE DEPONENT: It's difficult to answer because it's been split up and pretty quiet for the last eight, nine months, but let me try to estimate. Forty to

fifty.
BY MR. ASHKENAZI:
Q. Okay. 40 to 50 hours?
A. Hours.
Q. Okay. If you -- in front of you, you have a copy of Exhibit 1009. That's your declaration that you submitted in the matters we are dealing with today, correct?
(Exhibit No. 1009 marked for identification.)
THE DEPONENT: It looks like it is, yes.
BY MR. ASHKENAZI:
Q. Okay. Great. If you need to refer to it, I want to make sure you have it in front of you if you need. I know it's pretty lengthy, over 700 pages or so. Is that right?
A. Yes.
Q. Did you draft that?
A. Large part, yes.
Q. Then so these are your words?
A. The majority, yes.
Q. Okay. Have you reviewed your declaration before in preparation for your deposition today?
A. Yes.
Q. Okay. Is there anything you want to correct in your declaration?

A. No.
Q. Okay. What did you do to prepare for today's deposition?
MR. TORCZON: Objection. Relevance to the extent it gets into attorney-client privilege. I may stop you from answering, but go ahead, answer.
THE DEPONENT: I re-reviewed, reimmersed myself, is how I would put it, into this work of the declaration. It was mostly created earlier this year and, like I said, it had been a long layover, so I reread it, went through it, looked at a lot of the exhibits that I have reviewed previously, and then we had a couple tele -- one teleconference last week for a couple hours or so, and then I came up here yesterday and did some preparations.
BY MR. ASHKENAZI:
Q. Okay. Did you review any documents that are not included or referenced in your declaration in preparation for the deposition?
MR. TORCZON: Same objections.
THE DEPONENT: Not in terms of preparation. I read science constantly, so I -- I am actively still involved in clinical research and I may have read something that overlapped, but nothing targeted specifically for today.

BY MR. ASHKENAZI:
Q. Are you aware of a -- a Dr. Navari?
A. I'm sorry?
Q. Have you ever heard of a Dr. Navari, N-a-v-a-r-i?
A. I've seen the name --
Q. Okay.
A. -- in publications but I don't know him.
Q. Okay. Have you reviewed --
A. Or her.
Q. Have you reviewed a declaration by Dr. Navari?
A. No.
Q. Okay. You said you've reviewed some publications from Dr. Navari. Is that accurate?
MR. TORCZON: Objection. Misstates.
THE DEPONENT: For the declaration, he may have been an author on a few of the papers, but I can't honestly say.
BY MR. ASHKENAZI:
Q. Okay. Apologies. One second. I think you said -- I asked you if you have heard of Dr. Navari, and you said, "I have seen his name in publications."
Is that right?
A. As an author of certain publications.
Q. Okay. Do you know the subject matter of those

publications?
A. Not all of them, no.
Q. Do you know the subject matter of any of the publications that Dr. Navari authored that you reviewed?
A. My honest answer is, I read the authors' names when I read a paper to see if I know anyone, to be honest with you, and I only recall two names of people that I -- I know or I have spoken to, so I can't point to the papers he wrote.
Q. What are those two names?
A. Dr. Graduala is -- when I did research on nausea and vomiting a long time -- in the 1980s, he was a major key opinion leader, and I can recall meeting him and/or speaking with him about a project study I wanted to do. And then Scott Ryanis, who is one of the coauthors on one of the aprepitant papers, was at Johnson & Johnson when I was there about 20 years ago, and I knew him through other work that he had done.
Q. Okay. Other than your counsel, did you speak to anyone in preparation for your deposition today?
A. No.
Q. Okay. Now, as I mentioned, you have Exhibit 1009 in front of you. That's your expert declaration. You understand that there are four patents at issue in these matters, correct?

A. Yes.
Q. Okay. And you submitted one declaration related to all of the patents, correct?
A. Yes.
Q. Okay. And just for the sake of the record, the IPRs we're going to be discussing today are IPR2025-00945, 946, 947, and 948 and 949.
Do you understand that?
A. Right. They are different.
Q. There's five different IPRs that we are going to be discussing today, correct?
A. I will assume that's correct, but I don't know for a fact that there's five.
Q. Okay.
A. I mean, there's four patents.
Q. There's four patents. Either way, all of your opinions that you have provided in the IPRs are contained in the Exhibit 1009 we have in front of you, correct?
A. Correct.
Q. Okay. So you understand the questions I'm asking you today are going to go to your opinions to all of the patents, correct?
A. Correct.
Q. All right. Thank you.

And you understand the transcript is going to be submitted in all of the IPRs that you submitted a declaration, correct?

A. I don't know that for a fact.

Q. Okay. No problem.

So, Dr. Peroutka, you mentioned that you did some research in nausea and vomiting in the -- I think you said 1980s. Is that right?

A. Yes.

Q. Okay. Maybe if you can just give me a little bit of background and explain to me if you can your background on nausea and vomiting as it relates to chemotherapy.

A. Yes. As I was a medical student and MP Ph.D. pharmacology in John Hopkins and in my medical rotations, I noticed that there -- and also I should add, I was a medical intern here at Stanford, and I did rotations on oncology. I was getting a Ph.D. in pharmacology previously, and I noticed that the chemotherapy-induced nausea and vomiting was pretty severe then. I mean, it was to the point that patients would actually sometimes not take more chemo because of the side effects of nausea and vomiting.

And I was working on different, what's called, biogenic immune receptors, some of which like dopamine

at the time, had some evidence of antiemetic activity, anti-nausea drugs like Mermerinic (ph) drugs, et cetera. So I had this hypothesis that I wrote with my Ph.D. mentor, Solomon Snyder, that was published in The Lancet, talking about combinations of antiemetics is probably what we needed, that nausea and vomiting from chemo was probably multifactorial, multiple biological pathways, and that clearly the drugs we had at the time in single use were not very effective.

So I organized a study at Johns Hopkins with the oncology department, Dr. David Ettinger was the oncologist that help me, and his team, and we did a small study doing different combinations and published that at the ASCO, American Society of Clinical Oncology, meetings. Unfortunately, we didn't get great success.

Q. Okay.

A. The combos, they helped a little, but it was still pretty bad.

So then after that, my chemo-induced work decreased. I did a little more actually here at Stanford. I screened drugs, chemo drugs, at these receptors to see maybe that's where they were acting, you know, just -- and they didn't -- they didn't do anything. They are acting in a different location. That caused the nausea in different mechanism.

And then I worked on nausea and vomiting not specifically related to chemo, but migraine. And 5HT3 drugs were very hot back then. There was a hypothesis that 5HT3 drugs, antagonists, should work in migraine because they worked in nausea, well, vomiting in ferrets. That was the model that of a ferret vomiting. So I was working on it in that sense. I actually had a grant from NASA down the street here, NASA AMES for space sickness, that -- when you talk to astronauts, this was a big problem. They were treating them with dex -- dex -- amphetamines, dexedrine and scop --

THE REPORTER: Doctor, I have to ask you to slow down, especially on the technical.

THE DEPONENT: The names, yeah, dexedrine and scopolamine.

And that, you know, it was very memorable speaking to an astronaut in Houston at NASA, where he said, if you look out of the spaceship down to Earth, but the Earth is up, you can just vomit. So I did a research grant on that.

And then through early 2000s, I was at Johnson & Johnson, where we were developing a pain molecule. I was in the pain group called tapentadol that was supposedly to give less nausea and vomiting. Opioids induced nausea and vomiting from the chemo perspective,

mostly in the '80s, but nausea and vomiting through -- well, my last job relevant to that was a company called Zogenix, where we were developing a pure hydrocodone whose major side effect was nausea, vomiting, and also a migraine drug that stopped nausea and vomiting.

So in terms of pharmacology, controlling, managing nausea and vomiting, I have done a pretty broad base.

BY MR. ASHKENAZI:

Q. Okay. So let me just ask a few questions, then, specific to -- to your work. I think you've given a lot. I'm going to try to break it down into some small pieces, if we can.

So your research into chemotherapy-induced nausea and vomiting, that was in the 1980s. Is that correct?

A. Correct.

Q. Okay. And you've never treated patients with a 5HT3 antagonist or NK-1 receptor antagonist for chemotherapy-induced nausea and vomiting, correct?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. Meaning you left the practice of medicine and went into research sometime in the -- around 1990.

Is that accurate?

MR. TORCZON: Same objection.

MR. ASHKENAZI: And I apologize. You also need to give your counsel an opportunity to object, just so that the court reporter can, you know, get everything down right.

BY MR. ASHKENAZI:

Q. Okay. So you left the practice of medicine sometime around 1990. Is that accurate?

MR. TORCZON: Same objection.

THE DEPONENT: Not exactly. I kept my medical license and I use it. I was chief medical officer of numerous companies. I had to be the ba -- an adverse event reporting, clinical trial review of data. So I didn't practice in terms of prescription.

I worked in studies in the '90s, and even in the 2000s that required an M.D., and I just put my license -- medical license to practice in retirement phase in California. They allow us to keep the license. I'm still on the books, and I can activate it at any time without further testing or continuing education type proof. But it's an active license that's in, quote, retirement as of last year.

BY MR. ASHKENAZI:

Q. Okay. Let me just take a couple small pieces

there.

You have not prescribed any medications yourself since 1990, correct?

MR. TORCZON: Same objection.

THE DEPONENT: I'm thinking I did do a migraine study with an approved drug, which I can't remember whether I wrote the prescription, but it was part of the study. But I did give medications, approved products --

MR. ASHKENAZI: Okay.

THE DEPONENT: -- to patients in the late '90s.

BY MR. ASHKENAZI:

Q. You haven't prescribed a 5HT3 antagonist or treating CINV, correct?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. And you have not prescribed an NK-1 receptor antagonist for treating CINV, correct?

MR. TORCZON: Same objection.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. And when I say CINV, you understand I mean chemotherapy-induced nausea and vomiting, correct?

A. Correct.

Q. Okay. You did practice and you focused on

treating patients for about six years between graduating in 1990. Is that accurate?

MR. TORCZON: Same objection. Form.

THE DEPONENT: Ten years, I would say.

BY MR. ASHKENAZI:

Q. Ten years?

A. I was an intern one year, resident and fellow three years, and faculty six years.

Q. Okay. Great. And that ended in 1990, right?

A. Yes.

Q. Now, you then went into industry. Is that accurate?

A. (Moves head up and down.)

Q. And would you say that your --

A. Correct.

Q. I'm sorry. Would you say that your practice -- I think you mentioned this earlier -- focused on migraine medications, pain medications, and stroke? Is that -- is that right?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: I did transiently in different times focus on those things. I have spent 12 years since 2008, total, in the CRO world, where we looked at all sorts of neuro in -- neuropsychiatric indications.

///

BY MR. ASHKENAZI:
Q. Okay. So from 2008 until today, you have worked in the CRO world. Is that accurate?
A. Not completely, but 12 of the whatever years it's been.
Q. Okay. Have you done any research in -- into drugs after the year 2000 -- withdrawn.
Let me start again.
After the year 2000, have you done any research on drugs for treating chemotherapy-induced nausea or vomiting?
A. I haven't done any studies, but I have reviewed studies on the topic.
Q. When you say you have reviewed studies, you have read literature. Is that accurate?
A. And also in the CRO world, we will get RFPs, requests for proposals, and sponsors will bring us a protocol and say, can you do this study, and my job as the head of the neuroscience group was to review and comment on whether that was, you know, appropriately designed.
Q. Okay. So from 2000 until today, you haven't done any research into treatments for chemotherapy-induced nausea or vomiting, but you have reviewed proposals for protocols to study that topic.

Is that correct?

MR. TORCZON: Objection. Form. Asked and answered.

THE DEPONENT: I believe I had. I have reviewed a thousand proposals in 12 years, roughly, and so I -- I -- we have -- I definitely know I've seen proposals, but, you know, one is confidential. I can't disclose if I knew, but I would have to go and check the number exactly.

BY MR. ASHKENAZI:

Q. Okay. And only you would -- you would be focused on there is just to see if the study design was accurate, correct? Is -- withdrawn.

Your focus was to see if the study design or the protocol was proper. Is that right?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: I wouldn't say proper. I would say my role was to suggest what -- what could optimize it.

BY MR. ASHKENAZI:

Q. Okay. Now, part of study protocols is to look at -- part of evaluating a study design is to make sure that the study could provide you with information to determine if the drug has an effect or not, correct?

MR. TORCZON: Objection. Relevance.

Foundation.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. And as someone who is involved in the design of study protocols, you are also familiar with the statistics that are involved, correct?

A. Correct.

Q. Okay. In general, what's the purpose of statistics in a study design?

MR. TORCZON: Objection. Scope.

BY MR. ASHKENAZI:

Q. And --

MR. TORCZON: I'm sorry.

MR. ASHKENAZI: Withdrawn. Let me ask the question a little differently.

BY MR. ASHKENAZI:

Q. Statistics help us figure out if an effect we are seeing from a clinical study is actually real or if it could be due to chance, correct?

MR. TORCZON: Objection. Form.

THE DEPONENT: Well, I didn't opine on that matter, so should I -- I am -- I mean, that's not in my deck.

MR. TORCZON: You can go ahead and answer the question.

THE DEPONENT: So statistics are, as you said, Mr. Ashkenazi, designed to show the likelihood that the effect that is observed is, quote, real. And historically, less than .05 is considered a 1-in-20 chance. That's what the 05 is, 5 percent chance. That this is just, you know, flipping a penny 10 times and getting 10 heads. It can happen and it's real, but it's not the average. So the FDA has mandated and they have recently changed their mind, but certainly back then that you needed two studies powered, meaning statistically designed, with X number of patients with X or Y expectation of this success. You have to predefine what you think is going to happen, and then you have to show that within the boundaries of the P less than 05 twice and independently.

BY MR. ASHKENAZI:

Q. Okay. So scientists generally -- withdrawn.

If I use the term "person of ordinary skill in the art," you will understand I'm referring to what you have discussed in your declaration, correct?

A. Yes.

Q. Okay. And if I use POSA, P-O-S-A, you will understand that to mean person of ordinary skill in the art?

A. Yes.

Q. Okay. Great. It makes it a little easier for us.

So if I understand you correctly, statistics are an important part of any study design, correct?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: Yes, especially at the primary endpoint.

BY MR. ASHKENAZI:

Q. Okay. And scientists understand that in order to determine whether an effect is real or potentially due to random chance, we use statistics to make that determination, correct?

MR. TORCZON: Objection. Scope.

THE DEPONENT: Yes. But it varies on the importance based on the primary versus secondary versus exploratory endpoints.

BY MR. ASHKENAZI:

Q. Okay. And it'S generally accepted that a P value of less than .05 is -- would allow someone to make a determination of statistical significance, right?

A. Yes.

Q. Okay. Meaning if the P value is greater than .05, then it's generally understood by a POSA that whatever effect you're seeing is not statistically significant?

MR. TORCZON: Is there -- is that a -- then objection. I'm sorry. Let's track that.

THE DEPONENT: Yeah.

MR. TORCZON: Give me a second. Object. I lost track what the objection was. I'm sorry.

THE DEPONENT: Would you mind repeating it?

MR. TORCZON: Scope.

THE DEPONENT: Because now I've lost the train, too.

MR. TORCZON: Objection. Scope was going to be the objection.

BY MR. ASHKENAZI:

Q. If a P value is greater than .05, then it would generally be understood by a POSA that the effect or the difference in numerical values that you are seeing in the study are not statistically significant, correct?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: Correct. At a statistical level.

BY MR. ASHKENAZI:

Q. Yeah. And the FDA and scientists and POSAs generally understand that statistically -- statistical significance is relevant for making a determination on whether an effect is real, correct?

MR. TORCZON: Objection. Scope.

THE DEPONENT: For the primary endpoint.

BY MR. ASHKENAZI:
Q. And you will agree with me that statistics are not only used in clinical trials, correct?
A. Correct.
Q. And people conduct scientific analyses all the time and use -- withdrawn.
I'm sorry. I got computer problems here.
And in general in scientific literature, scientists use the value point P less than .05 to make the determination of statistical significance for effects in a study, correct?
MR. TORCZON: Objection. Scope.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Have you yourself used for non-primary endpoints the value -- the P value of less than .05 to make a determination of statistical significance?
MR. TORCZON: Objection. Scope.
THE DEPONENT: I have recommended it to sponsors.
BY MR. ASHKENAZI:
Q. Okay. In other words, in general, a POSA would understand that when you are looking at any data, in order to make an under -- to make -- to be able to conclude that the effect is real, as opposed to

potentially by chance, you use a P value of less than .05, correct?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: I don't. I think in general, P05 is a regulatory requirement. But if you want directionality in a study, if you want to do a phase 2 small study, P equals 10 is a 90 percent chance it's real. So I've -- I -- myself, I have recommended to sponsors that for directionality purposes in a small study, you can accept a lesser P value.

BY MR. ASHKENAZI:

Q. When you say "directionality," you mean a possibility that something may occur?

A. The possibility that it's a real effect, if you have a novel agent and you have a 90 percent chance and the study's, you know, it could take three years to do, but if you cut it down to P10 and you need less patients, it can be done more quickly, say, like a rare disease or something, you could not go by the P05. FDA is a regulatory body that requires, in general, but not always, two studies at P05 with the primary endpoint.

Q. Now, let's break that down to a couple of parts.

Your point is that you could take P value of .1, and that will give you generality, a general direction of effect, potentially, for you to conduct a study. Is

that accurate?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: You could accept a P10 as your statistical endpoint, not for registration with the FDA, not as a pivotal trial, but in a -- say, a phase 2 study where you want to see if the drug is doing what you think it should do.

BY MR. ASHKENAZI:

Q. Okay. In the literature that you reviewed in this case, have you seen any scientific article that found a statistical significance at a P value of between .10 and .05?

MR. TORCZON: Objection. Scope.

THE DEPONENT: Not that I recall.

BY MR. ASHKENAZI:

Q. Okay. And, in fact, you will agree with me that every piece of literature that you reviewed, when referring to statistical significance for this -- for these IPRs, that statistical significance value that was used was P equals .05 or lower, correct?

MR. TORCZON: Objection. Scope. Asked and answered.

THE DEPONENT: Yes.

BY MR. ASHKENAZI:

Q. And, in fact, you will agree with me that the

FDA has experts that they consult to determine that its proper to use a P value of .05 or less for making its determinations on cause and effect, correct?

MR. TORCZON: Objection. Scope. Asked and answered.

THE DEPONENT: For the primary endpoint.

BY MR. ASHKENAZI:

Q. And you will agree with me that the FDA does not allow someone to say, even for secondary endpoints, P -- that there is a statistical significance if the P value is greater than .05, correct?

MR. TORCZON: Objection. Scope. Relevance. Asked and answered.

THE DEPONENT: Well, if it's -- if that's not the data, then obviously you can't say. You have to say the truth.

BY MR. ASHKENAZI:

Q. Well, I want to be clear.

The FDA will not allow companies to assert that there's a statistically significant difference for any endpoint, whether it's primary, secondary, or otherwise, if the P value is greater than .05, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: I don't know about the secondaries, but you have to tell the truth of what it

is.
BY MR. ASHKENAZI:
Q. What -- so as someone who has been in the field for all these years, it's your opinion that the FDA will allow a company to say that there is a statistically significant difference in an effect for a secondary endpoint where the P value is .10?
MR. TORCZON: Objection. Scope. Relevance. Misstates.
THE DEPONENT: That is a mis -- misstatement. I mean, you can't claim a statistical significance if it's greater than .5 -- 05, right? But you can still use that data for directionality, basically.
BY MR. ASHKENAZI:
Q. Okay. So as far as the FDA is concerned, whether it's a primary, secondary, or other endpoint, if the P value is greater than .05, it is not significantly significant. Is that accurate?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: It's not -- I'm sorry.
It's not statistically -- statistically significant at that level. So you could define the level of significance at whatever you would like, whether the FDA accepts it is a second issue.
///

BY MR. ASHKENAZI:
Q. So my question was specific to the FDA. As far as you are aware, the FDA does not allow a company to say, whether it's for a primary, secondary, or other endpoint, that there is a significance if the P value is greater than .05, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: I need your clarification on when you say "say." Does that mean as a claim in the package insert, or is it just announce that it had an effect?
MR. ASHKENAZI: Either.
MR. TORCZON: Same objections.
THE DEPONENT: I think as a claim, I mean, as a claim, that's likely correct. The FDA wants to see .05. But in terms of saying that it had an effect on whatever, at P06, I don't think there's FDA oversight as long as its not in the package insert.
BY MR. ASHKENAZI:
Q. Okay. So your point is, the FDA does -- if it's not in the package insert, the FDA will not care, is your point?
MR. TORCZON: Objection. Relevance. Misstates.
THE DEPONENT: You can, as a sponsor, distribute published articles about your product where the primary endpoint is at P05 and there's a number of secondaries

that are not, and that's allowed, yes.
BY MR. ASHKENAZI:
Q. Sure. Okay. Apologies. I want to be very clear.
As far as the FDA is concerned, whether you're looking at a primary, secondary, or other endpoint, you cannot assert that there's a statistical significance if the P value is greater than .05. Is that accurate?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: I don't think so. You -- let me just explain where we're disconnecting here.
You can say what the statistics are. And when you say statistically significant, you can make up that point on your own. You can claim that you think that .06 is significant. For FDA approval and communication through the package insert, the 05 is the standard.
BY MR. ASHKENAZI:
Q. Okay.
A. And --
Q. As far as we've discussed today, in all the literature you reviewed for this action, you have not seen anyone assert that a P value of greater than .05 is statistically significant, correct?
MR. TORCZON: Same objections as earlier. I think scope, relevance.

THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. Now, so, Doctor, I want to, if we can, go back for a few minutes.
In terms of the publications that you have worked on with respect to chemotherapy-induced nausea and vomiting, is it safe to say that the last one you published was in 1989?
A. I would need to double-check, but that sounds -- the one, on the chemotherapeutic agent interactions I have to -- I have to double-check.
Q. Okay.
A. It was in the '80s. I'm not exactly sure.
Q. Sure. So I'll rephrase the question to make it a little clearer.
As far as your work on chemotherapy-induced nausea and vomiting, it's safe to say that the last you've published on that issue was in the 1980s. Is that accurate?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. Now, you have worked on, as you mentioned, pain, migraines, and stroke work over the years. Is that accurate?

A. Among --

MR. TORCZON: Objection. Misstates. Relevance.

THE DEPONENT: Amongst many other things.

BY MR. ASHKENAZI:

Q. Okay. Have you done any consulting work on NK-1 receptor antagonists?

A. It's possible back in the '90s. I consulted with many companies back then in the migraine field, and they were being used extensively in the field of migraine in the late '90s, but I don't specifically recall.

Q. So then other than work with respect to mi -- withdrawn.

Other than NK-1 receptor work, potentially, in the 1990s related to migraines, you have not conducted any other research on NK-1 receptor antagonists. Is that right?

MR. TORCZON: Objection. That's -- objection. Relevance.

THE DEPONENT: Actually, incorrect. So the failure of the NK-1s in migraine was of interest to me because I think it's, obviously, important to find drugs that work. But when you have animal models that predict efficacy and you don't find it, and that happened in the migraine field -- there was a very famous professor at

Harvard who had an animal model of migraine and these NK-1s were incredibly effective at -- they all failed in the clinic. So I did research where I wanted to understand why they failed, and I did publish it as an abstract at the headache -- International Headache Congress in roughly 2003 or '4, called "In Memorium" the neurogenic theory of migraine, where I specifically addressed the issue of why that class of drugs failed in humans, in migraine.

BY MR. ASHKENAZI:

Q. Okay. There's a lot there, so I will see if we can unpack some of that.

So you had mentioned that you were evaluating, with respect to NK-1 receptor antagonists, whether or why the animal models were not necessarily predictive of efficacy in humans?

A. In migraine.

MR. TORCZON: Objection. Form. Relevance.

BY MR. ASHKENAZI:

Q. Okay. Now, in general, you will agree with me that animal models are not always predictive of effects in humans, correct?

A. Well, they can be, for sure. But sometimes they are not. Correct.

Q. All right. And, in fact that's one of the

reasons why clinical research requires that even though you have preclinical data in an animal, you still need to conduct numerous clinical trials in order to get approved for use in humans. Is that accurate?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: I'd like you to say that again, because it's -- I mean, it's -- the concept of approving a drug for an indication in humans in an animal doesn't make any sense whatsoever because it's -- you know, for veterinary medicine. But in humans, you have to do human studies.

BY MR. ASHKENAZI:

Q. Okay. So let's -- let's take that.

In order to know if there -- a drug has an effect in humans, you have to do human studies, correct?

A. That's correct.

Q. And that's because preclinical animal models are not fully predictive of how a drug is going to react in a human, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: And other reasons, yes.

BY MR. ASHKENAZI:

Q. Okay. You can have drugs that show efficacy -- withdrawn.

You can have molecules that show efficacy in

preclinical models, but just don't work in humans. Is that accurate?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. And, in fact, there are NK-1 receptor antagonists that have shown efficacy in preclinical models, but were not actually shown to have effect in humans, correct?

MR. TORCZON: Same objections.

THE DEPONENT: In certain diseases, yes.

BY MR. ASHKENAZI:

Q. Okay. And there are drugs that have shown efficacy -- withdrawn.

For NK-1 receptor antagonists, there are molecules for CINV that actually moved forward into clinical development because they had positive preclinical data but couldn't get approved by the FDA, right?

MR. TORCZON: Objection. Scope.

THE DEPONENT: That falls outside my scope of this review, as to the reasons why they failed FDA.

MR. ASHKENAZI: Okay. Doctor, I know I told you I'd give you a break every hour. We started at 9:20, but we were in this room for over an hour.

A. Yeah, yeah.
MR. ASHKENAZI: Would you prefer to take a break now?
THE DEPONENT: That's fine.
MR. ASHKENAZI: Why don't we go off the record.
(A recess transpires.)
BY MR. ASHKENAZI:
Q. Okay. So, Dr. Peroutka, nausea and vomiting are two potential side effects of chemotherapy medication, correct?
A. Correct.
Q. Okay. And I want to make sure I'm being clear on that.
There's a difference between nausea and vomiting as it relates to side effects from chemotherapy medication, correct?
MR. TORCZON: Objection. Form.
THE DEPONENT: A difference in what? Mechanistic difference? What type of difference? Ep.
BY MR. ASHKENAZI:
Q. They are two -- okay. So let's break that up.
You will agree with me that nausea is different than vomiting, correct?
A. Correct.
Q. Okay. You will agree with me that the

mechanisms for nausea are not completely known even today, correct?
A. Correct.
(Discussion off the record.)
BY MR. ASHKENAZI:
Q. Okay. You will agree with me that two of the worst adverse effects of chemo -- of cancer chemotherapy is nausea and vomiting, correct?
MR. TORCZON: Objection. Form. Scope.
THE DEPONENT: Two of the -- out of how many?
BY MR. ASHKENAZI:
Q. In general, two of the worst adverse effects of cancer chemotherapy is nausea and vomiting, correct?
MR. TORCZON: Same objections.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. Now, by the way, when I refer to emesis, you understand I'm referring to vomiting, correct?
MR. TORCZON: E-m-e-s-i-s.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. And that's the way a POSA understands emesis, emesis is vomiting, correct?
A. Correct.
Q. Okay. Now, a patient can be treated for

vomiting, but still suffer from nausea when being given cancer chemotherapy, correct?

A. Correct.

Q. Okay. And, in fact, you will agree with me that as of 2009, while emesis was generally under control, nausea was a significant problem for cancer chemotherapy, correct?

MR. TORCZON: Objection. Scope.

THE DEPONENT: I would not agree.

BY MR. ASHKENAZI:

Q. Okay. It's your position that nausea was under control -- withdrawn.

Why would you disagree?

A. Well, if you look at some of the papers I cite, Campos is -- is a good one. You look at the nausea scores, and Herrington, I think is the other one where they were getting it down. So if -- if I may, there's a big difference between how we clinically measure nausea and how we clinically measure vomiting or emesis. So vomiting emesis is a categorical endpoint. Either you do or you don't, right? It's something you can see, something that can be quantitated simply objectively, and, you know, the definitions they put around it is within five minutes. So one episode of vomiting is done, and then if you don't vomit within five minutes,

you can go to episode two. Very clear.

Nausea, on the other hand, is a -- a visual analog scale that goes from zero to 100 millimeters. So it's a continuous variable. And it can change over the time course of day. It can change in the time course of minutes. It can be caused by memory. You can remember something and get nauseous. A smell, visual, seeing something. And mechanistically, it's a perception. It's not an event.

So when we talk about nausea and vomiting, they were clearly linked. People with nausea can vomit, people who vomit can feel nauseous, vice-versa. But mechanistically, one is a brain stem reflex, a neurological reflex, the other one, as you alluded to, is not as clearly understood in terms of pathways, but it's pretty clear that the cortex, cortices are involved because it's, like I said, a literal memoral -- memory of something traumatic, a -- a -- seeing something traumatic, smelling something can trigger nausea.

Q. Okay. I'm going to try to break some of that down. That was a lot. So let's see if we can take that into some pieces.

Mechanistically, nausea -- withdrawn.

Within the body, the causes for nausea can be different than the causes for vomiting, correct?

A. Yes.
Q. Okay. And treatments that work for vomiting may not necessarily work for nausea. Is that accurate?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: It's possible.
BY MR. ASHKENAZI:
Q. And, in fact, there are treatments that are used and that are shown to be effective for emesis, but are not effective for nausea, correct?
MR. TORCZON: Same objection.
THE DEPONENT: That's a more complicated question to answer because, as I just said, one is a categorical scale and one is a -- you know, so when you say not effective, is getting your nausea score down from a 70 out of 100 to 25, you still have nausea, but it's a lot better. So the naus -- my point is, the nausea measures are relative on a spectrum, and when you say treated, you have to define what that means. I can -- I know what no vomiting is, but they -- they -- the field of medicine has decided on a zero to 100, but less than 5 is no nausea. But it isn't, because if you got 4 out of 100, you still have, quote, nausea, and if you're less than 25 out of 100, you have no significant nausea.
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BY MR. ASHKENAZI:
Q. Well, let me -- let's take this a couple pieces.
There is a scale that is used by scientists, the VAS scale, for making determinations on nausea. Do you agree with me?
A. Correct.
Q. And that is something that's generally accepted by the scientists in this field, correct?
A. In the two thousand -- pre-2009 era, yes.
Q. Okay. And you will agree with me that there are objective criteria using that VAS scale, for example, that make a determination on reducing the severity of nausea, correct?
MR. TORCZON: Objection. Misstates.
THE DEPONENT: Well, first of all, to clarify, the scale is subjective. There can be objective guidelines, but adding objectivity to a subjective assessment.
BY MR. ASHKENAZI:
Q. Understood. So let's -- but to be clear, a POSA accepts the VAS scale, which is a subjective scale, for making determinations on the severity of nausea, correct?
A. Correct.
Q. Okay. And the field in general accepted that in

order for drugs to be known for treating, not necessarily preventing completely, but treating nausea, there was a way to make that determination, correct?

A. I'm not sure I would agree with that. At the time, I don't know what the FDA criteria was for a pure nausea drug.

Q. Now, you mentioned two -- two studies that you believe say that nausea was no longer an issue for people in 2009 who were being given cancer chemotherapy, correct?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: I -- I said that there was an effect on nausea when -- I disagree with there was no further problem. It was not 100 percent effective, but for a significant number, the majority of people, nausea was fairly well controlled in the end of the 2000s decade.

BY MR. ASHKENAZI:

Q. Okay. If I'm going fast, you stop me. Okay? Because I want to make sure I'm not making a hard time for you.

So that just to make clear, it's your position that at the end of the 2000s, around 2009, for the majority of people receiving cancer chemotherapy, nausea was fair ly well controlled and no longer a major issue?

MR. TORCZON: Objection. Misstates.
THE DEPONENT: We can look at the numbers if you would like but yes. I -- for the majority of patients, getting the triple combination of the day, the median numbers for nausea were pretty good.
BY MR. ASHKENAZI:
Q. Okay. You're looking at the absolute value of the medium values, not caring about statistical significance, when you make that determination, correct?
A. In this case, I'm thinking of two specific data sets.
Q. Which data sets are you thinking of?
A. Campos.
Q. Okay.
A. If you want to go look there.
Q. And what's the other dataset that you're referring to?
A. I'm pretty sure it's Herrington.
Q. Okay. So I just want to make sure we're clear.
It's your position that the reason -- or the evidence that in the 2009 time period nausea was no long a major issue for patients receiving cancer chemotherapy was due to the data contained in Campos and Herrstadt. Is that correct?
MR. TORCZON: Objection. Misstates.

THE DEPONENT: No, that's not correct. But your question was for the majority, meaning a median value is defined as the -- the middle of the entire spread. There were clearly patients who did not respond to those therapies that nausea was a problem for, so these were not 100 percent effective drugs. I think in the case of vomiting, the -- the state-of-the-art standard of care got up into the 70s and 80 percents reduction and elimination, complete vomiting decreased, whereas the nausea was overall reduced unequivocally, but not 100 percent.

BY MR. ASHKENAZI:

Q. Okay. Let's -- key points. With respect to nausea, it was no longer a major problem for patients receiving cancer chemotherapy in the 2009 time period. That's your position, correct?

A. No.

MR. TORCZON: Objection. Misstates.

THE DEPONENT: Once again, to clarify, the drugs that existed then helped a significant and, based on those two references, the majority of people with chemotherapy, but not everyone.

BY MR. ASHKENAZI:

Q. Okay. I -- so you would consider, then -- so it's -- you will agree with me, then, that nausea was

still a major problem for patients receiving cancer chemotherapy in 2009?
A. For --
MR. TORCZON: Objection to form. Misstates.
THE DEPONENT: For a number of patients, but not for all.
BY MR. ASHKENAZI:
Q. Okay. And the studies that you believe show that nausea was being treated for the majority of patients are Campos and Herrington?
MR. TORCZON: Objection. Misstates. Asked and answered.
THE DEPONENT: Those are two examples.
BY MR. ASHKENAZI:
Q. Okay.
A. There was others.
Q. Which other ones would show that nausea was being treated for the majority of patients being exposed to cancer chemotherapy?
MR. TORCZON: Objection. Scope.
THE DEPONENT: I would have to re-review the papers. I'm happy to do it and go through the ones I'm thinking of, but those two in particular, I have specific memories of the data.
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BY MR. ASHKENAZI:
Q. And it's your position that Campos was evaluating an FD -- a treatment that can be given to patients?
A. Well, at least one of the arms, yes.
Q. In other words, its your position that Campos is evidence of an FDA-approved protocol for giving -- for treating patients for a cancer-induced nausea and vomiting?
MR. TORCZON: Objection. Form. And scope.
MR. ASHKENAZI: I'm sorry. Withdrawn. My question was not clear. I will rephrase that. I forgot the chemotherapy in there.
BY MR. ASHKENAZI:
Q. It's your position that Campos is evidence of an FDA-approved protocol for treating patients for cancer chemotherapy-induced nausea and vomiting?
MR. TORCZON: Objection. Form. Scope.
THE DEPONENT: I would have to relook at Campos. I am -- I'm not sure it was a US study, so I don't know whether FDA approved it.
BY MR. ASHKENAZI:
Q. Okay. So what I'm trying to get at, and I want to make sure I have an understanding, is that do you believe that patients have been prescribed -- withdrawn.

Now, Dr. Peroutka, you are aware of what a review article is, right?
A. Correct.
Q. A review article is a -- well, maybe in your words, what's review article?
A. As the word says, it reviews a certain field of research or a certain disease, and it's not primary data, but it just assesses compiled data from others, or the author themselves.
Q. Okay. I'm going to hand to you what's already been marked as Exhibit 2036.
(Exhibit No. 2036 marked for identification.)
MR. ASHKENAZI: And this is a review article titled "Pharmacology Management of Chemotherapy-Induced Nausea and Vomiting Focus on Recent Developments."
Do you see that?
THE DEPONENT: Yes.
MR. TORCZON: I'm going to object to the exhibit on the basis of scope.
BY MR. ASHKENAZI:
Q. Now, Dr. Peroutka, you will agree with me that in the 2009 time period, would you say that you were familiar generally with the -- withdrawn.
So do you have this reference in front of you?
A. Yes.

Q. Exhibit 2036?

MR. TORCZON: Objection. Form.

Okay. I'm sorry. Withdrawn.

THE DEPONENT: I'm sorry. I missed the last --

BY MR. ASHKENAZI:

Q. Yeah. I just want to make sure you have Exhibit 2036 in front of you.

If you could turn to page -- and you'll agree with me that this is an article that describes a focus on recent developments in CINV management, correct?

A. Yes.

Q. Okay. And if you could turn to page 528. It's in the Future Development section.

Sorry. The page 528. On the left-hand side, I'm focused on.

You will see the second full paragraph starts:

"The control of nausea in patients receiving moderately and highly emetogenic chemotherapy remains a significant problem."

Do you see that?

A. Yes.

MR. TORCZON: Objection. Scope. Foundation.

BY MR. ASHKENAZI:

Q. And do you agree with that?

MR. TORCZON: Same objections.

BY MR. ASHKENAZI:
Q. As of 2009?
A. It's a significant problem for the subset of patients that don't respond to the current therapy. I agree.
Q. Well, this doesn't say who don't respond to the current therapy. The statement here says:
"The control of nausea in patients receiving highly emetogenic chemotherapy remains a significant problem."
Do you disagree with that statement?
MR. TORCZON: Objection. Scope. Foundation. Relevance.
THE DEPONENT: I'm going to repeat my answer. The control of nausea in patients receiving moderate highly emetogenic therapy remains a significant problem for those non-responders. I mean, an analogous situation being the people who don't respond to chemotherapy, death remains a major problem.
BY MR. ASHKENAZI:
Q. Okay. You'll agree with me that the caveat that you're inserting is not actually contained in the reference 2036, correct?
A. No. I have to read the article --
Q. Okay.

A. -- to know.
Q. Well, you've reviewed the Hearst article in this case, correct?
A. The Her -- how do you --
Q. I'm sorry.
A. -- pronounce it?
Q. I'm going to pronounce it improperly, so I am going to hand it to you. Exhibit 1010.
(Exhibit No. 1010 marked for identification.)
THE DEPONENT: Oh, Herrstedt.
BY MR. ASHKENAZI:
Q. Herrstedt?
A. Herrstedt.
Q. Now, you have reviewed the Herrstedt article, correct?
A. Yes.
Q. Okay. And on the first page -- okay. There's a first paragraph that says:
"Nausea and vomiting are ranked by patients as two of the worst adverse effects of cancer chemotherapy."
Do you see that?
A. Yes.
Q. And you agree with that, right?
MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: Yeah, I did answer that, and the answer again is yes.
BY MR. ASHKENAZI:
Q. Okay. And you will see here at the last sentence of this first paragraph of the article that you referenced, it says:
"Today, the majority of patients consider nausea as the main problem."
Do you see that?
A. Yes.
Q. And you agree with that statement, as of 2007, when this article was written, correct?
A. Honestly, I'm not sure. At that point in time, I think -- I always think of fatigue. The patients that I know were massively fatigued, and yes, very close second and third were nausea and vomiting. But the majority of the patients. I'd have to see the primary data to support that.
Q. You weren't actually treating patients in 2007 for chemotherapy-induced nausea and vomiting, correct?
A. Correct.
MR. TORCZON: Objection. Asked and answered.
BY MR. ASHKENAZI:
Q. Okay. And you hadn't conducted any research on chemotherapy-induced nausea and vomiting since 1990,

correct?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: Based in the late '80s.

(Exhibit No. 1030 marked for identification.)

BY MR. ASHKENAZI:

Q. Okay. And you will agree with me that the authors of this article are conducting a review of an article being Exhibit 1030?

A. Yes.

Q. Are conducting a review of antiemetic therapy in cancer chemotherapy, correct?

A. Yes.

Q. And this is an article that you relied upon in your declaration, correct?

A. Correct.

Q. And they have stated, contrary to what you are telling me today, that the majority of patients consider nausea as the main problem. Is that accurate?

MR. TORCZON: Objection. Form. Misstates.

THE DEPONENT: It's accurate that it says that. I would like to see the data that supports that.

BY MR. ASHKENAZI:

Q. Okay. Nonetheless you will agree with me that the authors of this article did state that, right?

A. Correct.

Q. Okay. Now, if you could turn to page 148, please.

Do you see on the right-hand side, there's a heading that says "Persistent Problems on Potential New AntiEmetics"?

A. Yes.

Q. Okay. You will agree with me that the authors -- why don't you take a moment and read that paragraph to yourself and let me know when you're done.

A. Just the one paragraph or the whole section?

Q. Yeah, just the one paragraph.

A. Okay.

Q. So you will agree with me that this article is written in 2007, after aprepitant was on the market, correct?

MR. TORCZON: Objection. Foundation.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. And aprepitant was more -- was approved in 2003. Is that accurate?

A. Correct.

MR. TORCZON: Objection. Scope.

BY MR. ASHKENAZI:

Q. Okay. And you will agree with me that the authors of this article, Exhibit 1010, the Herrstedt

article, acknowledge that nausea and loss of appetite are the main problems for the majority of patients, correct?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: Correct. That's what it says.

BY MR. ASHKENAZI:

Q. And that's what the authors of the article that you relied upon concluded in 2007, correct?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: As you mentioned, this was a review -- is a review article, so that's their opinion.

BY MR. ASHKENAZI:

Q. Okay. And is it your opinion that that's wrong?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: To answer that question, it really depends on the data. So if you look at the data, the majority, based on the median data, would not agree with that. So I accept that this is Professor Herrstedt and Thumbernouski's opinion, but there were data existing at that time point which would say that the treatment available then for the majority, based on the median data, were being served pretty well.

MR. TORCZON: Bless you.

BY MR. ASHKENAZI:

Q. Now, let's go back to the -- in Exhibit 1010,

the Herrstedt article. There's an abstract on the first page, if you could focus on that for a minute.

Now, middle -- about midway through, do you see it says:

"The improvement in prophylaxis -- prophylaxis of nausea with this combination is, however, modest."

Do you see that?

A. Correct.

Q. Okay. And it's referring to the combination of using a 5HT3 with a corticosteroid, correct?

A. I have to read it. Give me a second -- a minute.

Okay. Can you repeat the question?

Q. Yeah, sure. Okay. In 2003, aprepitant enters the marketplace, correct?

A. Correct.

Q. Okay. And aprepitant was shown to be effective for treating delayed emesis. Is that accurate?

A. Correct.

Q. Okay. Now, you will agree with me that despite aprepitant being on the market, being used with 5HT3s and corticosteroids, there was still a need for new antiemetics, correct?

MR. TORCZON: Objection. Relevance. Misstates.

THE DEPONENT: There was a need for improved

anti-emetics based on the fact that the existing drugs were not 100 percent effective for nausea and vomiting.
BY MR. ASHKENAZI:
Q. Okay. And you will agree with me that the major failure of anti-emetic regimens as of 2009 was for treating nausea, correct?
A. I don't think I could agree with that in the sense that, again, when I did treat patients, and that has not changed over the years, there was some where the vomiting alone was what really bothered them, and there were others where the vomiting didn't seem to bother them that much, but the nausea did. So...
Q. My question was a little different.
With the anti-emetic regimens that were available in 2009, you will agree with me that emesis was relatively under control as of 2009, correct?
MR. TORCZON: Objection. Form.
THE DEPONENT: No. I would agree that roughly 80 percent was under control. But for the 20 percent that it wasn't, that to me is a significant number of people that suffer from vomiting. And the same with nausea, for the -- there were -- the majority, I believe the data show with the triple combination that was, quote, under control, meaning less than 5 average scores through the five days of chemo, but then for those that

it wasn't, it was a significant problem.
BY MR. ASHKENAZI:
Q. Okay. So maybe if I understand you correctly, you'll -- that for -- it's your position that for the majority of patients, nausea and vomiting were properly controlled as of 2009 with existing anti-emetic regimens. Is that your position?
A. Based on the med --
MR. TORCZON: Objection to form and misstates. Go ahead.
THE DEPONENT: Based on the median data from the two papers I referenced that we have not looked at yet under those conditions that those studies were done. So this is another variable we haven't discussed, that every chemo study, highly emetic, median emetic therapies, the dosing schedule, the regimens, et cetera, for the papers that were published, the data published, would say that for that group of cancer patients, at those doses of chemo, of the doses of drugs specific chemo drugs, that indeed the majority did not vomit or have significant nausea.
BY MR. ASHKENAZI:
Q. Asking a broader question here.
Based on your review of the literature for this action, for these IPRs, is it your position that nausea

and vomiting were properly controlled in 2009 with existing anti-emetic regimens for the majority of patients?

MR. TORCZON: Objection. Scope.

THE DEPONENT: Based on the data, the majority, again, restricted to the study population, had complete control or very low levels of nausea, based on the Campos and Herrington data, for example.

BY MR. ASHKENAZI:

Q. Okay. But you agree with me that there's a -- there was a portion of patients for which nausea and, separately, vomiting were not properly controlled for cancer chemotherapy, correct?

A. Correct.

Q. Okay.

A. Absolutely.

Q. And for those portion of patients as of 2009, it was important to find new antiemetics that would help treat nausea and vomiting for that group of patients, correct?

A. Correct.

Q. Okay. And scientists were looking for new mechanisms of actions and new drugs using different mechanisms of actions for treating the portion of patients that cannot properly be treated for nausea and

vomiting as of 2009, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: There -- there would be scientific interest in that, yes.

BY MR. ASHKENAZI:

Q. That's what a POSA would be looking at, looking to find new drugs to help treat the patients that couldn't properly be treated for nausea and vomiting with existing antiemetics, right?

MR. TORCZON: Same objections and foundation.

THE DEPONENT: Yes, but also potentially new regimens, new formulations. So it's not just new drugs. It could be other things, too.

BY MR. ASHKENAZI:

Q. The point is that there would be a focus on finding new treatments for patients to treat them separately for nausea or vomiting or both, other than the existing antiemetics, right?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: Or new regimens formulations, so better -- the goal would be to improve the response rates of the various parameters.

BY MR. ASHKENAZI:

Q. Okay. You'll agree with me that there was a significant focus, based on your review of the

literature, for different mechanisms of actions for treating chemotherapy-induced nausea and vomiting?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: And I think it's out of scope. I was focused on the triple combination of the steroid NK-1 5HT3, so I didn't look at what else was happening in the nausea and vomiting world at that time outside of those three.

BY MR. ASHKENAZI:

Q. Okay. I want to make sure I understand what you're saying there.

So when you did your analysis for this case, you started with the triple therapy in hand and then looked at what you could do with the triple therapy?

A. I looked at the standard of --

MR. TORCZON: Objection. Misstates.

THE DEPONENT: I looked at the standard of care in, for example, MASCC. The MASCC paper was a key one because it was a review article and a guideline proposal from nine international oncology societies. So in medicine, that's a pretty, you know, important milestone in nausea and vomiting when multiple country experts can come together and agree upon a regimen. So the standard of care at that point was the triple therapy.

///

BY MR. ASHKENAZI:
Q. I don't think that -- that answered my question, so -- and I'm responding to what you said earlier, so I'm just trying to understand what your analysis -- how you did your analysis in this case, because when I asked you about other mechanisms of actions or other drugs that were being looked at, you said you didn't consider that. So with that, I'm going to re-ask my question. Is that okay?
A. (Moves head up and down.)
Q. All right. When you did your analysis for this -- these IPRs, you started with the triple therapy in hand that is identified in MASCC or other references and said, how can I put netupitant into that --
A. How can I put?
Q. Netupitant, n-e-t-u-p-i-t-a-n-t. Is that correct?
A. Into --
MR. TORCZON: Objection. Objection. Form. Asked and answered. Misstates.
THE DEPONENT: I didn't hear the whole spelling.
MR. ASHKENAZI: Sure.
THE DEPONENT: So.
BY MR. ASHKENAZI:
Q. When you did your analysis for these IPRs, you

started with the triple therapy identified in MASCC and other references, and looked to determine whether you would put netupitant and use that in place of aprepitant. Is that accurate?

MR. TORCZON: Objection. Misstates. Asked and answered. Form.

THE DEPONENT: No. I was asked to review the standard of care pre November 18th, 2009, and I looked at a number of things. You know, actually what I did was I went on to UPMED and put in pre November 18, 2009. And as you pointed out, there's different types of articles. There's review articles, there's scientific study reports, et cetera. And I found MASCC, which I felt was a key paper because it was clearly for the priority date, it was an international consortium of key opinion leaders in the field of oncology from nine different countries, and it was a really good summary, I felt, of what the standard of care was at that point. Clearly, MASCC mentioned some other things, but they point to the triple combo as their recommended.

BY MR. ASHKENAZI:

Q. So you did review the literature related to NK-1 receptor antagonist research, correct?

A. Yes.

MR. TORCZON: Objection. Asked and answered.

BY MR. ASHKENAZI:
Q. Okay. And you're aware that there were a number of different NK-1 receptor antagonists that were being evaluated by many different companies in -- by 2009, correct?
A. Well, there were others. I wouldn't say many, many companies.
Q. Okay. How many -- from your review of the literature, how many NK-1 receptor antagonists were there data for that were being evaluated or that could be evaluated for the treatment of cancer chemotherapy-induced nausea and vomiting?
MR. TORCZON: Objection. Scope.
THE DEPONENT: Four or five.
BY MR. ASHKENAZI:
Q. Four or five. And with respect to NK-1 receptor antagonist that had data that was available, preclinical data, showing efficacy in models, how many or so would you say were available as of 2009?
MR. ASHKENAZI: Objection. Scope. Relevance.
THE DEPONENT: Three to five.
BY MR. ASHKENAZI:
Q. Three to five. And when you say three to five, we're not talking about 3 to 5 FDA approved drugs. We're just talking about molecules that existed with

information out there relating to their potential effects, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. Now, it was your -- you -- when you looked at the literature, you looked for the standard of care for treating patients for cancer chemotherapy-induced nausea and vomiting as of 2009. Is that right?

A. Pre-2000.

Q. Pre-2009?

A. November 18.

Q. Thank you for that clarification.

When I refer to 2009, as I have been doing today and -- and continue going forward, you will understand I'm referring to pre-November 2009. Is that correct?

A. November 18th, to be accurate, yeah.

Q. Okay. But you understand that that's what we have been discussing today and will be continued to be discussed?

A. Correct.

Q. Okay. Thank you.

Now, you will agree with me that as of 2009, again, November 18th, 2009, it's your assertion that

MASCC is identifying the standard of care for treating patients with cancer chemotherapy-induced nausea and vomiting, correct?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: It's recommending, essentially, the review paper that's self -- sets up a recommended regimen as how patients should be treated based on existing data.

BY MR. ASHKENAZI:

Q. Okay. Now, is it your assertion that a POSA in 2009 would only focus on the existing standard of care and modifying the existing standard of care, as opposed to evaluating other new drugs or mechanisms of action for treating patients that were not being properly or adequately cared for with respect to nausea and vomiting?

MR. TORCZON: Objection. Relevance. Scope.

THE DEPONENT: That's a long question. A POSA, in my opinion, would certainly care about MASCC to understand where the field was and to evaluate that regimen and make an assessment if further improvements are -- are indicated or would be good, you know, and so make a decision based on that. So use what we have today, but if it's not 100 percent effective, obviously you'd want to look -- if you were in the business of

this field of doing research.
BY MR. ASHKENAZI:
Q. Okay. What I'm trying to understand is, we have a POSA sitting in 2009, and it's your assertion that that POSA is looking to see, can I improve -- well, withdrawn.
When you did your analysis, you looked at the MASCC reference and then you also noted that a netupitant was available based on the Bös or the Hoffmann reference. Is that accurate?
A. Correct.
Q. And then you -- the question that you posed to yourself was, would a POSA combine those two references. Is that fair?
A. Not in isolation, no. I mean, MASCC was just a review. You know, you'd have to look at the data from the other NK-1s, you would have to look at the psychological profile of the NK-1s to reach a conclusion.
Q. Okay. So if I understand your -- the analysis that a POSA would be doing in 2009, according to you, is they have MASCC in hand that shows the triple therapy of an NK-1, a 5HT3, and dexamethasone, correct?
MR. TORCZON: Objection to form.
THE DEPONENT: Wait.

BY MR. ASHKENAZI:
Q. I'm sorry. You said wait?
A. Wait.
Q. I believe you have to give a verbal response I'm sorry.
A. Well, could you repeat, please.
Q. Yeah. Apologies.
A. That's --
Q. Did I make a mistake on dexamethasone?
A. No. Yeah, go ahead.
Q. Okay. You'll agree with me that when you did your analysis, you had the MASCC triple therapy in hand, which was aprepitant, a 5HT3 receptor antagonist, and dexamethasone as the -- what you've been discussing a as the standard of care. Is that accurate?
A. Let me check, because I think it was broader. They -- they didn't just limit it to aprepitant. But let me check. Can we look at that, please?
MR. ASHKENAZI: Yes.
THE DEPONENT: It's in one of my books.
MR. TORCZON: They've got.
MR. ASHKENAZI: We're going to take care of it.
I'm going to hand to you what's been marked as Exhibit 1013.
THE DEPONENT: Thank you.

(Exhibit No. 1013 marked for identification.)
MR. TORCZON: Thank you.
BY MR. ASHKENAZI:
Q. And you will agree with me that this is a copy of the MASCC reference we've been discussing, M-A-S-C-C?
A. Yes.
Q. Okay. Now, with this in hand, I want to make sure I understand your analysis correct.
You said that a scientist would have the triple therapy discussed in MASCC and then would need to evaluate which NK-1 receptor antagonist can be used with the MASCC reference?
MR. TORCZON: Objection. Misstates.
THE DEPONENT: No. I said MASCC talks about the standard of care, recommendations on antiemetic regimens.
MR. ASHKENAZI: Right.
THE DEPONENT: Let's go to the -- if I can have time, please, to review --
MR. ASHKENAZI: Absolutely.
THE DEPONENT: -- what they say in terms of the...
BY MR. ASHKENAZI:
Q. While you're looking at that, Doctor, I just want to make sure you have an understanding. I'm

trying -- you mentioned something evaluating NK-1, so I'm trying to see how that evaluation of the NK-1s fits into your analysis for or in combination with the MASCC reference.

So with that, why don't you take a moment and read the MASCC reference, and then I'll restate my question. Okay?

A. Okay.

Q. And, Doctor, you will let me know when you're ready, right?

A. Yep.

Q. Okay. So let's take this, if we can, a couple of steps. Start with the first one.

You begin your analysis after your review of the literature with the MASCC reference, correct?

A. Correct.

Q. Okay. And the MASCC reference talks about a triple therapy. Is that accurate?

A. Correct.

Q. That triple therapy includes aprepitant in addition to a 5HT3 antagonist and dexamethazone, correct?

A. Correct.

MR. TORCZON: Objection. Misstates.

///

BY MR. ASHKENAZI:
Q. And you'll agree with me that aprepitant, as of 2000 and -- as of this time period, was the standard of care for treating patients for cancer chemotherapy-induced nausea and vomiting, along with other drugs, like 5HT3s and dexamethazone, correct?
A. Correct.
Q. Okay. Now, with the MASCC reference in hand, it's your assertion that a POSA would then look to evaluate all the different NK-1s -- withdrawn.
With the MASCC reference in hand and the triple therapy in hand, it is your assertion that a POSA would evaluate the NK-1 receptor antagonists that were known in the art by 2009 to determine which could be used with the triple therapy in place of aprepitant?
MR. TORCZON: Objection. Form.
THE DEPONENT: It's a little bit of a convoluted question, but. So I'll -- we'll go to MASCC, and there's a statement in there -- I have to find it exactly in here, but it's in my report -- that says:
"Aprepitant has been studied extensively" -- I'm sorry.
"Aprepitant is the first of a new class of drugs that selectively block neuro Neuorokinin-1 transmitter receptor.

BY MR. ASHKENAZI:
Q. Okay.
A. So that was, in a sense, the opening that to me suggests that they felt that NK-1 antagonists would be effective beyond aprepitant.
Q. Okay. So with that in mind, what was your next step? What was the POSA's next step in the analysis?
A. The analysis of what?
Q. That you did for this invest -- for this IPR.
MR. TORCZON: Object.
BY MR. ASHKENAZI:
Q. You have MASCC. What's your next step? What's a POSA's next step?
MR. TORCZON: Objection. Form. Scope.
THE DEPONENT: I look through the primary data from the research articles, trials.
BY MR. ASHKENAZI:
Q. Okay. So -- yeah. Sorry. You have asserted that the patents in -- the patents here, the four patents that are referenced on the front of your declaration, the '826, '357, '515 and '297, are obvious, right?
A. Correct.
Q. Okay. And I want to just make sure I understand your obviousness analysis.

You begin with the triple therapy that's included in the MASCC reference, correct?
A. I begin with the standard of care.
Q. And the standard of care, from your perspective, is the triple therapy that's identified in the MASCC reference?
A. One of the -- well, there's other review articles that talk about it too.
MR. ASHKENAZI: Okay.
MR. TORCZON: Can we pause? I've lost realtime. I am stuck way back at my last objection, which was a minute or two ago.
THE REPORTER: Is it updating?
MR. TORCZON: No. I got a flashing "follow, realtime."
THE REPORTER: Oh. Hit that.
MR. TORCZON: Hit that. Okay. There we go. Thank you. Sorry.
BY MR. ASHKENAZI:
Q. Okay. Let's start again.
You begin with what you believe your obviousness analysis with the standard of care as referenced, for example, in the MASCC reference, which included a 5HT3, aprepitant, and dexamethazone, correct?
A. Correct.

Q. Okay. And then you assert that a POSA would now change the NK-1 receptor antagonist that's in the standard of care, correct?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: A POSA would look at the data to see what's the basis of this combination, how do these three work together, and what's happening in the field. For example, dexamethasone is a steroid. That's the only one I can find of the steroid family. There's other steroids that can be given, variants that probably would work too because they're steroids. Okay?

5HT3 is a very large class of drugs that were approved for nausea and vomiting. '91, I think, ondansetron came out, roughly. So for a long time before this. And they were basically a class that were interchangeable.

And the third, the NK-1, at the time of the priority date was known to be a member of a -- aprepitant was the first of a member of a class. So then a POSA would like and say, okay, we know that there's variations when you vary the 5HT3 a little bit, we haven't really varied the dex, but a steroid is a steroid, so what -- what are the data out there on NK-1 and nausea and vomiting. And aprepitant clearly had the lead. It was the first. But there were other trials of

other NK-1s at the time. So a POSA would go, as I did, to look at what was available for this, quote, first in a new class of drugs.

BY MR. ASHKENAZI:

Q. Okay. Let's take that into a couple pieces. But I think I understand where we were having some discrepancies.

You mentioned dexamethasone is the steroid -- is the main steroid that's being considered and used for CINV, correct?

A. Correct.

Q. So a POSA, from your perspective in 2009, would not be looking to modify dexamethasone?

MR. TORCZON: Objection. Misstates.

BY MR. ASHKENAZI:

Q. In the triple therapy that was considered the standard of care?

MR. TORCZON: Same objection.

THE DEPONENT: It's possible that someone would, but scientific knowledge of the time would say all steroids are going to give you. Basically, if you get the right dose, and if you had what you thought was an effective dose, you'd stick with that.

BY MR. ASHKENAZI:

Q. Okay. Your next step is to look at the 5HT3

receptor antagonist, correct?

MR. TORCZON: Withdrawn.

THE DEPONENT: I don't remember which one I did first, but I did at one point.

BY MR. ASHKENAZI:

Q. Let --

A. And I knew the history, that there were many 5HT3s through the previous 15 years, whatever, that were a little different. So when -- in the pharmaceutical industry, when a class of drugs are first in class, is a -- there's frequent attempts to mimic it in some way, and with the 5HD3s, they did evolve in a sense of longer half lives or better absorption or not IV. So you can have variations within a class giving differences in clinical abilities, or clinical efficacy, I should say, and the question was, well, you know, was this a unique aprepitant effect or was this a class effect, if you will.

Q. Okay. Sorry. I want to take this just -- we looked at there's three components to the triple therapy that a POSA, from your perspective, is working with. One of them is a steroid, correct?

A. Correct.

Q. Which you said a POSA would stick with dexamethasone because there's no real expectation that

changing a steroid -- the steroid would change the effect on chemotherapy-induced nausea or vomiting, correct?

A. Although, it is --

MR. TORCZON: Objection. Misstates. You can...

THE DEPONENT: Although, it is possible.

BY MR. ASHKENAZI:

Q. Okay. Your next step in your obviousness analysis is to assert that a POSA would -- well, withdrawn.

Another part of the triple therapy that a POSA is evaluating, from your perspective, is the 5HT3 antagonist, correct?

A. Correct.

Q. And from your perspective, while there may be some minor differences in them, they were all considered interchangeable from your perspective, right?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: There were differences found between them.

BY MR. ASHKENAZI:

Q. But from your perspective, they were considered interchangeable?

A. Well --

MR. TORCZON: Objection. Misstates. Asked and

answered.

THE DEPONENT: If I can go back to MASCC. Is this the one?

So, for example, Table 3 in MASCC, they list five different 5HT3s where they provide the dosing for.

BY MR. ASHKENAZI:

Q. Okay.

A. And, you know, my sense of the review is there were some slight differences, but not anything that dramatic that wouldn't allow this international consortium of key opinion leaders to list all of them in the doses that were recommended to be used.

Q. So a POSA in 2009 looking to come up with a new regimen for treating cancer chemotherapy-induced nausea, and also for vomiting would have a steroid and would consider the ability to use any one of the 5HT3s that are identified in the MASCC reference. Is that accurate?

A. Correct.

Q. Okay. That includes ondansetron, granisetron, tropisetron, dolasetron, and palonosetron, correct?

A. Correct.

Q. Okay. Thank you. And a POSA is going to feel the ability to use any one of those in their triple therapy, correct?

A. At the recommended doses.
Q. At the recommended doses. Yes. Okay.
And now you have the class from your perspective. The last part of the triple therapy that a POSA is focused on working with, from your perspective, is the NK-1 receptor antagonist, right?
A. Yes.
Q. Okay. And I apologize. You do need to answer verbally. So if I go like -- if I ask you to move to do that, please do so.
A. No problem. Sorry.
Q. Okay. Okay. So now we have -- but you will agree with me that as of 2009, aprepitant was considered the gold standard NK-1 receptor antagonist at that time?
MR. TORCZON: Objection. Misstates. Or foundation, really.
THE DEPONENT: It was the only approved one.
BY MR. ASHKENAZI:
Q. Okay.
A. So, I mean, it was the gold standard. It was also the worst on the market. I mean, it goes both ways when you're the only one, right?
Q. All right. So we have aprepitant now. Now, your -- from your perspective, a POSA in 2009 is now going to see whether other NK-1 receptor an tagonists

existed or were known in the art, right?
A. Correct.
Q. Okay. And then would use -- potentially use those to treat for a new regimen of treating nausea and also vomiting?
MR. TORCZON: Objection. Form.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. And a POSA needs to evaluate which NK-1s to use, right? Not all of them are going to work, right?
MR. TORCZON: Same objection.
THE DEPONENT: Well, at that point, it's not clear, at the time when you only had clinical data on a couple. I mean, and -- but that's what the industry does. The pharmaceutical industry is a -- explores the derivatives of the lead molecule of a class and tries to come up with some advantage of a newer molecule, you know, formulation or half-life, or there's different things. But the question is, you know, what are the core needs to do that, to, at the very least, be as equivalent to the lead molecule.
BY MR. ASHKENAZI:
Q. Okay. So I want to take what you said, a couple of pieces there. So as of Feb -- as of November 2009, a

scientist working with the triple therapy would consider other NK-1 receptor antagonists, but would really have no idea whether those other MK-1 receptor antagonists could be effective for nausea and vomiting because the only one with clinical data was aprepitant. Is that fair?

MR. TORCZON: Objection. Form. Misstates.

THE DEPONENT: No. I mean, casopitant had been in clinical trials.

BY MR. ASHKENAZI:

Q. Okay.

A. So there were -- there were -- at the priority data, there were at least two with clinical trial data showing similar results to each other.

Q. Similar results. Okay.

You earlier mentioned, you stated that -- okay. Let's see if we could...

MR. TORCZON: While you're thinking, we're coming up on an hour, so just...

MR. ASHKENAZI: Let me see if I have just a couple more questions here. Oh, not a couple.

THE DEPONENT: That's fine.

MR. ASHKENAZI: It is just another -- I want to finish the module, if we can.

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BY MR. ASHKENAZI:
Q. So we have scientists working with the triple therapy from your perspective in two thousand -- a POSA working -- withdrawn. Let me start clean.
You have a POSA in 2009 working with the triple therapy. They have dexamethasone and any one of the 5HT3 and are now looking at the NK-1s. Is that fair?
A. Yes.
Q. Okay. And for the NK-1s, while there is clinical data for two, aprepitant and casopitant, there is no clinical data for the other NK-1 receptor antagonists, right?
MR. TORCZON: Objection. Foundation.
THE DEPONENT: There's data, but not that I'm aware of in CINV.
BY MR. ASHKENAZI:
Q. Okay. Fair enough.
So for CINV, there's data for two -- human clinical trial data for two NK-1 receptor antagonists as of 2009, aprepitant and casopitant, right?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. Now, from your perspective, there is also other NK-1 receptor antagonists that were known in the

art, correct?
A. Correct.
Q. And from your perspective, whether or not those would be effective would be the same or better than aprepitant, is what you would have to consider, right?
A. Consider to do what? To go into human studies?
Q. Well, withdrawn. That's a fair point. Let's see if we could take this into part.
It's your perspective that a POSA is looking for a regimen for treating a human for cancer-induced nausea and vomiting, right?
A. Correct.
Q. And that's both nausea and vomiting itself?
A. Correct.
Q. Okay. And it's your opinion that a scientist would evaluate the other NK-1 receptor antagonists that were known as of 2009, correct?
A. Yes. It's a reasonable thing to do.
Q. Right. It's something that they could consider. But at the same time, because there's no data for those other NK-1 receptor antagonists in humans, a POSA wouldn't know if the -- if using that NK-1 in a triple therapy would work. Is that accurate?
MR. TORCZON: Objection. Form. Relevance.
THE DEPONENT: Well, a POSA would look at the

pharmacological profile of the two agents that were known to work. So what were they? It they were NK-1 antagonist that got into the brain. And those were two key criteria. So you had to have CNS entry because that's where the receptors are theoretically located, and almost definitely correctly located, for the effect of an NK-1 antagonist. And then if they had additional information like foot tapping, in a gerbil, that would give evidence of CNS penetration. So that's an add-on to knowing its selective, it hits brain receptors, and that can get it into the brain. That's strong evidence that a class effect, if it existed, and the evidence that it existed was that we've already now gone from the first one, the lead molecule, aprepitant, to casopitant, and now you're going to another agent that in that profile way seems to be very similar to the two that have worked.

BY MR. ASHKENAZI:

Q. Let's be clear. Casopitant was not FDA approved?

A. Correct.

MR. TORCZON: Objection. Relevance.

BY MR. ASHKENAZI:

Q. Right. And, in fact, casopitant is not on the market today, right?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: My under -- well, this is after the priority date, so I don't know if I am -- it's not on the market, correct.

BY MR. ASHKENAZI:

Q. Okay. So the only data that we really had showing true effect for an NK-1 in cancer chemotherapy-induced nausea and vomiting was for aprepitant as of 2009, correct?

MR. TORCZON: Objection. Foundation. Relevance.

THE DEPONENT: No. I thought -- they had published articles. We can look at them if you want.

BY MR. ASHKENAZI:

Q. When you say they have published articles?

A. The sponsors of casopitant.

Q. Okay.

A. I think it was Glaxo.

Q. Okay. All right.

A. Do you want to look at that?

Q. No, not yet. But we will -- we may get to that. Let's see if we have time.

So is it your opinion that a POSA in 2009, based on preclinical data, would -- for -- for NK-1 receptor antagonists, would believe that if -- as long as there

were CNS entry and some data, for example, in foot tapping, that the -- that NK-1 receptor antagonist would be effective at the same level of aprepitant or better for treating CINV?

MR. TORCZON: Objection. Form. Misstates.

THE DEPONENT: It would be a high likelihood of success. And that's based, again, on the fact that in drug development, when you're the innovative molecule, when you're the innovator and you're the first one, everybody has got theories, but until you show it clinically, it's just theory. But then when you have the innovator, have certain characteristics, and have a clinical efficacy, then you go to the -- a second molecule of that class. It's, in -- in business terms, called probability of technical success. So that number keeps going up every time you have another agent in that class that shows efficacy. So after two, the probability of technical success was far higher to a POSA than, say, before the first aprepitant study.

BY MR. ASHKENAZI:

Q. What would you say the probability of success would be for a scientist in 2009 with the data that you have reviewed for any other NK-1 receptor antagonist that had CNS entry and had some preclinical data in animal models?

MR. TORCZON: Objection. It is out of scope and relevance.

THE DEPONENT: It is out of scope. I mean --

BY MR. ASHKENAZI:

Q. I'm asking the question. If you could answer it, I'd appreciate it.

MR. TORCZON: Same objection.

THE DEPONENT: Well, overall, phase 3s are, I would say, no more than 50 percent. So I would say it would go up to about 80-plus.

BY MR. ASHKENAZI:

Q. So you're saying that a drug that had any NK-1 receptor antagonist as of 2009, that had CNS entry and had some preclinical data, whether it's in foot tapping for gerbils or other known preclinical tests for C -- for CINV, would have an 80 percent likelihood of success of having a same or similar effect of aprepitant in humans?

MR. TORCZON: Objection. Scope. Relevance. Form. Misstates.

THE DEPONENT: An NK-1 selective antagonist that is already bioavailable and has been shown to get into the central nervous system in a reasonable time and has a half-life that's consistent with human intake, meaning not just a minute or two, and has been shown in an

animal model of CNS penetration to be CNS active, if you will, yeah, I think -- I mean, after two, it goes up.

BY MR. ASHKENAZI:

Q. So is that 80 percent? I just want to make sure we're clear.

MR. TORCZON: Objection. Asked and answered. Relevance. Scope.

THE DEPONENT: It's a guesstimate today. I have not reviewed that. And that's a reasonable number.

BY MR. ASHKENAZI:

Q. Okay. To be clear, it's your assertion that there's an 80 percent likelihood of success for a drug that's an NK-1 receptor antagonist that is bioavailable, that has CNS penetration, and with a decent half-life and some animal model, with that data -- withdrawn. Let's start again.

It's your assertion that if you have an NK-1 receptor antagonist in 2009 that showed -- but -- that -- that would be perceived to have bioavailability, CNS penetration, a decent half-life in some animal model, but had not been tested in humans, that there would be an 80 percent likelihood that that NK-1 receptor antagonist would be effective for treating CINV in humans as aprep itant, or better?

MR. TORCZON: Objection. Form. Scope.

Relevance. Asked and answered.

THE DEPONENT: That's my non-research-based sitting here today. Also to add to that, there had been no examples of such drugs that failed. So that was actually supportive that the next one would be successful.

BY MR. ASHKENAZI:

Q. So your assertion is that there has been no evidence of any can NK-1 receptor antagonist that had failed as of 2009?

MR. TORCZON: Objection. Form.

THE DEPONENT: That met all those criteria.

BY MR. ASHKENAZI:

Q. Okay. And it's your position that a POSA in 2009 is going to take the triple therapy and evaluate all the NK-1 receptor antagonists that were available and believe that you can mod -- use any one that had those criteria that you referenced, preclinical criteria, and use those with triple therapy, right?

A. At that point in time, it would be --

MR. TORCZON: Objection. Same objections.

THE DEPONENT: I'm sorry.

At that point in time, it would be reasonable to try.

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BY MR. ASHKENAZI:
Q. Reasonable to try.
A. And with a reasonable chance of success.
Q. With a reasonable chance of success.
And a POSA, you believe, would have the resources available to look at all the NK-1 receptor antagonists that were out there and to try each and every one of those in -- in the regimens that you've been opining on in this case, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: A POSA wouldn't do it, but the patent holder sponsor might.
BY MR. ASHKENAZI:
Q. The patent holder sponsor. So why do you -- what's the distinction you're drawing there when you say a POSA wouldn't do it?
A. Well, clinical research is very expensive and, for instance, to use cortisol, some steroid derivative, right, prednisone instead of dexamethasone, there's -- you know, it might work better. It probably doesn't because it's in the same class. But to do the studies, it's very expensive and, you know, your average POSA is not funded or capable of funding clinical research.
Q. All right. So it's your position that the average POSA doesn't have infinite resources, right?

MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Not that I'm aware of.
BY MR. ASHKENAZI:
Q. Okay. It's your position that an average POSA needs to evaluate a small number of things they could test in order to move forward or find a new treatment regimen, correct?
MR. TORCZON: Objection. Scope. Relevance. Misstates.
THE DEPONENT: Stating small is -- is qualitative. You know, what do you mean by small?
BY MR. ASHKENAZI:
Q. Okay. So when you said that the average POSA would not be evaluating all the different NK-1 receptor antagonists that were known to see if they could be used in the triple therapy, that's because the POSA doesn't have the resources to do all of those tests, correct?
MR. TORCZON: Same objections.
THE DEPONENT: In general, yes. I mean, a POSA may want to do it, but to make it happen, it's difficult for a POSA to do it on their own.
BY MR. ASHKENAZI:
Q. And you will agree with me that there is some -- that there is uncertainty with respect to which NK-1 receptor antagonist that had not entered into humans

would be effective for treating nausea or vomiting due to cancer chemotherapy, right?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: I think I already mentioned that in, you know, I'm a pharmacologist, and you look at the pharmacology of the innovator and then the second one, and you see certain similarities and then you base your likelihood of success on, if you can mimic those qualities, your chance of success goes up significantly.

MR. ASHKENAZI: Okay. Why don't we take a break. Thank you.

(A recess transpires.)

BY MR. ASHKENAZI:

Q. Dr. Peroutka, I just want to go back over a couple of things we mentioned.

With respect to the 5HT3 antagonists, you mentioned that some of them have different half-lives than others, correct?

A. Correct.

Q. Okay. But that's accounted for in the dosing regimen for each one of the 5HT3s, correct?

MR. TORCZON: Objection. Scope.

THE DEPONENT: I have to double-check.

BY MR. ASHKENAZI:

Q. But --

A. In general, it should be, but I can't state that for a fact.
Q. Okay.
A. I have to look.
Q. The point is, when a 5HT3 got approved by the FDA, it did it in a -- it's approved in an administration that would be effective for treating patients, right?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: The -- which 5HT3 and for which indication.
BY MR. ASHKENAZI:
Q. Sorry. Well, withdraw that. I -- I think I -- I think we're on the same page.
Okay. Just so we are -- we understand, when you looked at the MASCC reference, that's a reference that's talking about treatments for patients that are approved by the FDA, correct?
MR. TORCZON: Objection. Foundation.
THE DEPONENT: I have to -- I would have to look -- well, given that it's an international, I don't know that they restricted themselves to that.
BY MR. ASHKENAZI:
Q. Okay. Let me revise my question.
MASCC is talking about -- is a -- is a review

article based on a consortium of oncologists who are treating patients throughout the world, correct?
A. I would say key opinion leaders that, in general, treat patients, but not all.
Q. Okay. In other words, it's not talking about therapies that are currently in development that can't be given to patients?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: I have to reread it to see if they mention any non-approved drugs at some part in the --
MR. TORCZON: Can we pause that.
(Discussion off record.)
BY MR. ASHKENAZI:
Q. You would agree with me that as of 2009 a POSA would be considering drugs, also, that had different mechanisms of action than other -- than those that have already been approved for looking for a new treatment for chemotherapy-induced, whether it's nausea or vomiting, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Well, that wasn't within the scope of what I was doing for what -- what possibly was in there. But in general, unless a disease is 100 percent cured, there is always going to be a need

for better treatments and people interested in potentially finding them.

BY MR. ASHKENAZI:

Q. Okay. When you say it wasn't within the scope of what you were looking at, what do you mean by that?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: The standard of care before the priority date, not the future possibilities.

BY MR. ASHKENAZI:

Q. Okay. So when you were focused on your obviousness analysis, you began your analysis with the standard of care as opposed to looking at what potential research could be done for new treatments for chemotherapy-induced nausea or vomiting, right?

MR. TORCZON: Objection. Scope. Relevance. Form. Asked and answered.

THE DEPONENT: Step one was looking at standard of care and assessing as part of that where the field was in terms of how effective the drugs would be and seeing that they were very good, but not perfect.

BY MR. ASHKENAZI:

Q. In other words, when you did your analysis, you were not looking at it from the perspective of trying to solve a problem in the field that a POSA was faced with, right?

MR. TORCZON: Objection. Misstates. Relevance.

THE DEPONENT: Well, standard of care was just where they were then, and the analysis conclusion is that they got -- they did a pretty good job, but they weren't 100 percent there.

BY MR. ASHKENAZI:

Q. Okay. Again, I want to just make sure.

You said you were not evaluating what other research could be done for treating patients for chemotherapy induced, whether it's nausea or vomiting. Is that right?

MR. TORCZON: Objection. Scope. Relevance. Asked and answered.

THE DEPONENT: I wasn't investigating it.

BY MR. ASHKENAZI:

Q. Okay. In other words, as part of your analysis in this case, you were not balancing other potential research that a POSA may have focused on for looking for new therapies for treating chemotherapy-induced nausea, right?

MR. TORCZON: Objection. The same objections.

THE DEPONENT: I was not focused on that. There were some comments in some of the review articles about other possibilities, so I did read a few.

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BY MR. ASHKENAZI:
Q. Okay. So you do recognize that as part -- that a POSA in 2009 reviewing the articles would see that articles had said that there is a need for new mechanisms for treating chemotherapy-induced nausea, correct?
MR. TORCZON: Objection. Relevance. Scope.
THE DEPONENT: I don't think I saw anything that said chemotherapy-induced nausea. It's always CINV. They are linked.
BY MR. ASHKENAZI:
Q. Okay. I -- you do agree with me that nausea was a problem -- was a problem, at least for some patients, in 2009, correct?
A. Yes.
MR. TORCZON: Objection. Asked and answered.
BY MR. ASHKENAZI:
Q. And you will agree with me that there are articles that said that for -- for patients who are suffering from chemotherapy-induced nausea, that new mechanisms of action for drugs should be considered and developed, correct?
MR. TORCZON: Objection. Asked and answered.
THE DEPONENT: Yes.
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BY MR. ASHKENAZI:
Q. Okay. And you'll agree with me that -- but that wasn't part of your analysis in this case, right?
MR. TORCZON: Objection. Form. Misstates.
MR. ASHKENAZI: Withdrawn. I'll restate my question.
BY MR. ASHKENAZI:
Q. Now, you would agree with me that there are many different -- you have Herrst in front of you, right, Herrstedt, which is the Exhibit 1010?
A. Yes.
Q. Okay. And if you go down to -- in the abstract. It's in the abstract. The last sentence, you will agree with me that at least Herrstedt references that development of new antiemetics with other mechanisms of actions is awaited with interest, right?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: I'm sorry. I am agreeing that it says that?
MR. ASHKENAZI: Okay.
THE DEPONENT: No. I'm -- you guys crossed over, I thought, a little bit.
So you're asking me if I agree that's what this sentence says?
MR. ASHKENAZI: Yes.

THE DEPONENT: Yes.
MR. TORCZON: Same objection.
BY MR. ASHKENAZI:
Q. Let's see if we can try this again.
You'll agree with me that Herrstedt, an article that you referenced and relied upon, states at the bottom of the abstract that development of new antiemetics with other mechanisms of action is awaited with interest, right?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Yes.
BY MR. ASHKENAZI:
Q. And, in fact, you agree with me that a POSA in 2009 would be considering other mechanisms of action for drugs that can be -- withdrawn.
You will agree with me that a POSA in 2009 would be looking for drugs with different mechanisms of action than those already evaluated, like NK-1 receptor antagonists or 5HT3 receptors, for developing new treatment for CINV, correct?
MR. TORCZON: Objection. Scope and relevance.
THE DEPONENT: I would agree that a POSA could be looking at others.
BY MR. ASHKENAZI:
Q. And at least that's what the article is saying a

POSA should be doing, correct?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: I don't read that sentence that way. You know, it's going through what we have today and it points out, you know, the sentence before that, if I can read furthermore:

"The majority of clinical trials include highly selected groups of patients not permitting definitive conclusions for other and more heterogenous patient groups."

And what that -- then:

"The development of new with other mechanisms is awaited with interest."

In other words, the groups of patients for which all the data existed were relatively homogenous, as they should be in a clinical trial, but that there were lots of different chemotherapies and potentially other mechanisms that should be tried, which until we get to 100 percent is true.

BY MR. ASHKENAZI:

Q. So a POSA in 2009 would be developing other mechanisms of action in addition to, in your opinion, evaluating modifications that could be made to the triple therapy, right?

MR. TORCZON: Objection. Scope and relevance.

THE DEPONENT: A POSA could be.
BY MR. ASHKENAZI:
Q. I'm asking you what a POSA would be doing.
MR. TORCZON: Objection. Asked and answered.
BY MR. ASHKENAZI:
Q. So I'm going to ask my question again, because I -- a POSA in 2009, from your perspective, would be developing modifications of the triple therapy, as well as drugs with other mechanisms of action, in order to provide a new treatment for chemotherapy-induced nausea and vomiting, correct?
MR. TORCZON: Objection. Relevance. Asked and answered.
THE DEPONENT: Let's look at my definition of POSA, because on the surface of your question, my understanding is, I don't agree with that. But let's go -- can we go look at it? Which is?
MR. ASHKENAZI: Page 32. And I think paragraph 59 on page 33, and paragraph 60, is what you're referring to.
BY MR. ASHKENAZI:
Q. So with that in mind, I will ask my question again.
A POSA in 2009, from your perspective, would be developing modifications of the triple therapy as well

as drugs with other mechanisms of action in order to provide a new treatment for chemotherapy-induced nausea and vomiting, correct?

MR. TORCZON: Objection. Asked and answered. Relevance.

THE DEPONENT: I would say no. Reading 59 and 60, a POSA would have an understanding of the development process for antiemetic, but I don't see anything in there that says they are going to be working on developing new ones.

BY MR. ASHKENAZI:

Q. Okay. So let's break this down. From your perspective, a POSA is not evaluating any new antiemetics, right?

MR. TORCZON: Objection. Misstates. Relevance.

THE DEPONENT: A POSA to me is someone who has the knowledge to assess the issues in this case.

BY MR. ASHKENAZI:

Q. I understand, and I want to under -- I wanted to make sure we're clear because I -- you -- it's your perspective that a POSA would not be able to evaluate new antiemetics for treating chemotherapy-induced nausea and vomiting?

MR. TORCZON: Objection. Relevance and misstates.

THE DEPONENT: Maybe we have a miscommunication here.

Are you saying evaluate in the sense of looking at data to determine if they're good? Which I would agree with. But if you're saying evaluate as in clinical trials and preclinical research, no, a POSA wouldn't necessarily be involved in that.

BY MR. ASHKENAZI:

Q. Okay. So a POSA -- but a POSA is also -- okay. So I want to make sure I understand what your POSA does and doesn't do.

From your perspective, a POSA is a clinician looking to say, what can I use that's available to me to treat patients?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: No.

BY MR. ASHKENAZI:

Q. Okay. So please tell me what --

A. A POSA -- let's go back to the beginning here.

Someone with an advanced degree, for example, a Ph.D. M.D., M.S., or equivalent, in a field related to pharmacology, biochemistry, medicinal chemistry, oncology, or a related field, someone with knowledge, in other words, of those fields, that has worked with pharmacologists and/or medicinal chemists -- and you can

add in and/or oncologists, et cetera, as above -- and is familiar with the dosing of the compositions.

Q. Okay. So what is the POSA doing in 2009, from your perspective?

A. Any one of those activities.

Q. So a POSA could be evaluating new drugs for treating antiemetics, correct?

A. Again, I need you to clarify. Evaluating in the sense of reviewing data and reviewing studies and looking at endpoints?

Q. Yes.

A. Yes, a POSA should be able to do that.

Q. Okay. So a POSA is not focused only on the existing therapies that are approved by the FDA, but a POSA would be considering adding to the existing therapies potential new drugs that are known but that have different mechanisms of action than the other approved antiemetics?

MR. TORCZON: Objection.

BY MR. ASHKENAZI:

Q. Correct?

MR. TORCZON: Objection. Scope.

THE DEPONENT: I look at a POSA as someone who can look at anything in this field that we're talking about, which is antiemetic therapy as of 2009, but it's

not that they would do it unless there's a need to look at the other ones. In other words, the issues in this case relate to the claims and the obviousness of the multiple claims, right? And so that was the POSA's needs for this declaration, is what's stated here.

BY MR. ASHKENAZI:

Q. What is the POSA's needs, when you say it's stated here? Explain to me what you mean by that.

A. That in order to evaluate the issues in this case, the claims and the obviousness arguments and the anticipation arguments, you would have to have these abilities and some combination of those abilities to be considered a person of ordinary skill in the art to assess these issues.

Q. Okay. And I -- what is the problem the person of ordinary skill in the art is trying to solve?

A. They are not solving the problem. They're just reviewing the information.

Q. So when you did your obviousness analysis you didn't consider any problem that the person of ordinary skill in the art would be trying to solve?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: For example? Give me an example of a problem. I'm not sure what you're talking about.

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BY MR. ASHKENAZI:
Q. I'm trying to figure out what analysis you did here. So --
A. Well --
Q. So let me ask my question again.
When you did your obviousness analysis, you did not consider any problem that the POSA is trying to solve, correct?
MR. TORCZON: Objection. Foundation. Misstates.
THE DEPONENT: I'm having a challenge with the words you're using, a problem that I'm trying to solve. I'm trying to provide information on it. I'm giving -- I'm providing an opinion on the obviousness of the various claims involved here.
BY MR. ASHKENAZI:
Q. Okay. So you began your analysis with the claims and then looked to see if those would be obvious?
MR. TORCZON: Objection. Misstates.
THE DEPONENT: I first focused on the standard of care, then I looked at the claims and iterate -- I mean, I was iterating between the primary data from the various trials with the review articles, with the patent claims, and trying to integrate all that to see what a POSA would think of the claims as of 2009.

BY MR. ASHKENAZI:
Q. Okay. So you're looking at the -- the -- withdrawn.
From your perspective, was a POSA faced with any problem in treating chemotherapy-induced nausea and vomiting as of 2009?
A. You have to define problem. That's where the -- our -- your words are not making sense to me, in the sense that, you know, problem to be solved, I'm just not understanding what you mean by that.
Q. Okay. What was the goal of what a POSA was trying to do in 2009?
A. Well, to me, a POSA has the skill set that could do things. And in this case, could a POSA -- a POSA would be needed to review the state of -- the standard of care, to review the research articles and then iterate with the claims to see if it was obvious in a legal sense.
Q. Okay. So the POSA's goal in two thousand -- I'm just taking your POSA and I'm putting them in 2009, and I'm asking, did they have a goal with doing anything? Was -- was there any goal of what they were trying to accomplish, in your mind?
MR. TORCZON: Objection. Asked and answered.
THE DEPONENT: I mean, there -- a POSA is -- is

a skill set, a person with a certain skill set, and I'm sure people with this level of education were working on problems, quote, problems, but I'm just disconnected from what you're calling a problem.

BY MR. ASHKENAZI:

Q. Okay. So from your perspective, a POSA has a certain skill set, and in 2009 is looking at the standard of care, looking at their literature, and looking at the claims, and trying to see if the claims would be obvious?

MR. TORCZON: Objection. Asked and answered. Misstates.

THE DEPONENT: In 2009, I am -- honestly, I'm just -- a POSA is someone with the ability to look at that at any date in retrospect, or today in my case, to go back in time, if you will, to see what was available back then.

BY MR. ASHKENAZI:

Q. Mm-hmm.

A. So in 2009, was I working on this issue? I wasn't. But I am today, and I am a POSA. See what I'm --

Q. Okay. So let's state, in 2009, you were not a POSA. You'll agree with me?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: Well, I could have been.
BY MR. ASHKENAZI:
Q. You could have been. But you were not working in the field of chemotherapy-induced nausea and vomiting?
MR. TORCZON: Objection. Relevance. Misstates.
THE DEPONENT: No, I wasn't working in it. But I would have been qualified to be considered a POSA in a legal proceeding.
BY MR. ASHKENAZI:
Q. Okay. Meaning you had the requisite background, education?
A. And training.
Q. And training. Okay. So now, take a POSA in 2009. They have the triple therapy in hand. What is their -- what are they trying to do? What is their task?
A. A POSA in the field of CINV, is that what you're asking.
Q. Yes.
A. Okay.
Q. So let's go. A POSA in the field of CINV in 2009, according to your opinions in this case, what is their task?
A. Their task is to see if -- one of their tasks

could be to see if they can improve upon the standard of care.

Q. Okay. Now, if one of their tasks is to see if they can improve upon the standard of care, you'll agree with me that that would include evaluating drugs that had different mechanisms of action than those that are a part of the standard of care.

Do you agree?

MR. TORCZON: Objection. Scope. Relevance. Asked and answered.

THE DEPONENT: It could or it could not.

BY MR. ASHKENAZI:

Q. But it's one of the options a POSA had and would have evaluated, right?

A. Correct.

MR. TORCZON: Objection. Same objections.

THE DEPONENT: Could or could not, depending on if they were working for a company making NK-1 antagonists, they would probably stay focused on that and not consider anything, given that they had a potential product that had patent protection, CNS entry, et cetera, et cetera.

BY MR. ASHKENAZI:

Q. Okay. You will agree with me that one of the options a POSA had and would have evaluated was looking

for drugs with different mechanisms of action than the standard of care, correct?

MR. TORCZON: Objection. Asked and answered. Misstates.

THE DEPONENT: Not would, could. I don't agree that they would because, again, depending on their personal situation, they may be highly motivated to stick within the NK-1 world.

BY MR. ASHKENAZI:

Q. Okay. And there are other POSAs that had different perspective that -- okay. Withdrawn.

Does your POSA work at a company making NK-1 receptor antagonists?

MR. TORCZON: Objection. Relevance. Foundation.

THE DEPONENT: No. A POSA could, but not necessarily.

BY MR. ASHKENAZI:

Q. So while one POSA could evaluate only NK-1 receptor antagonists, from your perspective, another POSA that fits your definition could also be looking at drugs with different mechanisms of action than the standard of care, correct?

MR. TORCZON: Objection. Scope and relevance.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:
Q. Okay. In other words, what you're saying here is that there -- a POSA has a certain skill set and there are many different options that are available to a POSA to consider when trying to come up with a new chemotherapy-induced nausea and vomiting treatment, correct?
MR. TORCZON: Objection. Misstates. Asked and answered. Relevance.
THE DEPONENT: In general, yes. A POSA in -- can look at all possibilities.
BY MR. ASHKENAZI:
Q. Right. And a POSA -- and your point is, if a POSA is working in NK-1s, they would focus on NK-1s, correct?
A. Most likely, yes.
Q. Okay. But even if the POSA is focused on NK-1s, they would look at the NK-1s that were available at that time, right?
MR. TORCZON: Objection. Form. Foundation.
THE DEPONENT: You have to clarify the question.
BY MR. ASHKENAZI:
Q. Sure.
A. Because I'm not sure.
Q. Yeah.

A. Look at them in terms of what?
Q. Okay. So the analysis that you put within your declaration that was looking at things from the perspective a POSA, that had the standard of care and was looking at -- and was focused on the NK-1s to see if they could modify those, correct?
MR. TORCZON: Objection. Misstates. Asked and answered.
THE DEPONENT: No. A POSA is a person at that time that could evaluate the existing data in terms of what could be tried.
BY MR. ASHKENAZI:
Q. I understand. I'm trying to say the -- the -- you provided a -- an opinion in your cay -- in your declaration on what a POSA would have done, correct?
A. No. It's not a -- you are -- we're confusing would do with opinions of what the existing science was.
Q. So -- so you didn't provide an opinion in this case on what a POSA would have done, just on what a POSA could have done. What were the options that a POSA -- what is one of the options a POSA would have had?
MR. TORCZON: Objection. Form. Misstates.
THE DEPONENT: What they could have done and were likely to do and what was obvious to try in light of the data that existed at the time.

BY MR. ASHKENAZI:
Q. So you will agree with me that a POSA would also have evaluated drugs with another mechanism of action for -- in order to come up with a treatment for -- a new treatment for CINV, correct?
MR. TORCZON: Objection. Asked and answered. Relevance.
THE DEPONENT: Evaluate in what way.
BY MR. ASHKENAZI:
Q. The same way they were evaluating changing netupitant with aprepitant?
MR. TORCZON: Same objections.
THE DEPONENT: Well, there were three classes, and we've discussed this. So a POSA could have considered switching prednisone for dexamethasone with a very high likelihood of success if the dosing were equivalent. POSAs already driven by the pharmaceutical industry tried five different 5HT3s and got, you know, pretty similar data. So a POSA, if had access to a new NK-1, would be, I think, highly motivated and obvious to try it in CINV, given the prior art. I mean, there was patent saying it worked in -- netupitant was patented for use in CINV. It had shown CNS activity. It was NK-1. So it had a lot of things going for it, as did casopitant and as did others that would meet that same

profile. They were all obvious to try.
BY MR. ASHKENAZI:
Q. Okay. One of the things that you mentioned was the fact that casopitant, that at the time of November 18th, 2009, from your perspective, the reason why a POSA would feel that there is -- withdrawn.
Let's start fresh.
As of November two thousand -- November 18th, 2009, from your perspective, one of the reasons why a POSA would have a likelihood of success with using any NK-1 that had shown some preclinical data and efficacy is because there were -- there was clinical data with aprepitant and casopitant, correct?
A. Correct.
MR. TORCZON: Objection. Misstates.
BY MR. ASHKENAZI:
Q. Now, from your perspective, there was no known failures of any NK-1 receptor's antagonists as of November 18th, 2009, correct?
A. No. No known CINV failures with a triple con -- NK-1s with CNS penetration.
Q. Okay. You're not saying that -- so if I understand what you're -- withdrawn.
If I understand you correctly, what you're saying is there have been NK-1 receptor antagonists for

CINV that had failed, just none that were given to patients with the triple therapy, correct?

MR. TORCZON: Objection. Foundation. Relevance.

THE DEPONENT: No. I didn't say that. I -- I said none that had the --

BY MR. ASHKENAZI:

Q. Okay.

A. -- the profile.

Q. So as of November 18th, 2009, were there NK-1 receptor antagonists that showed promise in preclinical data but did not actually -- or that eventually failed to show efficacy in humans?

MR. TORCZON: Objection. Scope. Form. Relevance.

THE DEPONENT: I didn't consider anything after the priority date.

BY MR. ASHKENAZI:

Q. Okay. As of the priority date, were there any NK-1 receptor antagonists that showed promise in preclinical data but actually failed to show eff -- but that failed to get to show safety and efficacy in humans?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Yeah, I -- I didn't review which

ones after the priority date went into humans.
BY MR. ASHKENAZI:
Q. I'm not asking about after. As of the priority date, meaning as of November 2000, November 18th, 2009.
A. I'm not.
Q. To the best of your knowledge, were there -- have you evaluated whether there were any NK-1 receptor antagonists that showed promise in preclinical data but then actually failed to show safety and efficacy in humans?
MR. TORCZON: Objection. Scope. Relevance. Form.
THE DEPONENT: I'm not aware of any of those data.
BY MR. ASHKENAZI:
Q. Okay. And that's important because if an NK-1 receptor antagonist had shown promise in preclinical data but failed to show safety and efficacy in humans, that would lower the likelihood of success of another NK-1 receptor antagonist being able to be used to treat chemotherapy-induced nausea or vomiting, right?
MR. TORCZON: Objection. Scope and relevance.
THE DEPONENT: I would have to see the data because you keep saying "safety," which is the first time that's come up. So a drug that fails for safety

could have nothing to do with NK-1. It could have to do with, say, you know, a different organ.
BY MR. ASHKENAZI:
Q. You -- each drug needs to be -- if -- you will agree with me that the claims of the patents in this case are talking about treatments for humans, right?
A. Correct.
Q. And you as a doctor wouldn't be treating human with a drug that's not considered safe, right?
MR. TORCZON: Objection. Relevance. Scope.
THE DEPONENT: Well, that's a relative term, safe. So chemotherapy is, in a sense, very toxic, but it's for good purposes, so.
BY MR. ASHKENAZI:
Q. As a doctor, you wouldn't be treating a patient with a drug for chemotherapy-induced nausea and vomiting that was not considered safe, correct?
MR. TORCZON: Same objections.
THE DEPONENT: Considered safe per FDA criteria.
BY MR. ASHKENAZI:
Q. Yes. Correct.
A. Right.
MR. TORCZON: Objection. Relevance.
BY MR. ASHKENAZI:
Q. Okay. Now, so to go back to it, if you had an

NK-1 receptor antagonist that showed promise in preclinical data but failed to show safety and efficacy in humans, that would lower the likelihood of success of another NK-1 receptor antagonist being able to be used to treat chemotherapy-induced nausea or vomiting, correct?

MR. TORCZON: Objection. Foundation. Scope. Relevance. Asked and answered.

THE DEPONENT: Yeah, that is beyond the scope. And it also needs to be clarified. When you say in preclinical studies, I would need to know what those were.

BY MR. ASHKENAZI:

Q. Okay. You didn't evaluate any of that for the purposes of your opinions in this case, correct?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: Any of?

BY MR. ASHKENAZI:

Q. You didn't evaluate what the likelihood of success of -- withdrawn.

You did not evaluate what information there existed for other NK-1 receptor antagonists other than aprepitant and netupitant for the purposes of your opinion in this case, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Incorrect.
BY MR. ASHKENAZI:
Q. Okay.
A. I --
Q. What other NK-1 receptor antagonist data did you evaluate for purposes of this case?
A. Casopitant.
Q. Okay. And besides for casopitant?
A. There were a couple others. I don't recall the specific names, but they were -- they never got to humans.
Q. Okay. They never got to humans?
A. Well, as of the priority date.
Q. Okay. So as -- if I understand correctly, to the -- for all your opinions in this case, the only NK-1 receptor antagonists you evaluated were aprepitant, casopitant, netupitant, and a couple of others that you can't remember right now. Is that accurate?
A. Well, I didn't really evaluate the other ones because they didn't get to humans.
Q. Okay. So you only --
A. By the priority date.
Q. All right. So let's break that up.
So for the purposes of your opinions in this case, the only NK-1 receptor antagonists that you

evaluated were aprepitant, casopitant, and netupitant, correct?

MR. TORCZON: Objection. Relevance. Asked and answered.

THE DEPONENT: There was a pro -- the pro drug of aprepitant or vice verse, the IV formulation, I'm not sure when that came out, so I'd have to check.

BY MR. ASHKENAZI:

Q. That was fosaprepitant, and I think that was around 2008.

A. Yeah.

Q. So with that, let me ask my question again.

For the purposes of your opinion in this case, the only NK-1 receptor antagonists were aprepitant, fosaprepitant casopitant, and netupitant. Is that correct?

MR. TORCZON: Same objections.

THE DEPONENT: Yes, in terms of human CINV.

BY MR. ASHKENAZI:

Q. I'm not asking you about human CINV. I'm asking in general for all the opinions you provided in this case.

Is it correct that the only NK-1 receptor antagonists that you evaluated were aprepitant, fosaprepitant netupitant and casopitant?

MR. TORCZON: Same objections.
THE DEPONENT: Yes.
BY MR. ASHKENAZI:
Q. Okay. And aprepitant, fosaprepitant, and casopitant had human data, correct?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: I believe so, yeah.
BY MR. ASHKENAZI:
Q. Okay. The only NK-1 receptor antagonist that did not have human data, that you evaluated, was netupitant, right?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Yes.
BY MR. ASHKENAZI:
Q. Okay. Now, you are not aware of how many other known NK-1 receptor antagonists existed in the art as of November 18th, 2009, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: It's around 10.
BY MR. ASHKENAZI:
Q. 10. Okay. Now, one of the things you mentioned earlier is that when you have one drug that's approved for -- by the FDA that showed safety and then you have another and another, there becomes an increasing likelihood of success for follow-on drugs with the same

mechanism of action. Is that -- did I characterize your opinion correctly?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: Yes.

BY MR. ASHKENAZI:

Q. Okay.

A. For example, if I may, you know, there's over 20 beta blockers on the market. There's over 20 non-steroidals on the market. And that's the triptans. Once the innovator came out, there were six, seven more. So that's the way the pharmaceutical industry works. When they find a valuable mechanism, they want to figure out if they can optimize it, if you will.

Q. Now, aprepitant came to the market in 2003, correct?

A. Correct.

Q. Okay. And one of the reasons why you say there would be a higher likelihood of success for an NK-1 receptor antagonist like netupitant in 2009 is because casopitant was also successful, correct?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: Because casopitant was clinically effective in CINV based on the data available.

BY MR. ASHKENAZI:

Q. Okay. Now, you do recognize that casopitant did

have issues in which it, therefore, couldn't get approved, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: After the priority date.

BY MR. ASHKENAZI:

Q. Okay. If that was aware before the priority date, would that affect your obviousness analysis here?

MR. TORCZON: Objection. Foundation. Scope. Relevance.

THE DEPONENT: Not in terms of efficacy in CINV.

BY MR. ASHKENAZI:

Q. In terms of -- but in terms of safety, being able to treat a patient, wouldn't there be a concern if it were known that there was a problem with casopitant that maybe other NK-1 receptor antagonists could have similar issues?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: I'd have to review the safety data from the earlier, the first generation, the 1990s NK-1s that were used for migraine, I think, three to five, depression. They were used for other things, and I'm not aware of any major -- major safety signal from that class. And I would also have to learn more, which was beyond the scope of this, of what the exact issues were with casopitant.

BY MR. ASHKENAZI:
Q. So you have -- the point is, you haven't done that evaluation. For the purposes of your declaration here, you have not evaluated the likelihood that a POSA would feel confident that you could give other NK-1 receptor antagonists and it be safe for treating humans, correct?
MR. TORCZON: Objection. Scope. Relevance. Asked and answered. Misstates.
THE DEPONENT: Well, as of the priority date, the -- the first generation, if you will, the 1990s NK-1s were all deemed safe.
BY MR. ASHKENAZI:
Q. That wasn't my que -- I'm sorry.
A. So at that point there was really no class safety signal.
Q. In your declaration, have you provided any analysis about the likelihood that a POSA would feel confident that the other NK-1 receptor antagonists with no data in humans would be safe for treating humans?
MR. TORCZON: Objection. Scope. Relevance. Asked and answered.
THE DEPONENT: It was beyond the scope of what I did.
///

BY MR. ASHKENAZI:
Q. Okay. Now, what was the only NK-1 receptor antagonist that you looked for that didn't have human data -- withdrawn.
What was the only NK-1 receptor antagonist that you evaluated that didn't have human data netupitant?
MR. TORCZON: Objection. Asked and answered. Relevance.
THE DEPONENT: That was -- that was the subject of this patent dispute.
BY MR. ASHKENAZI:
Q. Okay. So bec -- you looked at netupitant as the only NK-1 receptor antagonist that a POSA would consider at that time because that is what was in the claims of the patent?
MR. TORCZON: Objection. Misstates. Relevance.
THE DEPONENT: No, not at all. The dispute was not before the priority date. In 2009, your options, they go beyond aprepitant or casopitant.
BY MR. ASHKENAZI:
Q. So from your perspective, the only options that a POSA had in 2009 beyond aprepitant were casopitant and netupitant?
MR. TORCZON: Objection. Asked and answered.
THE DEPONENT: There was an -- a few more coming

down the road, but they hadn't shown the CNS activity, that I'm aware of.

BY MR. ASHKENAZI:

Q. But you didn't evaluate that?

MR. TORCZON: Objection. Asked and answered. Misstates.

THE DEPONENT: Well, based on all the articles in the exhibits that talked about other agents in development, I didn't see anything else mentioned.

Q. Okay. There -- you say there are articles that discuss other agents in development. What are you referring to?

A. That the first in the line of NK-1s. I think -- what was that? MASCC recorded that, or one of -- Herrstedt? It's the first in the line. It's either MASCC or -- I have to go back and look.

Q. Okay. All right. Let's see if we can --

A. Here, here is casopitant in Navari that you gave, me which I didn't have before. But he mentions casopitant is another one which is under review by the FDA, a recent completion of phase 3. So, you know, I didn't have this at the time.

Q. So let's -- you are -- you did not re -- look at articles like Navari, which is Exhibit 2036, in --

MR. TORCZON: Objection.

BY MR. ASHKENAZI:
Q. -- as part of your opinions in this case, right?
MR. TORCZON: Objection. Form. Relevance. Foundation.
THE DEPONENT: Well, I did earlier today. You gave it to me. So...
BY MR. ASHKENAZI:
Q. Before -- for your declaration, you did not review articles like Navari which is Exhibit 2036, correct?
MR. TORCZON: Same objections.
THE DEPONENT: In -- incorrect. I reviewed review articles.
BY MR. ASHKENAZI:
Q. Okay.
A. MASCC is one.
Q. You didn't review Navari, right? That's what I'm trying to get at?
MR. TORCZON: Objection. Asked and answered.
THE DEPONENT: Correct.
MR. ASHKENAZI: Sorry. What are you saying?
MR. TORCZON: Relevance.
BY MR. ASHKENAZI:
Q. So you didn't review Navari. That's all I was trying to get at.

You do recognize that Navari talks about a number of -- and you just pointed to it, so I just want to ask you some questions.

If you looked at the table of contents, it talks about a whole host of different antiemetic medications.

Do you agree with me?

MR. TORCZON: Objection. Form. Scope. Relevance.

THE DEPONENT: I agree.

BY MR. ASHKENAZI:

Q. Okay. These were all different agents that a -- that would have been available for treating patients -- or to consider for treating patients with chemotherapy-induced nausea and vomiting, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: They all had some evidence to support their --

MR. ASHKENAZI: Yeah.

THE DEPONENT: -- antiemetic potential.

BY MR. ASHKENAZI:

Q. Okay. So dopamine receptor antagonists, those had evidence to suggest, as of 2009, they could have antiemetic potential, correct?

A. Correct.

MR. TORCZON: Objection. Scope. Relevance.

BY MR. ASHKENAZI:
Q. Same thing with 5HT3 antagonists, correct?
MR. TORCZON: Same objections.
BY MR. ASHKENAZI:
Q. Okay. I'm sorry, Doctor. I don't know if you answered the question.
A. Can you repeat it? Because he interrupted you and I was...
Q. Dopamine -- I'm sorry there was evidence that showed that in 2009, 5HD3 receptor antagonists had the ability to -- had antiemetic potential, correct?
A. 5HT3, yes.
Q. And if we look down, dopamine, serotonin receptor antagonists, as of 2009, had shown potential for -- as an antiemetic medication, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Yes. But dopamine, serotonin, it was -- for both dopamine and serotonin 5HT3, it was not just evidence. It was strong human data to support they had antiemetic efficacies.
BY MR. ASHKENAZI:
Q. Okay. You'll agree with me that corticosteroids were antiemetic agents that would be considered for treatment of patients with chemotherapy-induced nausea and vomiting, correct?

MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. And you will agree with me that olanzapine was an agent that was considered as showing promise for treating patients with chemotherapy-induced nausea and vomiting, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Agree.
BY MR. ASHKENAZI:
Q. And, in fact, olanzapine is a drug that showed significant eff -- showed promise for treating chemotherapy-induced nausea, correct?
MR. TORCZON: Objection. Form. Scope. Relevance.
THE DEPONENT: I did not review that -- the actual data for that, but it would make sense, since it's got dopamine antagonism.
BY MR. ASHKENAZI:
Q. So you didn't review whether olanzapine would be an option for a POSA to evaluate a new antiemetic agent in 2009 to -- -- withdrawn.
You did not evaluate whether a POSA would consider olanzapine for a new antiemetic treatment in 2009, correct?

MR. TORCZON: Objection. Foundation. Scope. Relevance.

THE DEPONENT: No. That was not part of my report.

BY MR. ASHKENAZI:

Q. And you did not --

A. Declaration.

Q. And you did not evaluate whether olanzapine was an option for modifying the existing triple therapy to help patients with chemotherapy-induced nausea, correct?

MR. TORCZON: Same objections.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. And you did not evaluate whether olanzapine was an option for a POSA looking to modify existing therapy to help patient with chemotherapy-induced vomiting, right?

MR. TORCZON: Same objections.

THE DEPONENT: No.

BY MR. ASHKENAZI:

Q. You put a no, but there was a negative in the question.

Did you do that evaluation?

I will ask the question again. There's a double negative with your answer on no, so.

You did not evaluate whether olanzapine was an option for a POSA looking to modify existing therapy to help patients with chemotherapy-induced vomiting, correct?

MR. TORCZON: Same objections and form.

THE DEPONENT: Not directly. But olanzapine has got dopamine-blocking abilities, and so, in theory, it would have. If you go up to the top, the first one you list are dopamine antagonists.

BY MR. ASHKENAZI:

Q. So olanzapine is something that a POSA would have considered modifying existing triple therapy in 2009 to help patients with chemotherapy-induced nausea and vomiting, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: It's possible.

BY MR. ASHKENAZI:

Q. But you didn't evaluate that for the purposes of your opinions in this case?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. And gabapentin is another agent that would have been considered as a potential for modifying existing triple therapy for treating patients with

chemotherapy-induced nausea or vomiting, correct?

MR. TORCZON: Same objections.

THE DEPONENT: I would say it's a possibility, but not all POSAs would have thought that.

BY MR. ASHKENAZI:

Q. When you say not all POSAs would have thought that, what do you mean by that -- well, withdrawn. Let me ask the question differently.

That's because from your perspective there's different POSAs, right, whether a POSA is working in the industry as opposed to working with NK-1 receptor antagonists, whether it's a clinician -- is that accurate?

MR. TORCZON: Objection to form. Scope.

THE DEPONENT: No. I mean, you're going way off scope. I mean, as a neurologist, gabapentin has -- is a well-known drug in the field. Many, many people take it, and the evidence to support it in CINV, you know, maybe somebody would believe it, but I think you would have a hard case convincing many, you know, people to invest in studying it, since it's so frequently used and has no obvious traumatic effect.

BY MR. ASHKENAZI:

Q. Have you evaluated whether gabapentin would have been an agent for treating patients for CINV in the 2009

time period as part of your expert report in -- expert declaration?

MR. TORCZON: Objection. Scope. Relevance. Asked and answered.

THE DEPONENT: No.

BY MR. ASHKENAZI:

Q. Okay. And the last category here, cannabinoids. You'll agree with me that cannabinoids was a potential agent for a POSA to consider for modifying existing triple therapy to help patients with chemotherapy-induced nausea and vomiting, correct?

A. You said that really fast.

MR. TORCZON: Same -- same objections.

BY MR. ASHKENAZI:

Q. You will agree with me that cannabinoids was something that a POSA would consider as a potential for modifying existing triple therapy to help patients with chemotherapy-induced nausea, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: It was a potential thing to consider.

BY MR. ASHKENAZI:

Q. But you did not do that as part of your declaration in this case, correct?

MR. TORCZON: Same objections.

THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay.
MR. TORCZON: We're coming up on an hour, just --
MR. ASHKENAZI: Why don't we take a break.
MR. TORCZON: Okay.
(A recess transpires.)
BY MR. ASHKENAZI:
Q. Dr. Peroutka, let's talk about MASCC, if you have that in front of you. And that's Exhibit 1013.
A. Okay.
Q. Okay. You mentioned this is done by a panel of experts, right, 23 oncology professionals, right?
A. Correct.
Q. Okay. And these include people in the field of clinical medicine, medical oncology, radiation oncology, oncology nursing, statistics, pharmacy, medical policy and decision-making, and pharmacology, right?
A. Yeah. I -- I did remember reviewing that and I agree with you, but I would like to find the source documentation of that.
Q. If you take a look under materials and methods on the first page?
A. Ah, yes.

Q. So the answer is correct?
A. Correct, yeah. I know I saw it.
Q. Thank you. And the experts represent nine oncology professional societies, and they came from 11 different countries on four different continents, right?
A. Yes.
Q. Okay. Now, if we turn to page 21, you will see the first full paragraph. I will wait for you to get there. I want to turn to the bottom of the first full paragraph. It says:
"For a guideline recommendation to be accepted, a consensus of at least 75 percent of the expert panel was needed."
Do you see that?
A. No. I'm looking on 21, which --
Q. First full paragraph, a little up from where your finger is, last sentence right there. Last sentence in that paragraph.
A. Okay.
Q. So I'll ask my question again. For a guideline recommendation to be accepted, a consensus of at least 75 percent of the expert panelists was needed, right? Is that accurate?
A. Yes.
Q. Okay. Now, just so we're clear, you'll agree

with me that if we look at the headings of each of the sections -- sorry. And that's the -- the bolded text throughout this article. Each one is focused on emesis, correct, as opposed to nausea. Is that accurate?

A. Yes.

Q. And none of the headers are instructing physicians -- that are instructing physicians or even mentioning preventing nausea, correct?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: None of the headings are addressing emesis -- I'm sorry, nausea, correct.

BY MR. ASHKENAZI:

Q. And if we look at the -- take a look at the first paragraph under immunogenicity of anti-neoplastic agents on page 21?

A. Okay.

Q. You will see at the bottom it states -- it's -- well, it's about six lines up from the bottom of that first paragraph, "Most schemas."

Do you see that?

A. 21?

Q. Left-hand side under immunogenicity?

A. Most schemas. Okay.

Q. Okay. And here it says:

"Most schemas have not differentiated between

the various types of emesis."

It says:

"There is acute delay of anticipatory, none have addressed nausea, and only a few have accounted for important treatment of patient-related variables."

And it goes on.

Do you see that?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: Yes, I see it.

BY MR. ASHKENAZI:

Q. Okay. In other words, this is another reason why they are not addressing nausea, because it hasn't always been a -- it's not really a focus of the development of these agents up until now, correct?

MR. TORCZON: Objection. Foundation. Scope. Relevance.

THE DEPONENT: No. I wouldn't necessarily agree with that.

BY MR. ASHKENAZI:

Q. Okay. To the best of your knowledge, MASCC is not telling patients -- is not telling doctors -- was not focusing on nausea with respect to treating patients with cancer chemotherapy, correct?

MR. TORCZON: Objection. Foundation. Relevance.

THE DEPONENT: MASCC is focused on emesis.
BY MR. ASHKENAZI:
Q. Okay. As opposed to nausea, correct?
MR. TORCZON: Objection. Asked and answered.
BY MR. ASHKENAZI:
Q. Did you say correct, sir?
A. Correct.
Q. Now, if you go to page 134, if you can.
Apologies. I'm sorry. Apologies. I am -- let me -- let me ask it differently.
MASCC is a 2006 reference, right?
A. Correct.
Q. Okay. Is there any mention of netupitant in this reference?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Not to my knowledge.
BY MR. ASHKENAZI:
Q. Even though they're talking about cancer chemotherapy -- I'm sorry. Withdrawn.
Even though MASCC is talking about potential therapies or therapies -- withdrawn.
Even though MASCC is talking about therapies for treating patients for cancer chemotherapy-induced nausea and vomiting, netupitant is not referenced in this publication as of 2006, correct?

A. Correct.

MR. TORCZON: Objection. Relevance. Asked and answered.

BY MR. ASHKENAZI:

Q. And, by the way, the Bös reference that you rely upon, that's from 2001, correct?

A. I believe so. I will double-check.

Q. Dr. Peroutka, I'm going to hand you Bös to make life a little easier, and that's Exhibit 1014.

(Exhibit No. 1014 marked for identification.)

BY MR. ASHKENAZI:

Q. And I will re-ask my question.

You will agree with me that the Bös reference that you referred to and relied upon in your declaration is from 2001, correct?

A. Correct.

MR. TORCZON: Objection. Relevance.

BY MR. ASHKENAZI:

Q. Okay. The only NK-1 receptor antagonist referenced in the MASCC article is aprepitant, correct?

MR. TORCZON: Objection. Foundation. Relevance.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Now, why don't we turn to page 22 of the

reference.
A. I'm sorry. Which reference?
Q. MASCC. Now, the portion that you discussed related to this article -- withdrawn.
The portion of the article that you discussed related to aprepitant, that's contained on this page, correct?
MR. TORCZON: Objection. Form.
THE DEPONENT: Yes.
BY MR. ASHKENAZI:
Q. Okay. And it talks about -- this is as of 2006. MASCC is discussing aprepitant's efficacy for treating emesis, correct?
A. Yes.
Q. These key opinion leaders do not reference aprepitant's use for treating nausea at all, correct?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Give me a second here to check something.
Not directly, but indirectly via the references.
BY MR. ASHKENAZI:
Q. When you say via the references, you mean in the cited articles mention that?
A. Right.
Q. But not the art -- but not MASCC itself?

A. Well, it does say it in the reference section, but not in the text of the article.
Q. Okay. When you say in the reference section, you mean the citations that are included in the references, the title of the articles --
A. Correct.
Q. -- that are cited?
A. Right. So, for example, Herrstedt says:
"Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy."
Q. Okay. Despite those articles being referenced, this committee of key opinion leaders did not reference the fact in the article that aprepitant can be used to treat nausea due to cancer chemotherapy, correct?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: In the text of the article, no, they did not.
BY MR. ASHKENAZI:
Q. Okay. So let me ask you -- you could put that to the side.
Now, okay. I want to sort of shift gears a little. I want to talk about aprepitant and the studies that you referenced for aprepitant.

You referenced a number of studies that you say show aprepitant showed a benefit for patients with respect to nausea, correct?
A. Correct.
Q. Okay. And I can go in any order you want. Is there a specific order you want to go through with respect to those references?
A. Do Campos first.
Q. Campos. That may take us a second.
A. Thank you.
Q. So I'm handing you Campos, which is Exhibit 1023.
(Exhibit No. 1023 marked for identification.)
BY MR. ASHKENAZI:
Q. Now, just so I understand correctly, Campos was published in 2001, correct?
A. Correct.
Q. And that's before the approval of aprepitant and fosaprepitant, correct?
A. Correct.
Q. Okay. And Campos was a study using -- was comparing -- well, withdrawn.
Campos is published by Merck, correct?
MR. TORCZON: Objection. Relevance. Scope.
THE DEPONENT: It was published by Journal of

Clinical Oncology.
BY MR. ASHKENAZI:
Q. And the -- the scientists here, as we see on the right-hand side of the first page, were from Merck, amongst other places, correct?
MR. TORCZON: Same objections.
THE DEPONENT: Amongst other places.
BY MR. ASHKENAZI:
Q. You are aware that Merck is the company that developed aprepitant and emet (ph), correct?
MR. TORCZON: Objection. Scope. Relevance.
BY MR. ASHKENAZI:
Q. Okay. Now, so you will agree with me that this is early data before the FDA had approved aprepitant for treating cancer chemotherapy-induced nausea and vomiting, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. And, again, the approval of aprepitant was in 2003, correct?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. Now, it is your opinion that Campos

provides that aprepitant, a 5HT3 antagonist, and dexamethasone provide -- provided nausea ratings that were significantly lower in the acute phase compared to the control, right?

A. I don't think that's what I said. I said overall nausea.

Q. Okay. So acute is one component of nausea, right?

A. (Moves head up and down.)

Q. All right. So let's break this up. It's going to be Table -- we're going to focus on Table 4, right? That's the table you focus on in the Campos reference, one -- Exhibit 1026.

A. Figure 2 and Table 4.

Q. Okay. So with those in mind, I want to just make sure I understand correctly.

They are evaluating four different treatment groups, right?

A. Correct.

Q. Okay. And those four different treatment groups are in the Table -- Table 1?

A. Correct.

Q. Okay. And the dose of aprepitant that was being used in treatment group 3, which is the focus of your data that you analyze here, was 400 milligrams orally,

correct?
A. Correct.
Q. Okay. On day one. Is that right?
A. I have to read it here.
Q. Okay. Well, why don't we take a look at Table 1. Why don't we look at treatment group 3.
A. Oh, yeah. Okay.
Q. Okay. And now I'm going to break this up into parts. I want to make sure we have an understanding of what was being evaluated in Campos. Is that okay?
A. Sure.
Q. So looking at Table 1, treatment group 3, on day 1, patients were being given 400 milligrams of aprepitant orally, correct?
A. Correct.
MR. TORCZON: Objection. Relevance.
BY MR. ASHKENAZI:
Q. Then, day 1 following the -- I'm sorry. That's day minus 1.
Evening cisplatin, right?
A. Correct.
Q. Okay. So let's start again.
Before, cancer chemotherapy patients are given 400 milligrams of aprepitant orally, correct?
MR. TORCZON: Objection. Relevance.

THE DEPONENT: Correct.
MR. ASHKENAZI: Counsel, are you saying that the treatment group for aprepitant in the Campos article that he has discussed is not relevant?
MR. TORCZON: I am saying that it's not relevant to the question of obviousness, yes.
MR. ASHKENAZI: Okay. I disagree, and I think the -- well, why don't we move on.
BY MR. ASHKENAZI:
Q. You -- Dr. Peroutka, you did discuss the Campos article in your expert declaration, correct?
A. Correct.
Q. And you did discuss the data in the Campos article, did you not, in your declaration?
A. Correct.
Q. Okay. Isn't it fair for us to have a discussion about that data?
MR. TORCZON: Objection. Relevance.
THE REPORTER: I'm sorry. The answer?
THE DEPONENT: As a legal issue, I can't opine, but it's fine.
BY MR. ASHKENAZI:
Q. Okay. Well, why don't we keep moving through this.
So day -- day minus 1, evening pre-cisplatin

treatment. Patients are given 400 milligrams of aprepitant orally. Then day 1 post cisplatin treatment, patients are given 400 milligrams of aprepitant orally. Is that right?

MR. TORCZON: Same objection.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. And then days two to five, the patients are given 300 milligrams of aprepitant orally, right?

MR. TORCZON: Same objection.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. And, by the way, just as -- as a point, do you know what the approved dose of aprepitant is by the FDA for treating patients with cancer chemotherapy-induced nausea and vomiting?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: I think that I would rather double-check before I opine. Do you want me to look it up, the Emend label?

MR. ASHKENAZI: I'm going to hand to you what's been marked as Exhibit 2016.

(Exhibit No. 2016 marked for identification.)

MR. TORCZON: I object to the exhibit on the basis of scope.

THE DEPONENT: Thank you.
BY MR. ASHKENAZI:
Q. Do you recognize Exhibit 2016 as a copy of the Emend label from March of 2003, which you see on the last page?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Yeah, the one I do -- I think the one I downloaded was 2008. I have to double-check whether that -- unless it's been changed. Probably not.
MR. ASHKENAZI: I'm also going to hand to you what's been marked as Exhibit 1030.
(Exhibit No. 1030 marked for identification.)
THE DEPONENT: Yeah.
MR. ASHKENAZI: This is a copy of the Emend IV fosaprepitant label.
BY MR. ASHKENAZI:
Q. Do you recognize that?
A. Yes.
Q. Okay. Well, let's stick with Exhibit 2016. Okay?
A. Okay.
Q. You can see --
MR. TORCZON: Objection. Scope.
BY MR. ASHKENAZI:
Q. You can see that this is an Emend IV label,

correct -- sorry, an Emend label, correct?
A. I'm sorry. Emend?
Q. Label?
A. Yes.
Q. Okay. In other words, this is the FDA-approved package insert for Emend oral capsules, correct?
MR. TORCZON: Objection. Foundation.
THE DEPONENT: It appears to be, yes.
BY MR. ASHKENAZI:
Q. And with this, you will agree with me that the approved dosage for aprepitant was 125 milligrams, correct?
MR. TORCZON: Objection. Scope.
THE DEPONENT: On day 1?
MR. ASHKENAZI: Correct.
BY MR. ASHKENAZI:
Q. Is that correct?
A. On day 1, correct.
Q. Yeah. So where Campos is providing 400 milligrams of aprepitant orally, the only approved -- the FDA approved dose of aprepitant was actually 125 milligrams, correct?
A. On day --
MR. TORCZON: Objection. Relevance.
///

BY MR. ASHKENAZI:
Q. On day 1?
A. On day 1.
Q. And then on day post cisplatin treatment, the patients are given another 400 milligrams, correct?
MR. TORCZON: Objection. Scope. Relevance.
BY MR. ASHKENAZI:
Q. Of aprepitant in the Campos study?
A. Wait. You're switching --
Q. I'll ask that question. I want you to keep two things in front of you, the Emend label and the Campos study. Okay?
A. Yeah.
Q. I just want to make sure we have an understanding of the different dosages that are used.
You will agree with me that prior to treatment, Campos gives 400 milligrams of aprepitant orally and the Emend label has two dose -- has only one dosage of 125 milligrams, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Then Campos actually gives another 400 milligrams on day 1, right?
MR. TORCZON: Same objections.

THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. And the Emend label does not. Is that correct?
MR. TORCZON: Same objections.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Now, you will agree with me that on days 2 through 5, Campos gives 300 milligrams each day, and the Emend label only gives 80 milligrams on days 2 and 3, correct?
MR. TORCZON: Scope and relevance.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. So you will agree with me that Campos has a significantly larger amount of aprepitant being given to patients over the time course of the treatment compare today the FDA approved label, correct?
MR. TORCZON: Same objections.
THE DEPONENT: Well, it's a larger amount. I can't opine if it's statistical or not with NF1, but it is larger.
BY MR. ASHKENAZI:
Q. So you discussed statistics here. Why --
A. Well, you said significantly, so not in -- I don't know if it's statistically significant. It is a

much larger -- a larger amount.
Q. So when we talk about the term significant, that means statistically significant in your mind?
A. When I hear it, it does. And --
Q. Okay.
A. And I associate it with it.
Q. Okay. You'll agree with me that it's almost three -- well, withdrawn.
Just as a separate point, isn't it true that higher amounts of aprepitant are known to have side effects of nausea?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: It can, yes.
BY MR. ASHKENAZI:
Q. A side effect of an NK-1 antagonist, instead of treading nausea, could actually be causing nausea, right?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Yeah, it's out of scope.
BY MR. ASHKENAZI:
Q. I -- you can answer the question.
A side effect of an NK-1 receptor antagonist as known in 2009 is that, from your -- from your perspective and the opinions you're providing in this case, instead of treating nausea could actually be

causing nausea, right?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: I'd have to look at the AE table. I know I've seen it. It's slightly higher. It's not a dramatic effect.

Here, where is it? It's, in the label, 12.7 to 11.8. It's not a big difference. I don't know that it's in the Campos paper, but I'll look.

BY MR. ASHKENAZI:

Q. Well, I'm sorry. You looked at the Emend label and I'm asking you a different question, not about the FDA approved dose, but I'm asking you, higher amounts of aprepitant have been known by 2009, according to you, to cause nausea. Is that true?

MR. TORCZON: Objection. Misstates. Scope. Relevance.

THE DEPONENT: I said it's possible.

BY MR. ASHKENAZI:

Q. I'm asking you, is -- so withdrawn. Let me ask the question again.

You believe it's possible that high amounts of aprepitant can cause nausea for patients, and that would have been known as of 2009, correct?

MR. TORCZON: Again, foundation, scope, relevance.

THE DEPONENT: It's out of scope. I would have to research it in greater detail.
BY MR. ASHKENAZI:
Q. So you -- you don't know the answer to that question?
MR. TORCZON: Objection. Misstates.
THE DEPONENT: It's not listed in the Campos paper, so that it's possible that super high doses of anything can cause nausea, but in the Campos paper with the doses they use, there's no mention of nausea.
BY MR. ASHKENAZI:
Q. Okay.
A. Increase.
Q. Well, why don't we take a look at your declaration, paragraph 100 and -- 1347, which is on page 763 to 764.
A. Okay. Say the number again. 1337?
Q. 1347, page 763.
A. 1347.
Q. Are you there, Doctor?
A. Okay.
Q. Okay. And you will see on page 764, paragraph 1347 of your declaration, about two, four, six, seven lines from the bottom, you state:
"The affidavit comparatives failed to account

for such a large single dose of aprepitant might affect nausea and vomiting, such as whether adverse events, including nausea and vomiting, could arise."

Do you see that?

A. Mm-hmm.

Q. And you're referring to a single dose of aprepitant at 255 -- 285 milligrams given orally. Do you see that, on day 1?

A. Yes.

Q. Okay. So now with this in mind, is it your position -- don't you agree that doses at least of 400 milligrams of aprepitant orally, according to you, would have concerns that they could have a side effect of nausea?

A. Can you repeat that, please?

Q. According to your opinions in this case, it would be your -- you would agree with me that 400 milligrams of orally given on pre -- pretreatment, 400 milligrams orally given post treatment on day 1, and 300 milligrams being given orally on days 2 through 5 could have a concern to have a side effect of nausea?

MR. TORCZON: Objection. Misstates. Scope.

THE DEPONENT: It could. As I state here, it could.

///

BY MR. ASHKENAZI:
Q. Okay. There would be a concern for a POSA that giving such high amounts of aprepitant as identified in Campos could actually cause nausea as opposed to treating nausea, correct?
MR. TORCZON: Objection. Misstates. Scope.
THE DEPONENT: No. I think it does misstate scope. If you go back to Campos, they show you the data and there's no reports of nausea. It could, but according to Campos, it did not.
BY MR. ASHKENAZI:
Q. So you don't believe that 285 milligrams of aprepitant given orally, as shown from Grunberg, would have a concern for nausea, right?
MR. TORCZON: Objection. Misstates.
THE DEPONENT: I mean, again, I think it does misstate because depends on what the chemo is. It could have a big effect what the patient population is.
BY MR. ASHKENAZI:
Q. So let's make sure we're clear.
It's your opinion that high doses of aprepitant may cause nausea within patients, right?
A. My opinion is it's possible. It could arise.
Q. Okay. And that was one of your criticisms of the Halsons analysis with respect to the Grunberg

reference, right?
A. In part.
Q. Okay. But as we see from Campos, they are giving very large amounts of aprepitant, right?
A. Correct.
Q. Okay. Now, you will agree with me that the FDA -- Merck did not seek approval for a 400-milligram dose of aprepitant, right?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: I don't know the FDA filings of Merck with this. I know what they didn't get approved. I mean, that was not the approved dose.
BY MR. ASHKENAZI:
Q. Right.
A. But I don't know what they submitted.
Q. And MASCC, when it provides a recommended dose for patients to be given aprepitant, does not recommend 400 milligrams of aprepitant being given in the dosing regimen identified in Campos, correct?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Double-check, but I think that is correct. Let me look. MASCC. Here it is. It's here. Here it is. Yeah, 125 is their single daily recommended dose.
///

BY MR. ASHKENAZI:
Q. In fact, MASCC is not recommending -- this -- withdrawn.
In fact, the esteemed group of scientists who put together the MASCC reference is not recommending a dose of aprepitant anywhere close to what -- and a dosing regimen anywhere close to what we see in the Campos reference, right?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: It depends on the definition of close in pharmacological terms. What's the difference? It's about --
BY MR. ASHKENAZI:
Q. Let's break this into two parts, Doctor.
You'll agree with me that the MASCC reference is not recommending the doses and the dosing regimen of aprepitant shown in Campos for treating patients with cancer chemotherapy-induced nausea and vomiting, whether highly immunogenic or highly immunogenic, correct?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. And you will agree with me that the dose that is being recommended by the 16 group of scientists is 125 milligrams orally, right?

MR. TORCZON: Same objection.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. So let's go to the -- and, by the way, just so we're clear, NK-1 receptor antagonists as a class, there would be a concern for the potential for an adverse event to be nausea, correct?
MR. TORCZON: Objection. Scope. Foundation.
THE DEPONENT: Yeah. I mean, that's a scope issue, number one, and the antagonists -- I haven't seen any discussion of that anywhere.
BY MR. ASHKENAZI:
Q. Okay. Let's break this down.
When you say it's a scope issue, what do you mean? Do you mean that you have not considered whether or not the NK-1 receptor antagonist potentially could have an adverse event of nausea?
MR. TORCZON: Objection. Relevance. Scope.
THE DEPONENT: I mean, drugs can have any adverse event.
BY MR. ASHKENAZI:
Q. The point is, you did not consider that adverse event with respect to your obviousness analysis in this case when you say it's beyond the scope?
MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: Well, based on the data in Campos, if you want to look at the graph, I would find that's something I didn't need to consider.
BY MR. ASHKENAZI:
Q. That you --
A. It wasn't -- it wasn't raised by anybody, and the data in Campos is very strong evidence that it doesn't occur, when you look at Figure 2, which is highlighted in my declaration somewhere if you want to see it better. But the -- the multiple doses of aprepitant -- look at the daily median. The majority of people in the study were basically under 10.
Q. So -- so would you like to withdraw your opinion that you provided in paragraph 1347 that you believe that Grunberg did not evaluate the possibility that aprepitant at 285 milligrams orally would -- could cause -- could actually cause nausea and vomiting?
MR. TORCZON: Objection. Misstates. Relevance.
THE DEPONENT: No, I don't want to withdraw it, because the Grunberg patients were different than the Campos patients.
BY MR. ASHKENAZI:
Q. So from your perspective, because there's different -- potential for different patients, you cannot expand the Campos patients beyond what we see in

the Campos study, from your perspective?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: In terms of the dose of aprepitant, it is evidence that in this paper it significantly helped nausea.

BY MR. ASHKENAZI:

Q. I understand that you -- that's what you say about Campos. But you're saying, even though Campos showed the high doses that were given on all the other days, day 1 and all the other days -- withdrawn.

Let me start again.

It's your assertion that Campos has shown that there -- that it -- that aprepitant at the doses that were being tested, 400 milligrams, 400 milligrams, and 300 milligrams for days two to five showed efficacy for treating nausea, correct? That's your position?

A. In the Campos paper?

Q. Yes.

A. Yes.

Q. Okay. Now, it's your position that even though Campos showed that, because that was only in that patient class, there could still be a concern that aprepitant could cause nausea for a different patient class, as we see in the Grunberg reference, when Grunberg is giving once at 285 milligrams orally. Is

that accurate?

MR. TORCZON: Objection. Misstates. Relevance.

THE DEPONENT: It's a possibility and unlikely, but it's a possibility.

BY MR. ASHKENAZI:

Q. Unlikely, you said?

A. If -- it is unlikely that it would cause it, based on the data in Campos.

Q. So you --

A. But it's possible.

Q. Possible. But it's unlikely?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: I mean, yeah. I mean, it's less likely than it -- I mean, any drug can cause nausea. And if you give a high dose in one group, in general, that will translate to other patient populations, but not always, based on the concurrent therapies, the cancer, et cetera.

BY MR. ASHKENAZI:

Q. So are you willing to withdraw your opinion that there was a concern with the Grunberg reference giving a single dose of aprepitant orally at 285 milligrams?

A. That's --

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: I'm sorry.

Can we get to exactly the line, to make sure I am -- we're on the same page here? 1347?

MR. ASHKENAZI: Yeah, paragraph 1347.

THE DEPONENT: I think it lessens the chance, but it's still possible.

BY MR. ASHKENAZI:

Q. You do agree, at least, that there's a potential -- it's your position that high doses of aprepitant can potentially cause nausea, right?

A. Potentially yes.

Q. Therefore, not every NK-1 antagonist given at any dose would be expected to treat patients for nausea, right?

MR. TORCZON: Objection. Calls for speculation. It's pure speculation. My -- my preface, what I said earlier, is any drug in high dose has that potential. Nausea is probably one of the most common side effects of all drugs if given at high doses.

BY MR. ASHKENAZI:

Q. Okay. All right. Why don't we -- okay. I'm going to hand you another reference that you discussed. I believe it's Poli --

A. Poli-Bigelli.

Q. Bigelli, which is Exhibit 1039.

(Exhibit No. 1039 marked for identification.)

BY MR. ASHKENAZI:
Q. All right. Now, this is one of the references that you discussed in your declaration?
A. Yes.
Q. Okay. And you focused on Table 2 from Poli-Bigelli, right?
A. Correct.
Q. Okay. And that -- is that what you're looking at right now?
A. Correct.
Q. All right. Let's make sure we're on the same page here.
Now, can you do me a favor? Can you pull up the Emend 2003 label, which is the Exhibit 2016?
MR. TORCZON: Again, objection to scope.
MR. ASHKENAZI: It's the one -- yes, that's the one.
BY MR. ASHKENAZI:
Q. Okay. And I'm going to ask you to turn there at Table 2.
A. Okay.
Q. And I'm doing this just to -- if you know the answer, then we can skip it, but to show that Poli-Bigelli is referencing the study that's reported in Table 2 of the Emend IV label, Exhibit 2016 -- sorry,

the Emend label that's Exhibit 2016.
A. Correct.
Q. And you're aware of that, right?
A. Yes.
Q. Okay. So I don't have to bother matching up the numbers, right?
A. Correct.
Q. Okay. Now, just so we're clear, the Emend label that you have in front of you, I pointed out is the date at the back is, March 2003, right? We did that earlier?
A. Yes.
Q. Okay. And the Poli-Bigelli reference, that is from 2003 as well, correct?
A. Yes.
Q. Okay. Now, you point to the data here to say that aprepitant was known to be able to treat patients for nausea, correct?
MR. TORCZON: Objection. Form.
THE DEPONENT: These were the data to support its indication in the treatment of CINV.
BY MR. ASHKENAZI:
Q. Okay. CINV. That's fine. But you do reference the fact, when we look at the -- the data here with respect to Table 2 -- I'm going to use the Emend label. You can feel free to use whichever one you want. But

this study says, for no nausea, the aprepitant group overall showed a statistically significant difference in your mind at a P value of 0.021. Is that accurate?
A. Correct.
Q. Okay. And for no nausea delayed phase, that was at a P value of 0.004, right?
A. Correct.
Q. Okay. And it's this is what you use to say there is a statistically significant difference showing aprepitant's impact on nausea. Is that accurate?
A. It's one of multiple data points.
Q. Right. We have Campos. We're going to go through each study. But this is one of the data points you used, right?
A. Correct.
Q. Okay. But you will agree with me that when it comes to no significant nausea, the P values are greater than .05, correct?
A. The P values, yes, are greater.
Q. Meaning they don't show a statistically significant difference as determined by the P values provided in Table 2 or in -- in the Pol -- Poli-Bigelli Table 2, correct?
A. Well, it's the same data, so the -- the numbers in -- we're talking no significant nausea. Overall, 71

percent versus 64, so numerical superiority that does not reach statistical significance in this patient size.

Q. And the article that's provided and listed in a peer-reviewed article, Poli -- Poli-Bigelli, they use a P value threshold of .05, right?

A. I'd have to check. But I'll --

Q. You could take a look at the C that's included at the bottom of Table 2.

A. Oh, yeah, yeah, right, which is consistent with the .021.

Q. So just so we can make sure that the question is clear, the statistical threshold that the authors of Poli-Bigelli use is 0.05 for the P value, right, to show statistical significance?

A. Correct.

Q. Okay. Now, you are aware that -- I want to -- I'm sorry.

Now, if you could take a look at Table 2 in then Emend label, which is Exhibit 2016. Do you have that in front of you?

A. Yes.

MR. TORCZON: Same objections of scope.

BY MR. ASHKENAZI:

Q. Now, you will see here, at the bottom of the table it says:

"Table 2 includes nominal P values not adjusted for multiplicity."

Right?

A. Yes.

Q. Okay. And you are aware that there's a bunch of statistical rules on how you could do analyses to determine whether something is statistically significant, right?

A. Correct. The Bonferroni correction, B-o-n-f-e-r-r-o-n-i.

Q. Is that a standard correction?

A. It's one of the major ones, yes.

Q. And that's one that accounts for multiplicity, right?

A. Correct.

Q. Okay. That's actually should be done, correct?

A. In general.

Q. Yeah, okay. So now, the data that we have for Poli-Bigelli and for the Emend label Exhibit 2016 both state that they did not -- withdrawn.

So the data that's from the Emend label in Poli-Bigelli did not account for -- did not adjust for multiplicity, right? That's what we see in the Emend label at the bottom of Table 2?

MR. TORCZON: Objection --

THE DEPONENT: Correct.
MR. TORCZON: -- to form, scope and -- form and scope. And relevance.
BY MR. ASHKENAZI:
Q. Okay. Let's take this now, and I want to take a look at Tab 103 -- I'm sorry, Exhibit 1030. That's the Emend IV label, the fosaprepitant label. I'm sorry. I know you've got a couple things in front of you, and I'm going to guess it's underneath that. There we go.
So, Dr. Peroutka, you're aware that the Emend IV label was -- included data on oral aprepitant, right?
A. Yeah, Tables 1 and 2.
Q. Right. Now, Emend IV, that's fosaprepitant, right?
A. Sorry?
Q. You didn't answer.
A. Yes.
Q. You nodded your head?
A. Yes, the Fos -- yeah, the prodrug.
Q. All right. So let's -- let me start again.
Exhibit 1030 is the FDA-approved label for Emend IV fosaprepitant dimeglumine, correct?
A. Correct. Dimeglumine.
Q. But as you've said, it's a prodrug of aprepitant, correct?

A. Correct.
Q. And that's because aprepitant can -- the scientists at Merck wanted to be able to come up with an IV version of aprepitant, right?
MR. TORCZON: Objection. Foundation. Scope.
THE DEPONENT: I don't know that for a fact, but it would make sense.
BY MR. ASHKENAZI:
Q. Well, let's just use straight fact -- straight dates.
2003, oral aprepitant is approved, applied for by Merck and approved by the FDA, correct?
A. Correct.
Q. 2008, IV fosaprepitant, which is a prodrug of aprepitant, is approved by the FDA and filed for by Merck, correct?
A. Correct.
Q. Okay. And from your perspective, they're the same in terms of efficacy, correct?
MR. TORCZON: Objection. Scope.
THE DEPONENT: They should be very similar. The way you give the drug can have an effect on its metabolism.
BY MR. ASHKENAZI:
Q. Okay. What they submitted to the FDA was to

show that this should be considered -- IV aprepitant is -- is essentially -- well, withdrawn.

You will agree with me that, nonetheless, the Emend IV label does include data on aprepitant, right?

A. Correct.

Q. Yes?

A. Correct.

Q. Okay. Let's take a look at Table 2 of Exhibit 1030.

You will agree with me that this is the same Table 2 -- well, I'm sorry. Withdrawn.

You will agree with me that Table 2 of Exhibit 1030 reports data from the same study referenced in Poli-Bigelli and in the Emend -- Emend label from 2003, Table 2, correct?

A. It -- it looks like that.

Q. Yeah. But there is one difference here.

A. Right.

Q. You will agree with me that the FDA -- in the FDA-approved label that Merck submitted and the FDA approved in 2008, the FDA removed the statistical significance for the aprepitant regimen for no nausea and no -- overall and delayed phase. Do you agree?

A. I can. It could have been a typo or they could have removed it.

Q. Okay. Either case, you will agree with me that as of 2008, the FDA said -- the FDA approved label that Merck files for shows that aprepitant had no statistical significant difference compared to standard therapy for no nausea overall and delayed phase, correct?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: There is a discrepancy between the two tables. I don't know the basis of the discrepancy.

BY MR. ASHKENAZI:

Q. Well, we do know earlier that the FDA -- I mean, that in the FDA approved label for Merck in 2003, it said that it did not account for multiplicity, correct?

A. Yes.

MR. TORCZON: Objection. Relevance.

BY MR. ASHKENAZI:

Q. Okay. Now, if you go to the next page, which is still a continuation of the table, of Table 2, and we are now in Exhibit 1030, the 2008 Emend label, Emend IV, you will see that there is a star and it says:

"Not statistically significant when adjusted for multiple comparisons." Correct?

A. Correct.

Q. So you will agree with me that Merck and the FDA stated that when looking at the Poli-Bigelli study, the

study that's included in the 2003 label and the study that's included in 2008 label, that aprepitant did not show a statistically significant difference compared to standard therapy for treating -- for no nausea, whether it's overall or delayed phase, correct?

MR. TORCZON: Objection. Foundation and relevance.

THE DEPONENT: It showed a numerical superiority for all the four conditions you're referring to, and it did -- it still led to the approval for CINV.

BY MR. ASHKENAZI:

Q. Sir, you didn't answer my question. I want to make sure it's very clear. You will agree with me that Merck and the FDA stated, when looking at the Poli-Bigelli study, the study that's included in the 2003 label and the study that's included in the 2008 label, both Tables 2, that aprepitant did not show a statistically significant difference compared to standard therapy for no nausea, whether it's overall or delayed. Is that accurate?

MR. TORCZON: Objection. Foundation. Relevance.

THE DEPONENT: That is accurate, statistically accurate.

MR. ASHKENAZI: We've been going for about an

hour. Do you want to take a break?

THE DEPONENT: We can go -- we can keep going.

BY MR. ASHKENAZI:

Q. And just to be clear that the Merck -- that Merck and the FDA, when looking at the Poli-Bigelli study, the study that's in the 2003 label and the study that's included in the 2008 label, both under Tables 2, that aprepitant did not show a statistically significant difference compared to standard therapy for no significant nausea overall and delayed phase, correct?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: It only showed a numerical superiority, not statistical.

MR. ASHKENAZI: I have a -- why don't we go off the record.

(A recess transpires.)

BY MR. ASHKENAZI:

Q. By the way, the studies that are included in the aprepitant label, the Tables 1 and 2 in both the 2003 and 2008 labels, those are the pivotal studies that led to the approval of aprepitant for treating CINV, correct?

A. Correct.

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Sorry.

BY MR. ASHKENAZI:
Q. Now, just so we're on the same page, for the aprepitant, is it your belief that -- withdrawn.
Is it your belief that 5HT3s are effective for treating nausea?
A. They have some effect.
Q. You will agree with me that the pivotal studies that permitted approval for aprepitant for CINV as we -- well, withdrawn.
Why don't we do Table 1. Can you go to Table 1 in the aprepitant label? And this is going to be Figure -- I'm sorry, Table 1 in 1030, in Exhibit 1030.
All right. Let me start again. I'm making this a mess.
If you could pull in front of you Exhibit 1030. That's the aprepitant Emend IV label. I think it's that one.
Are you there?
A. Yes.
Q. Okay. Now, Table 1 is the other pivotal study that was included in the label for approval of aprepitant for treating CINV, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Correct.
///

BY MR. ASHKENAZI:
Q. Okay. And you will agree with me, then, in the second pivotal study, which is included in Table 1, aprepitant showed no statistically significant difference for no nausea overall in delayed phase compared to standard therapy. Is that correct?
MR. TORCZON: Same objections.
THE DEPONENT: It shows a numerical superiority, but not a statistical superiority defined as less than .05.
BY MR. ASHKENAZI:
Q. And when you say a numerical superiority, why are you focused on that?
A. 48 to 44, 51 to 48, these are the numbers in the columns.
Q. Okay.
A. No significant nausea, 73 to 76, 75 to 69.
Q. Okay. So the point is, the numbers are different. But you'll agree with me that for both no nausea and no significant nausea, overall and delayed phase, aprepitant in Table 1, the study reported in Table 1 of the aprepitant label, Exhibit 1030, showed no statistically significant difference compared to standard therapy, right?
MR. TORCZON: Objection. Form. Misstates.

Relevance.

THE DEPONENT: In this study, that is correct.

BY MR. ASHKENAZI:

Q. So now we have two studies, two pivotal studies that we're looking at that were included in the aprepitant label that was approved by the FDA for treat -- correct? Sorry.

MR. TORCZON: Same objections.

BY MR. ASHKENAZI:

Q. Let me start again.

A. Well, for --

Q. We just reviewed -- we've just reviewed the two pivotal studies that were included in the Emend label approved by the FDA, correct?

MR. TORCZON: Same objections.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. And those are shown in Tables 1 and Tables 2, right?

A. Correct.

Q. And you will agree with me that in both Tables 1 and Tables 2, for no nausea and no significant nausea, whether overall or delayed phase, aprepitant showed no statistical -- statistically significant difference compared to standard therapy, correct?

A. Correct.
MR. TORCZON: Same objections.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Now, nonetheless, the FDA still approved aprepitant for CINV, treating CINV, correct?
MR. TORCZON: Objection. Foundation.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. And that's because the primary endpoints were emesis, right, were related to emesis, for both the pivotal studies, Tables 1 and 2, correct?
A. I would not agree with that. It wasn't because the primary was emesis. It was because they had had an agreement sponsored with the FDA that if they could get improvement in complete response with this combo versus standard, they would get approval for CINV.
Q. Right. Okay. Now, you will agree with me that for the no nausea and no significant nausea, they don't have any statistically significant difference though, right?
A. But the study wasn't powered to do that.
Q. The FDA did not approve -- the FDA -- withdrawn.
You've done a number of FDA approvals, correct?
A. Mm-hmm.

Q. I'm sorry. You have to --
A. I'm sorry. Yes.
Q. Okay. And you are aware that if you do not show a statistically significant difference, the FDA will not approve you for a specific indication, correct?
A. With the primary endpoint.
Q. Right. And now, the FDA -- the primary endpoint is going to the overall indication, correct?
MR. TORCZON: Objection. Misstates.
THE DEPONENT: Yes. But with preapproval of the FDA on that endpoint for the indication you're seeking. So there is an end of phase 2 meeting and then there is FDA buy-in on the pre phase 3, end of phase 2 meeting that says, okay, this is our plan, if we achieve this with the primary endpoint, will we get approval for that, and they -- I assume that they had that because that's what they did. The secondary endpoints are not powered in this study. The power of the number of subjects is to achieve the primary endpoint. So if a statistician looked at all these secondaries, given the differences you see, there could have been studies designed to achieve statistical significance, but with the power to get the primary, these did not have enough patients.
///

BY MR. ASHKENAZI:
Q. Now, you'll agree with me that these studies included 260 or so patients, correct?
A. Correct.
Q. These are pretty large clinical trials, correct?
MR. TORCZON: Objection. Form.
THE DEPONENT: It is -- everything is relative at Genentech. When I was at Genentech, we did a 20,000-patient heart attack study to show a 1 percent difference in mortality. 22,000, I think is an incredible number, so it depends on the difference you expect the effect side in statistical terms, and then you power, meaning you use statistics, to determine what's the power to show 90 percent chance that they're different. And that number varies by every endpoint.
BY MR. ASHKENAZI:
Q. So -- and the reason you do that is because, otherwise, if you don't -- if you're not powered, you don't know if the -- you see a numerical change is actually borne out as a true effect as opposed to being done by chance, correct?
MR. TORCZON: Objection. Foundation. Relevance.
THE DEPONENT: It determines the percent likelihood of seeing a real effect.

BY MR. ASHKENAZI:
Q. Right.
A. Which is the P value.
Q. No matter how you slice it, the two pivotal studies that were included in the Emend label did not show a statistically significant difference for no nausea and no significant nausea, correct?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: They showed numerical, not statistical significance.
BY MR. ASHKENAZI:
Q. Right. Now, sorry. Okay. I'm going to hand to you a couple of articles. We will try to make them one at a time.
A. Okay.
Q. But for the sake of simplicity, we'll do them.
First one is the Hesketh reference. It's Exhibit 1037.
(Exhibit No. 1037 marked for identification.)
MR. ASHKENAZI: The second one is the Warr reference, W-a-r-r, Exhibit 1034.
(Exhibit No. 1034 marked for identification.)
THE DEPONENT: Thanks.
BY MR. ASHKENAZI:
Q. Okay. Now, Doctor, I'm going to ask you to

first turn back to Exhibit 1010 for a minute. Keep those two in front of you, but see if we can pull up the Herrstedt article. Let me see if I can help you here for a second. This one might be --

A. Thanks.

Q. So for the Herrstedt article, you did use this to identify studies that you asserted showed aprepitant being used to treat patients with nausea, right?

A. Correct.

Q. And specifically, if we look at page 10 -- 146 of Exhibit 1010, on the right-hand side, you discussed four phase 3 clinical trials. That's -- that's where you got those references, right?

A. I'm sorry. Say that again.

Q. If you're on the Herrstedt article.

A. Yeah.

Q. Page 146.

A. Okay.

Q. If you go to the right-hand side, second full paragraph, you will see it discusses --

A. Am I -- am I -- I'm trying to see which page you are on. No.

MR. TORCZON: 146.

THE DEPONENT: Wait, this is Hesketh.

MR. ASHKENAZI: Yeah.

MR. TORCZON: Oh.
MR. ASHKENAZI: That one.
MR. TORCZON: He wants Herrstedt.
THE DEPONENT: It's that one. Sorry. Or Herrstedt, Hesketh. I'm sorry.
MR. ASHKENAZI: I know. It's very confusing for me so, I'm sure it is confusing for the record as well. Why don't we start again.
THE DEPONENT: Okay.
BY MR. ASHKENAZI:
Q. We're looking at the Herrstedt reference, Exhibit 1010?
A. Yes.
Q. And, again, this is the reference that you used to identify what you believe are aprepitant studies that showed efficacy for treating nausea, correct?
A. I'm sorry. This is the review article, right?
Q. Yes. And it identifies certain studies that you've discussed, and this is -- I'm looking at page 146, on the right-hand side, for phase 3 trials.
A. Thank you.
Q. Right?
A. Yes.
Q. Okay. So let's start again, now that you have it. Why don't you read the first sentence to yourself.

Are you there, Doctor?
A. Yeah. You said -- oh, just the first sentence.
Q. Just the first sentence.
A. First paragraph.
Q. Yes. Okay. So let's start new. Let's start fresh?
A. Okay.
Q. So you discussed a number of studies -- or a couple of studies that you say were done of aprepitant that showed efficacy for treating nausea, correct?
A. Treating CINV.
Q. CINV. Is it your position that there are any studies that show that aprepitant can be used for treating nausea specifically?
MR. TORCZON: Objection. Form.
THE DEPONENT: Not that I'm aware of, pure nausea.
BY MR. ASHKENAZI:
Q. Pure nausea. Okay. So -- and I want -- let me be clear what I mean by that.
You're not aware of any studies that would show that aprepitant is useful for treating chemotherapy-induced nausea specifically?
MR. TORCZON: Objection to form.
///

BY MR. ASHKENAZI:
Q. Right?
A. No. I reference Campos as data that shows the effect on nausea in a graph and table, and was at Herrington.
Q. Okay. Those are the studies that you're relying upon to say that aprepitant has a benefit for treating chemotherapy-induced nausea, right?
A. In part. And also the numerical differences. So, for example, if we can go back and you want to do the Emend label or it was a 49 to 39, if 39 percent of people have no nausea or no significant nausea, right, that's 60 percent that could use some help. And you go up 10 percent, not statistically significant, but that's 25 percent of what you would have had without it. You get 25 additional benefit in the population. That's a big jump. And it may not reach statistical significance, but it is clinically significant.
Q. Well, you don't know that it's clinically significant because you don't know that that's not due to chance. Isn't that correct?
A. That's a statistical issue.
Q. And as a scientist, we work on and evaluate information based on statistics, don't we?
A. Correct. But we don't do sample size

calculations, power calculations, and statistics on secondary endpoints.

Q. So and I'm asking, so my question is: Do you have any data proving that aprepitant is useful for treating patients for chemotherapy-induced nausea?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: I think the data on Camp -- from Campos and Herrington show a significant effect that wasn't statistically analyzed, which is allowable in exploratory endpoints. Secondly, or thirdly, the -- I think it is called complete protection does include significant nausea, and those variables in the package inserts were positive.

BY MR. ASHKENAZI:

Q. Okay. So I'm going to go through -- we've gone through now the Poli-Bigelli study. We've gone through the package inserts, right? So now let's go through -- by the way, just so we're clear, the studies on aprepitant that are referenced in the -- in the Herrstedt reference, Exhibit 1010, are references 37 to 40, right?

A. Need to look.

Q. It's in that paragraph, that sentence we were just --

A. Oh, 37 to 40 here, not in my report.

Q. Yes. Is that correct?
A. 30 -- 30 -- ah, yes.
Q. And if we can go to the back of this reference, Exhibit 1010, page 150, reference 37 is Hesketh?
A. Correct.
Q. Reference 38 is Poli-Bigelli?
A. Correct.
Q. Reference 39 is Schmoll, right?
A. Correct.
Q. And reference 40 is Warr, right?
A. Correct.
Q. Okay. And you discussed in your expert declaration the Hesketh, Poli-Bigelli, and Warr references, correct?
A. Correct.
Q. You did not discuss the Schmoll reference, right?
A. I don't recall that one.
Q. Okay. So let's go through. We already went through the Poli-Bigelli one. You have Hesketh in front of you, right? Hesketh. Is that accurate?
A. It's close enough. Okay. Got it.
Q. Okay. So Exhibit 1037 is Hesketh, right?
A. Correct.
Q. All right. And that's titled "The Oral

Neurokinin 1, Antagonist of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting," and then it goes on, right?

A. Correct.

Q. Okay. This was published in 2003, correct?

A. Correct.

Q. And this is the Hesketh article that's referenced in the Herrstedt article that we just discussed, right?

A. One of them, yes.

Q. Yes. And this is work that was funded by Merck, correct?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: You see it on the bottom left-hand side.

MR. TORCZON: Objection. Relevance.

THE DEPONENT: Yes.

BY MR. ASHKENAZI:

Q. And Merck, as we said, is the company that markets and sells aprepitant under the trade name Emend, correct?

A. Correct.

MR. TORCZON: Same objection.

BY MR. ASHKENAZI:

Q. Now, on the first page, on the right-hand side,

it says, that last paragraph, "aprepitant" and then, parentheses, "Emend."

Do you see that?

A. I'm sorry. Say that again. Yeah, first page, bottom right.

Q. Yeah. Now, you'll see four lines down, it says that:

"Aprepitant, an NK-1 receptor antagonist has demonstrated prone-ability to inhibit emesis induced by chemotherapy, correct?

A. Correct.

Q. And then it continues to talk about that unlike 5HT3s, NK-1 receptor antagonists have demonstrated efficacy against acute and delayed emesis, right?

A. Correct.

Q. Okay. Now, if you could keep that open, just we're going to go to it, but I want to also go to paragraph 327 in your declaration. Okay? It's on page 183. Are you there?

A. 327 paragraph?

Q. Yes. You state that Hesketh also confirms the triple therapy dosing combination of Herrstedt treats nausea and vomiting in response to highly mutagenic chemotherapy (i.e., cisplatin) during both acute phase and delayed phase."

Is that right?
A. Correct.
Q. And then you cite Table 2 of Hesketh, right?
A. Correct.
Q. And you'll agree with me that nausea and emesis, or vomiting, are different endpoints, right?
Let -- let me make that clear?
You'll agree with me that nausea and emesis are considered different endpoints in Table 2, correct?
A. Not in complete protection section. They're combined.
Q. I'm talking about the -- okay. So your point, is complete protection may combine it, but you'll agree with me separately, they do evaluate no nausea separate from no significant nausea, separate from no emesis, correct?
A. Right, and combined. And in total control is also -- has some nausea component.
Q. Now, you'll agree with me that for no nausea -- withdrawn.
You'll agree with me that for no emesis and no rescue therapy, the data in Table 2 shows that the aprepitant regimen was statistically superior, right?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Please repeat that, because I

am -- I was looking at something different.
BY MR. ASHKENAZI:
Q. Let's look at no emesis.
A. Yes.
Q. And no rescue therapy.
A. Yes.
Q. Right? And we will see that for the -- that both -- that the aprepitant group shows a statistically significant difference compared to standard therapy, right?
A. Correct.
Q. Okay. But you'll agree with me that for no nausea and no significant nausea, there is no statistically significant difference, right?
MR. TORCZON: No -- objection. Relevance.
THE DEPONENT: Well, they only analyze part of the data. That little squiggly line thing means, it says "analysis not planned." So they didn't analyze that, I assume, because that's what it says.
BY MR. ASHKENAZI:
Q. Let's take a look at, overall, days 1 to 5 for the aprepitant regimen versus standard therapy.
You would agree with me that no nausea and no significant nausea showed no statistically significant difference, right?

A. Showed numerical significance, but not statistical.
Q. And it's your position, that numerical difference of 44.2 versus 47.5 is a meaningful difference with respect to no nausea for overall days 1 to 5, correct?
A. Probably not. But it's still a difference.
Q. And your point is, if there is a difference, if there's a numerical difference, then that shows some benefit?
A. If confirmed and with appropriate powering. It has to be confirmed and powered correctly.
Q. So a numerical difference from your perspective does have to be confirmed and powered correctly in order to show a true effect with that -- from that treatment regimen?
MR. TORCZON: Objection. Misstates. Relevance.
THE DEPONENT: No, but it -- the study was not powered to look at that.
MR. ASHKENAZI: Right.
THE DEPONENT: And so it has a different statistical value.
BY MR. ASHKENAZI:
Q. Sorry. I just want to be clear. I said:
"And your point is, if there's a difference, if

there's a numerical difference, then that shows some benefit?"

And you said:

"If confirmed and with appropriate powering. It has to be confirmed and powered correctly."

Is that right?

A. Right. So if you did 500 patients per condition and you got a smaller difference, you know, it's possible that that difference is clinically significant. It may not be, because it's not confirmed.

Q. Okay.

A. Or powered.

Q. Now, I just want to be clear.

For the delayed phase and for the overall phase, there's no squiggly lines, correct?

A. Correct.

Q. And there's no statistically significant difference for the aprepitant regimen compared to the standard therapy for no nausea and no significant nausea, right?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. Now, for -- you referenced complete protection before, right?

A. Correct.
Q. Okay. Now, complete protection is a composite endpoint, right, in the sense that it covers numerous different things that are being evaluated at the same time. Is that accurate?
A. Three things.
Q. Three things. And what are those three things?
A. It says here:
"Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale less than 25 millimeters.
Q. Okay. Now, is it your position that because nausea is included in there and there's a statistically significant difference that this data shown in Table 2 of Hesketh means that there is a statistically significant difference for treating nausea?
MR. TORCZON: Mis -- objection. Misstates relevance.
THE DEPONENT: Well, it states that it is statistically more likely to have complete protection if you have the triple combination.
BY MR. ASHKENAZI:
Q. Right, complete protection. But that doesn't change the fact that this data here does not have a statistically significant difference for no nausea and

no significant nausea, correct?

MR. TORCZON: Same objections.

THE DEPONENT: Correct. But, again, you have to look at the powering of the -- that endpoint.

BY MR. ASHKENAZI:

Q. And the powering of the endpoint gets much worse when you consider a composite, right? In order for you to draw a conclusion that there's any impact on nausea from a composite endpoint, you would need a much higher percent powering. Isn't that correct?

MR. TORCZON: Objection. Scope.

THE DEPONENT: That's outside of scope. My instinct would say that's not necessarily true. Sometimes you do composites purposely to make it more likely to detect a signal.

BY MR. ASHKENAZI:

Q. A signal for one endpoint that you couldn't find otherwise?

A. Correct.

Q. In other words, if I can't prove that there's no nausea, if I test emesis and no rescue, that's going to make it higher, more likely to tell the difference for nausea?

A. There are scenarios --

MR. TORCZON: Objection. Scope.

THE DEPONENT: Oh, sorry.
MR. TORCZON: You can answer.
THE DEPONENT: Well, for example, complete protection, that's -- that's sort of the goal. No significant nausea, no vomiting, no rescue therapy. I mean, that's getting up there to what the goal of the treatment of CINV should be. I'd like to see that, obviously, at 100 percent across the board, right? So, in a way, complete protection is one of your best measures of the efficacy in CINV because it -- we talked earlier, what is the real goal here. In the zero to 100 scale, you know, less than 25, that's nausea, but that's -- that's not significant. I mean, clinically, as distressing as, say, a 70 out of, right? So it's a -- it's a composite that actually reflects well on what is the treatment of CINV.
BY MR. ASHKENAZI:
Q. Isn't it possible that one of the endpoints separately measured is what's driving the statistically significant difference, as opposed to it being no nausea?
MR. TORCZON: Objection. Scope. Calls for speculation.
THE DEPONENT: Well, it is speculation for sure. But -- you know, it's beyond the scope. But it is the

goal. In other words, complete protection is the goal. And I think what it's highlighting -- I'm speculating. If I -- do you want me to speculate or not? I can probably not speculate. But there's different explanations that it still in my mind would be the best endpoint for the composite assessment of CINV.

BY MR. ASHKENAZI:

Q. You did not evaluate whether or not the no emesis difference skewed the data in a way to show a statistically significant difference for complete protection, correct?

MR. TORCZON: Objection. Foundation. Relevance scope.

THE DEPONENT: Yeah. Well, you can't do that because those data are not available.

BY MR. ASHKENAZI:

Q. And you did not do that, right?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: It was not possible to do it.

BY MR. ASHKENAZI:

Q. Okay. So you do not know that any of the other composite endpoints are why we're seeing a statistically significant difference for complete protection, as opposed to that being driven by no nausea, correct?

MR. TORCZON: Same objection.

THE DEPONENT: We know that when you -- well, complete protection to me says, that's the goal and is it significantly better with the triple than the double therapy.

BY MR. ASHKENAZI:

Q. That wasn't my question. So I want to make sure we're clear.

You do not know whether the other composite endpoints for complete protection with respect to no emesis and no rescue therapy had an impact on the statistically significant difference of complete protection such that -- withdrawn. I'll ask the question the way I had it worded before.

You do not know that any of the other composite endpoints are why we're seeing a statistically significant difference for complete protection, as opposed to that being done because of no nausea?

MR. TORCZON: Objection. Relevance.

MR. ASHKENAZI: Correct.

THE DEPONENT: I would need to see the data to make that assessment.

BY MR. ASHKENAZI:

Q. Okay. Now, and just to be clear, no emesis and no rescue therapy are component endpoints of the composite complete protection, right? Let's -- let me

ask the question a little differently.
A. Yes.
Q. Complete protection, according to you covers, no emesis, no rescue therapy, and no nausea. Is that accurate?
A. No.
MR. TORCZON: Objection. Misstates, and asked and answered.
BY MR. ASHKENAZI:
Q. Complete protection covers no emesis, no rescue therapy, and no significant nausea, correct?
MR. TORCZON: Same objections. Well, a visual analog scale of less than 25, which in the field is considered no significant nausea. So technically, it's less than 25, and that's -- you used the term "no significant," but that's the field's acceptance.
BY MR. ASHKENAZI:
Q. The field accepts no significant nausea is less than 25 on a VAS score, right?
A. Correct.
Q. Okay. So then let's be clear. Complete protection, the components are no emesis, no rescue therapy, no significant nausea, correct?
A. Correct.
Q. And you cannot tell me whether a statistically

significant difference for complete protection is due to differences in the treatment being able to provide a benefit for no significant nausea as opposed to the treatment regimen showing a -- you know, a difference for no emesis and no rescue therapy, correct?

MR. TORCZON: Objection. Form. Foundation. And relevance.

THE DEPONENT: I could tell you if I had the data.

BY MR. ASHKENAZI:

Q. But you haven't done that analysis?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: The data are not publicly available, to my knowledge.

BY MR. ASHKENAZI:

Q. Okay. What we do know is that when those endpoints -- when the endpoints of no nausea and no significant nausea are looked at for delayed and overall, there is no statistically significant difference for the aprepitant regimen compared to standard therapy?

MR. TORCZON: Objection.

BY MR. ASHKENAZI:

Q. Correct?

MR. TORCZON: Objection. Asked and answered.

Relevance.

THE DEPONENT: And did you say for no nausea and no significant?

MR. ASHKENAZI: Yes.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. Can you turn to the Warr reference, which is Exhibit 1034?

A. Yes.

Q. Okay. Now, Warr is another reference that was referenced in the Hesketh article, correct -- Herrstedt article?

A. Yes.

Q. And I apologize. But let's -- I -- if I make a mistake, since the record has to be clear, we -- we need to -- you know, please help.

So again, the Herrstedt article referenced four aprepitant studies, one of those studies is the Warr reference, which is Exhibit 1034, correct?

A. Yes, reference 40 in Herrstedt.

Q. Okay. And you discuss -- and this is Exhibit 1034 to your declaration, correct?

A. Yes.

Q. Okay.

A. Wait. 1034 on my report. You said 10340, I

thought.
Q. I said 1034, but...
A. That's what I thought.
Q. Perfect. We're on the same page. And the title of this reference is "Efficacy and Tolerability of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting," and then it goes on. Is that right?
A. Correct.
Q. Okay. Now, if we turn to page 2824 of this reference, there's a paragraph that -- under the heading Statistical Methods. Do you see where it says "Statistical Methods"?
A. Yes.
Q. Okay. You will see there's a paragraph on the right-hand side, under the heading Statistical Methods. The paragraph starts, "A modified intention to treat."
Do you see that?
A. Yes.
Q. Okay. Now, if you go about 12 lines down, you will see that it says:
"There is no significant differences."
I just want you to let me know when you get there.
A. Right side, "A modified attempt to treat," 12

lines down? I may be on the wrong page.
Q. Okay. Sorry. It says "exploratory endpoints." Apologies it take as little -- it's a little tough. I'm going to show you on mine, Doctor.
A. Oh, okay.
Q. Okay?
A. Yeah.
Q. All right. So let's start, make sure we're clear for the record that we're looking at Exhibit 1034, the Warr reference. We're on page 2824. You will see there's a heading that says "Exploratory Endpoints Include Complete Response in the Acute and Delayed Time Periods."
Do you see that?
A. Yes.
Q. Okay. And this means no emesis, no use of rescue therapy, and no significant nausea, right? And no nausea?
A. Let me make sure here. Yes.
Q. Okay. Now, if we could turn to page -- so in this study, no significant nausea, no nausea were viewed as exploratory endpoints, right?
A. Correct.
Q. Okay. If you could turn to 2827. In the left-hand side, three lines down from the top, it says:

"There was no significant differences between the two treatment groups in reports of overall nausea, VAS less than 5 millimeter; 33 percent for both, or significant nausea (VAS less than 25 millimeter; aprepitant 61 percent, control 56 percent)."

Did I read that correctly?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: Yes.

BY MR. ASHKENAZI:

Q. Okay. So you will agree with me that for aprepitant, for the aprepitant regimen being evaluated in the Warr reference, which is the third of the four studies that discussed in the Hesketh article, there was no -- no significant differences between the treatment groups for overall nausea and significant nausea, correct?

MR. TORCZON: Same objection.

BY MR. ASHKENAZI:

Q. Herrstedt.

A. It's a complicated answer. I actually had recent experience with exploratory endpoints and FDA opinions, and my understanding is you're not supposed to do statistics on them, that they're there for directionality and hypothesis testing. So, you know, clearly, the study was not powered to look at this, and

so...
Q. Well, let's be clear. It says there's no significant difference between two treatment groups in reports of overall nausea, VAS less than 5 millimeters, 33 percent for both. Do you see that?
MR. TORCZON: Objection. Relevance. Asked and answered.
BY MR. ASHKENAZI:
Q. Do you see that, Doctor?
A. I see the writing.
Q. Which means that the numerical value was 33 percent for both, for both treatment groups, right?
A. Correct.
Q. No difference in numerical value, correct?
MR. TORCZON: Objection. Misstates.
THE DEPONENT: For overall nausea, you're talking about?
MR. ASHKENAZI: Yes.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. And for no significant nausea, the aprepitant group had 61 percent and the control group had 56 percent in this Warr reference?
MR. TORCZON: Objection. Relevance.
///

BY MR. ASHKENAZI:
Q. Correct?
A. Correct.
Q. Okay. Let's take a look at Figure 4, which is on the next page. For total score involvement domain, Figure 4 does show a statistically significant difference, right, for the aprepitant group compared today the control regimen, right?
A. Correct.
Q. But for the nausea domain, there is no statistically significant difference for the aprepitant group compared to the control regimen in the Warr reference, right?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Well, once again, there is numerical, but not statistical significance.
BY MR. ASHKENAZI:
Q. And the numerical difference you're talking about is 50.5 percent for the control and 53.5 percent for the aprepitant regimen, right?
MR. TORCZON: Same objection.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. And, by the way, while we're here, you'll agree with me that it was known in the field that substance P

may play a relatively more important role in the pathogenesis of vomiting as compared to nausea, right?
A. In general, I would agree.
Q. Okay. And substance P, that is what binds to an NK-1 receptor, right?
A. Correct.
Q. Okay. So, in other words, NK-1 receptor antagonist, the mechanism for that was known to have a more important role in the pathogenesis of vomiting compared to nausea in the 2009 time period, right?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: No. As we discussed earlier, multiple things can cause nausea, and vomiting is a reflex. They're different physiological. One is a perception media; most likely it's in the cortex. One is a reflex meaning in one area of post treatment. So they're different mechanisms.
BY MR. ASHKENAZI:
Q. So let's make sure I get this right.
In other words, NK-1 receptor antagonists the mechanism that they work by were known to be more important -- have a more important role in the pathogenesis of vomiting compared to nausea in the 2009 time period, right?
MR. TORCZON: Same objection.

THE DEPONENT: In general, yes.
BY MR. ASHKENAZI:
Q. Okay. Now, going back to the Warr reference, if you could turn to -- again, we're in Exhibit 1034. I'm looking at page 2828, and it continues to 2829. This is the paragraph that starts, "In the present study."
A. Yes.
Q. Why don't you give yourself a few seconds and read that, and then I'll ask you a few questions.
A. The whole paragraph?
Q. Yeah, but briefly. I will point you to the specific part in a minute.
Okay, Doctor, you ready? All right.
So at the end of the Warr reference, Exhibit 1034, looking at pages 22 -- 2828 to 2829, there's a paragraph that starts, "In the present study." But specifically, I want you to go to the last word on page 2828. It says, "There." It continues:
"Was no significant effect of aprepitant on nausea."
Do you see that?
A. Yes.
Q. You have no reason to dispute that statement, correct?
MR. TORCZON: Objection. Relevance.

THE DEPONENT: Again, no -- I would add the word "statistically" significant effect.
BY MR. ASHKENAZI:
Q. But that's not what they -- they wrote, "There was no" --
A. Right.
Q. -- "significant" --
A. Correct.
Q. -- "effect of aprepitant on nausea" in the Warr reference.
That's what the authors wrote, correct?
A. Yes.
MR. TORCZON: Same objection.
THE DEPONENT: I'm sorry.
BY MR. ASHKENAZI:
Q. They're the ones who have access to the data, you don't have access to all their data, right?
A. Correct.
Q. Okay. So they would be in a better position, as the authors of any of these articles, to evaluate the differences that could be seen from the data, compared to you, right?
A. In general. I mean, there are papers that provide enough detail.
Q. But in general, the authors --

A. Under --
Q. In general, the authors are in a better position than you are to evaluate their data?
A. Yes, in general.
Q. Yeah. Okay. Why don't we move down a little in that paragraph. It says:
"The more pronounced effect of aprepitant of 5HT3 receptor antagonists on the prevention of vomiting compared with nausea implies that serotonin and substance P may play a relatively more important role in the pathogenesis of vomiting than of nausea, and that other neurotransmitters may also be involved in the pathogenesis of these symptoms, especially nausea."
Do you see that?
A. Yes.
Q. And I think, based on what you said earlier, you would agree with that statement. Right?
A. Yes, especially because of the sentence you skipped that says that they gave ondansetron in the control group for, what, three days versus only day one. So these were not identical groups of patients.
Q. You agree with the statement that I read?
MR. TORCZON: Objection. Relevance. Misstates.
THE DEPONENT: Yes.
///

BY MR. ASHKENAZI:
Q. Okay. With respect to nausea, you agree that there were other drugs different than NK-1 receptor antagonists that were thought can be used to specifically treat nausea, like olanzapine, correct?
MR. TORCZON: Objection. Relevance. Scope.
THE DEPONENT: I didn't review all nausea therapeutics in the scope here.
BY MR. ASHKENAZI:
Q. You -- you weren't evaluating nausea therapeutics to determine what a POSA would or would not do with standard therapy in 2009, correct?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Only as it relates to CINV. Motion sickness, no, sea sickness, no.
BY MR. ASHKENAZI:
Q. Sorry.
A. Space sickness, no.
Q. Let's -- let's look at this again.
With respect to nausea, you will agree with me that there were other drugs that -- withdrawn.
With respect to chemotherapy-induced nausea, you will agree with me that there were other drug -- drugs different than NK-1 receptor antagonists that were known that could be used to specifically treat nausea, like

olanzapine, correct?

MR. TORCZON: Objection. Scope. Relevance. Asked and answered.

THE DEPONENT: That were known to potentially try, but not known to treat it.

BY MR. ASHKENAZI:

Q. Okay. Did you evaluate what other drugs can be used, other than NK-1 receptor antagonists and 5HT3 antagonists, for treating nausea induced by chemotherapy, cancer chemotherapy?

MR. TORCZON: Same objection. Scope. Relevance. Asked and answered.

THE DEPONENT: That was outside the scope --

MR. ASHKENAZI: Okay.

THE DEPONENT: -- of my report.

BY MR. ASHKENAZI:

Q. Okay. And you were focussed on -- for the purposes of your report, you were focused on the standard of care, as you've put it, the triple therapy, and netupitant and other NK-1 receptor antagonists?

A. I was focused on the standard of care and the prior art to November 18th, 2009, and how that related to the claims.

Q. And the prior art being specifically Bös and Hoffmann, which disclosed netupitant?

MR. TORCZON: Objection. Misstates.
THE DEPONENT: It does misstate. Those were certainly direct citations, but the whole field, the casopitant, the effectiveness of aprepitant, and the FDA's approvals, the significance of the aprepitant effects, the netupitant effects.
BY MR. ASHKENAZI:
Q. Okay. Can we please turn to declaration page 34, please, for a second?
MR. TORCZON: While we're doing that, I think we are coming up on an hour again.
MR. ASHKENAZI: I am trying to make this --
MR. TORCZON: Just alerting. I'm sorry, which?
THE DEPONENT: 34.
MR. ASHKENAZI: Paragraph 62.
THE DEPONENT: Okay.
BY MR. ASHKENAZI:
Q. And I just -- this is your summary of opinions section. Is that accurate?
A. Yes.
Q. Because I just want to -- using this, I want to make sure I understood the process that you undertook with respect to the obviousness opinions here. Okay? Is that fair?
A. Yes.

Q. Yeah, sorry, Doctor. I know you're nodding, but you have to say --
A. Yes.
Q. -- "yes."
Okay. Now, the first step you did in the obviousness analysis, as we can see from paragraph 62, for this specific round is you evaluated whether the combination of prior art references, in this case MASCC and Hoffmann, disclosed the claim features of the two -- '826 patent, right?
A. Correct.
Q. Doctor, I -- I notice you keep looking over at counsel, so I'm just -- if we could, you know -- that's fine. Why don't we move on.
So the first step that you did in your obviousness analysis was look whether the prior art reference combinations that you're discussing disclose the claimed features of the specific claims that you were evaluating, right?
A. Correct.
Q. And then it says your next step you did was -- and then you then go on to say in your opinion that those references do disclose the limitations, correct?
A. Correct.
Q. And your next step, then, is to say that there

would have been a good reason to combine those references to arrive at the claimed invention, right?
A. Correct.
Q. Okay. In other words, you start with the references, you compare those to the patents, see if the combination is there, and then you evaluated whether or not there would be a good reason to combine those references. Is that an accurate representation of the exercise you undertook?
A. It's one way to describe it. I described it previously, actually, where I said I look at different things, reviews, primary, standard of care, patents, looked at all the available prior art to see what combinations, potentially, of those could be obvious to do.
Q. So you looked at all the prior art to see which combinations would disclose the claims of the invention, and then you evaluated whether or not there would be a reason to combine. That's what you're saying in paragraph 62, right?
MR. TORCZON: Objection. Misstates.
THE DEPONENT: I would like you to repeat that because that's not -- I don't think I exactly agree with that, but it's close.
///

BY MR. ASHKENAZI:
Q. Okay. You looked at all the prior art to see which combinations -- sorry.
A. Not all the prior art. I looked at the prior art that's referenced here.
Q. Okay. Now I think I get -- so you looked at the prior art that you reference in your declaration to see which combinations would disclose the elements of the claimed inventions.
Is that fair for the first step?
A. Yes.
Q. And then you evaluated whether or not there would be a reason to combine those references to arrive at the claimed invention. Is that accurate?
A. Correct.
MR. TORCZON: Objection. Relevance.
BY MR. ASHKENAZI:
Q. That's your obviousness analysis?
MR. TORCZON: I said it misstates.
MR. ASHKENAZI: Okay.
THE REPORTER: Sorry. Is there an answer?
BY MR. ASHKENAZI:
Q. You answered "correct"?
A. Yes, correct.
Q. Okay.

MR. ASHKENAZI: All right. Why don't we take a break.

(A recess transpires.)

BY MR. ASHKENAZI:

Q. Now, Doctor, we did discuss the -- in the Herrstedt reference, one of the aprepitant studies was the Schmoll reference.

Do you remember that?

A. Yes.

Q. Okay. So I would like to take a look at that.

MR. ASHKENAZI: I need to mark this as Exhibit 2073.

(Exhibit No. 2073 marked for identification.)

MR. TORCZON: Okay. You're marking this what?

MR. ASHKENAZI: 2073.

MR. TORCZON: Okay. I'm going to object on scope.

BY MR. ASHKENAZI:

Q. Now, Dr. Peroutka, this -- you're looking at Exhibit 2073. That is the Schmoll reference that was identified in the Herrstedt article, correct?

MR. TORCZON: Let me check.

THE DEPONENT: Yes.

BY MR. ASHKENAZI:

Q. And this is the aprepitant regimen -- I mean,

aprepitant study that you did not reference in your declaration, correct?

A. Correct.

Q. Okay. And the title is "Comparison of an Aprepitant Regimen With a Multiday Ondansetron Regimen, Both With Dexamethasone, for Antiemetic Efficacy in High-Dose Cisplatin Treatment." Is that right?

A. Correct.

Q. Okay. Now, if we look at page 1004, on the right-hand side, do you see that it's discussing here the aprepitant treatment regimen, which is aprepitant, a 5HT3, and a corticosteroid? Right?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: I really have to read it. I have to read the methods and all that. If you want me to take the time, I mean.

BY MR. ASHKENAZI:

Q. The point is, you didn't analyze this at all --

A. Correct.

Q. -- for your declaration, even though it was referenced in the Heshes -- Herrstedt article as one of the four phase 3 clinical trials on aprepitant, right?

MR. TORCZON: Object -- same objection. Scope. Relevance.

THE DEPONENT: I mean, happy to read it if you

want me to sit here and read it, to be able to answer you, but this is not something, you know, I've reviewed.
BY MR. ASHKENAZI:
Q. My question was: In your declaration, you did not reference the Schmoll reference, Exhibit 2073, or even analyze it for your opinions in this case, even though it was identified and referenced in the Herrst article as one of the four phase 3 clinical trials in aprepitant, right?
MR. TORCZON: Same objections.
BY MR. ASHKENAZI:
Q. Can you just take a look at the authors of the article?
A. Yes.
Q. Do you agree with me that the authors come from a number of different institutions and from Merck Research Laboratories?
MR. TORCZON: Objection. Scope. Relevance.
BY MR. ASHKENAZI:
Q. Did you answer that question?
A. Yes. I looked at the -- in some -- two of them looks like come from Merck.
Q. Okay. Now, you did discuss the Herrington reference in your declaration, correct?
A. Yes.

Q. Okay. So we will take a look at that. It's Exhibit 1016.

(Exhibit No. 1016 marked for identification.)

MR. TORCZON: Thank you.

THE DEPONENT: Thank you.

BY MR. ASHKENAZI:

Q. Do you have in front of you Exhibit 1016, the Herrington reference?

A. Yes.

Q. And, again, this is -- this is titled, at least the beginning, "Randomized Placebo-Controlled Pilot Study Evaluating Aprepitant Single-Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-Induced Nausea and Vomiting," right?

A. Yes.

Q. Okay. Let's look at the first paragraph.

You will agree with me that Herrington attributes the significant improvement in the control of acute and delayed emesis to palonosetron and --

A. I'm sorry. You said the first paragraph. I lost you there. Where is it first page?

Q. Okay. Let's read the first page.

A. Okay.

Q. First paragraph. You will agree with me, the

first sentence is referencing the fact that there is a significant improvement in the control of acute and delayed emesis due to palonosetron and aprepitant, right?

A. Yes.

Q. And they use the term "acute and delayed chemotherapy-induced emesis," which they abbreviate to be CIE, right?

A. Yes.

Q. And, again, emesis is vomiting, right?

A. Yes.

Q. Okay. Now, if we take a look at Table 4, which is on page 2084 of Exhibit 1016, you did review this table, correct?

A. Yes.

Q. Okay. And Table 4 is evaluating the severity of nausea using VAS, right?

A. Yes.

Q. Okay. And you will agree with me that there were three arms to this study, right?

A. Yes.

Q. Arm A was palonosetron with three-day aprepitant, right?

A. Yes.

Q. Arm B was palonosetron with one-day aprepitant,

right?
A. Yes.
Q. And arm C was palonosetron with placebo, right?
A. Yes.
Q. So that means that arm C did not have aprepitant, right?
A. Yes.
Q. And directly under the table is a paragraph, and Herrington determined that the incidence of all nausea, overall nausea, significant nausea, and the severity of nausea was not different amongst the three arms. Is that accurate?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: I'm trying to find the exact quote here. The incidence.
That is a correct statement, but misses my interpretation of the data.
BY MR. ASHKENAZI:
Q. Did you *say it's a correct statement?
A. It's the statistical -- no statistical difference, but when you look at arm C, it's higher than arm A or B on all five days, and when you look at the averages, days 2, 3 are above 25 averages, whereas it's -- it never averages above 25 on the VAS scale with arms A and B.

Q. So I just want to make sure that we have a full understanding here.

The study -- the authors of this article explicitly stated that:

"The incidence of overall nausea, significant nausea (greater than 25 millimeter on the 100 millimeter visual analog scale), and the severity of nausea was not different among the three arms (Table 4 and Figure 1).

Did I read that correctly?

A. You read that --

MR. TORCZON: Objection. Relevance.

MR. ASHKENAZI: Figure 2.

THE DEPONENT: That's what they said. And that's how they interpreted it.

BY MR. ASHKENAZI:

Q. Now, they did not -- the authors of this article did not make the interpretation that you're saying, which is, well, let's ignore the statistics and say I'm just going to look at the absolute values between arm C, arm A, and arm B, correct?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: It shows that, again, you see a numerical difference between A, B, versus C that almost definitely does not reach significance because it's a very small study, 26, 26, 16. So it's a very small

study. This is the first, to my knowledge, that I saw standard deviations with the nausea scores. And perhaps that's part of the issue that should be discussed in greater detail. There is variability amongst the patients. You know, the average of A is about 12 on the scale. The average of C is higher. But look at the standard deviations. I mean, there's wide variations. I mean, it's clear from the overall review that the -- the nausea scores in many patients, and I don't know if this is the one. Let me see if this is the paper that shows it. But the nausea scores are highly variable and the drugs apparently, the triple combo, help the majority based on median analysis. A lot of people are helped completely, and then there's some that aren't helped. And why that is, we don't understand that today. But this is supportive of the fact that I look at this and I say, I can do A or B, and on average, everybody has no significant, on average, the average patient in the trial had no significant nausea; C, on days 2 and 3, the average patient had significant nausea.

BY MR. ASHKENAZI:

Q. Dr. Peroutka, we've looked at all the studies that you asked us to look at on aprepitant. We looked at the Herrst, we looked at Schmoll, we looked at Warr,

we looked at Hesketh, we looked at Herrington, and we looked at the aprepitant label, we looked at Poli-Bigelli, right? I'm taking Campos to the side.

For every of those -- every one of those studies, besides for Campos, there was no statistically significant difference for the aprepitant regimen in treating nausea or severe nausea, correct?

MR. TORCZON: Objection. Misstates and relevance.

THE DEPONENT: There is a numerical improvement with the aprepitant that does not reach significance statistically based on the sample size done in the studies.

BY MR. ASHKENAZI:

Q. Okay. So let's make sure we're clear. For every study other than Campos, the aprepitant regimen did not have a statistically significant difference for treating nausea or significant nausea compared to the control in every study that we looked at, other than Campos. Is that accurate?

MR. TORCZON: Objection. Form. Misstates. Relevance. Asked and answered.

THE DEPONENT: Yes, with the caveat in that sample size.

///

BY MR. ASHKENAZI:
Q. Okay. You have not identified a single study other than Campos that has shown any statistically significant difference in the prior art for aprepitant -- for an aprepitant regimen treating nausea or significant nausea, correct?
MR. TORCZON: Objection. Relevance. Asked and answered.
THE DEPONENT: If you count the -- what did they call it? The composite. You call it the value. Then there would be data to support that.
BY MR. ASHKENAZI:
Q. That wasn't my question, though. So I'm asking you -- I want to be very clear -- you have not identified a single study other than Campos that has shown a statistically significant difference in the prior art for aprepitant -- for an aprepitant regimen treating nausea or significant nausea, correct?
MR. TORCZON: Same objections.
THE DEPONENT: Can I look at Campos again?
MR. ASHKENAZI: I said other than Campos. So can you please answer the question before we go to Campos?
MR. TORCZON: Same objections.
THE DEPONENT: I -- I would like to take the

time to review everything before I say that. But -- because of the -- the composite. But if you restrict it to no nausea -- let me see. Let me check one other thing. This is not made for easy checking.

Well, is it this one, the Poli-Bigelli, where before they did the multiple comparisons? So there was a statistical difference.

BY MR. ASHKENAZI:

Q. We've explained how Poli-Bigelli -- you'll agree with me that we explained that Poli-Bigelli, when you do the proper statistical analysis as shown in the 2008 Emend label, no longer considered any statistically significant difference for nausea or significant nausea for the aprepitant regimen, correct?

A. Correct.

MR. TORCZON: Objection. Scope and relevance.

(Discussion off record.)

BY MR. ASHKENAZI:

Q. Now, to go back to my question, Doctor, putting Campos to the side, you have not identified a single study that has shown a statistically significant difference in the prior art for an aprepitant regimen treating nausea or significant nausea, correct?

MR. TORCZON: Objection. Scope. Relevance. Asked and answered.

THE DEPONENT: I still say Poli-Bigelli did report that, and I take your point about the statistical correction.

Correct. Statistical differences were not identified with the sample sizes used, although there were numerical superiorities.

BY MR. ASHKENAZI:

Q. Okay. Now, with respect to Poli-Bigelli, we did discuss how the -- the -- that study, when evaluated in the 2008 FDA label for Emend IV, did -- no longer was reported as having a statistical significance for nausea or significant nausea for the aprepitant regimen compared to control, correct?

MR. TORCZON: Objection. Relevance. Asked and answered.

THE DEPONENT: Whether the analysis was correct, the statistical reanalysis, I can't judge this. I don't know exactly what they did.

BY MR. ASHKENAZI:

Q. But that's the way they reported it?

MR. TORCZON: Same objections.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. And now with respect to Campos, we did address how Campos was providing 400 milligrams of

aprepitant in 2001, two years before the FDA-approved label, on day 1 prior to treatment, 400 milligrams of aprepitant after treatment, and 300 milligrams every day, days 2 through 5. Is that accurate?

A. As I recall.

Q. Yeah?

A. Yes.

Q. And the FDA-approved label for aprepitant, the dose that the FDA approved for treating CINV was 125 milligrams on the first day and 80 milligrams days 2 and 3, correct?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. Now, I would like to take a look, if we -- you can put some of those references to the side.

I would like to -- now, you recall a Yeo reference?

A. I see Yeo.

Q. Okay. Well, I will say, then, Yeo. I am handing you what's been marked as been identified as Exhibit 1048. It is the Yeo reference titled "A Randomized Study of Aprepitant Ondansetron and Dexamethasone for Chemotherapy-Induced Nausea and Vomiting in Chinese Breast Cancer Patients Receiving

Moderately Emetogenic Chemotherapy."

Do you see that?

A. Yes.

Q. Okay. And this is a reference that you identified and discussed in your declaration, right?

A. Yes.

Q. Okay. If you could please turn to page 50 -- 532, and I want to focus on the second full paragraph, if we can.

Are you there, Doctor? I just want --

A. Yes.

Q. Okay. Great. You will agree that for the aprepitant regimen in the overall timeframe in cycle 1 of AC chemotherapy, there was no significant difference and no significant nausea and no nausea, correct?

A. There was no significant difference in anything.

Q. So is the answer to my question yes?

A. Yes.

Q. Okay. Why don't we take a look at Table 4, if we can.

Table 4 shows that the P value for the nausea domain between the aprepitant regimen and the standard regimen without aprepitant is greater than .05, correct?

A. For which one?

Q. Nausea.

A. For no nausea?
Q. Yes.
MR. TORCZON: Objection. Relevance.
BY MR. ASHKENAZI:
Q. I'm looking at Table 4, Doctor.
A. Ah.
Q. So let me state the question again.
The P value for the nausea domain for the -- for the -- between the aprepitant-based regimen and the standard regimen without aprepitant is greater than 0.05, correct?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Yes.
BY MR. ASHKENAZI:
Q. You will agree with me, however, that for the vomiting domain there is a statistically significant difference between the aprepitant regimen and the standard regimen, correct?
MR. TORCZON: Same objection.
THE DEPONENT: Yes.
BY MR. ASHKENAZI:
Q. Okay. And I want to turn to page 534 if we can. You'll see the first full paragraph, nausea and vomiting are frequently associated. Are you there?
A. Yes.

Q. Okay. Now, you will agree that the present study -- that this study revealed that the use of aprepitant-based anti-emetic regimens improved patient quality of life, especially on aspects of vomiting, but there was no difference in the nausea domain, correct?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: That's what it states.

BY MR. ASHKENAZI:

Q. That's what the data provided for and the authors concluded, correct?

MR. TORCZON: Objection. Foundation.

THE DEPONENT: That's what they concluded from a quality-of-life questionnaire, not from the actual traditional assessments of nausea, vomiting, CINV.

BY MR. ASHKENAZI:

Q. These patients -- now, have you ever heard of the -- this is a clinical trial review that's being -- I mean, article that's being provided for in the breast cancer -- I actually don't know what that -- withdrawn.

Let me start again.

This is a journal article, correct?

A. Breast cancer --

MR. TORCZON: Objection. Scope.

THE DEPONENT: It looks like one.

///

BY MR. ASHKENAZI:
Q. Okay.
A. I assume it is.
Q. And you will agree that this is a peer-reviewed journal article? We see the data was received, accepted, and published in 2008 on the first page, under the authors' names?
A. No, I would not agree with that.
Q. Okay.
A. I -- most journals today are pay for -- pay for play, pay for publication, and they don't go through any kind of peer review. You just pay $2,000 and you get them published. So I don't know this journal.
Q. You don't know this journal and -- but it's your belief that because it's in 2009, it was a pay for play without being --
A. It's possible. It's possible that it did not go through clinical review. You said, did it go. I -- I cannot state that.
Q. Okay. So I apologize.
Your point is, you do not know if this is a peer-reviewed journal article. Is that fair?
A. Yes.
Q. Okay. I wasn't trying to put words in your mouth. I want to make sure I understand what you're

saying. Okay.

Nonetheless, you do agree with me that it is a journal article that's being published and the conclusion of the authors was that the aprepitant regimen helps with emesis, but has no difference in nausea, correct?

MR. TORCZON: Objection. Foundation. Relevance.

THE DEPONENT: They also showed it had no statistical effect on acute or delayed vomiting. So there seems to be inconsistency with their conclusion.

BY MR. ASHKENAZI:

Q. Do you agree that that was their conclusion?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: That is what they state.

BY MR. ASHKENAZI:

Q. Okay. Now, when we talk about NK-1 receptor antagonists, just generally, do all NK-1 receptor antagonists function in the same way?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Define function, please.

BY MR. ASHKENAZI:

Q. Sure. Let's break it down.

You will agree with me that different NK-1 receptor antagonists will have different molecular

structures, correct?
A. Correct.
Q. Okay. Have you evaluated the similarity of the molecular structure between aprepitant and netupitant?
A. Just that they come in the -- from the same class, I read.
Q. When you say class, what does that mean? NK-1 receptor antagonists?
A. They have gross similarities when you look at them in this little chemistry in the patent. You know, there's -- they're very small variations.
Q. So it's your belief that aprepitant and netupitant have very small structural variations between the two of them?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Honestly, I'm not a medicinal chemist, so structures is not my specialty.
BY MR. ASHKENAZI:
Q. And that's really what I was getting at. You have not done an analysis to determine the similarity of structure between aprepitant and netupitant, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: I mean, I infer that they're different. They have to be different, obviously, but all that -- that's all I can say.

BY MR. ASHKENAZI:
Q. All right. And you do not know if aprepitant and netupitant bind the neural -- the NK-1 receptor in the same way, correct?
MR. TORCZON: Same objections.
THE DEPONENT: What do you mean by the same way?
BY MR. ASHKENAZI:
Q. Do they literally bind at the same place, with the same atoms interacting with each other?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: It's -- it's -- I did not review anything on that, and you look at the affinity, which gives you an indirect measure of the antagonism.
BY MR. ASHKENAZI:
Q. Affinity is just going to tell you whether or not there was antagonism, correct?
A. No, it doesn't tell you that at all. Affinity could be -- it could be an agonist.
Q. Okay. But let's take a step back. I am -- you have a number of different NK-1 receptor antagonists. That's what they're categorized. And they have different structures. You will agree with me that it's possible that between any two, there can be different ways in which they bind the NK-1 receptor?
MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Again, I mean, it's possible.
BY MR. ASHKENAZI:
Q. You haven't done any analysis to determine any similarities between aprepitant and netupitant with respect to its binding of the receptor or its interaction with the NK-1 receptor, correct?
MR. TORCZON: Objection. Objection. Scope. Relevance.
THE DEPONENT: Only indirectly in terms of the doses used in humans should be correlated with how well they bind, comparatively.
BY MR. ASHKENAZI:
Q. It's your belief that the dose is directly related with how well a compound binds. Is that -- is that correct?
MR. TORCZON: Objection. Misstates. Outside scope.
THE DEPONENT: That's way outside the scope. But it is one of the correlates. Bioavailability is another one. So it's a rough estimate. That in general would be true, doses that are very potent, you use a low dose if you have same bioavailability, and doses that are not very potent have a higher dose.
BY MR. ASHKENAZI:
Q. And you evaluated the difference between

netupitant and aprepitant with respect to bioavailability in your declaration?
A. No.
Q. Okay. Did you evaluate the specific doses that would be expected that could be used for netupitant in your declaration?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Only was it the dose that was saying 10 to a gram recommended doses.
BY MR. ASHKENAZI:
Q. And when you say 10 to a gram, what is that difference between the low dose and the high dose that you're referencing that was identified in the Bös patent?
A. I believe it -- well, let me look. Can I see the Bös patent?
Q. I thought I handed that to you already.
MR. TORCZON: I think you did.
BY MR. ASHKENAZI:
Q. It's in Exhibit 1014. Is it a 10,000-fold difference?
A. I have to look.
Q. Okay. It's a large difference?
A. Here it is. Let me see. You can point me to it or I can go through it.

Q. Well, why don't we put it to the side, because I, frankly, don't know where it is. So you're asking for a very specific thing.

I'll do, then, to point --

A. It's in my report. I know that.

Q. Okay. Let me ask my question a little differently, because my original question said, did you evaluate the specific dose that would be expected -- expected that could be used for netupitant for treating nausea in your declaration?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Let me review what I wrote and see. So Bös describes 10 to 1,000 that's 100-fold, right?

BY MR. ASHKENAZI:

Q. Okay. That's the -- that's the only thing you did to evaluate the dose that would be expected of netupitant to work for treating nausea, according to your opinion, right?

A. And I believe I read that it was 9nM affinity, which would be pretty much consistent with this.

Q. Did you evaluate what the affinity is for aprepitant in that same assay?

A. No.

Q. Do you know -- do you have any data whatsoever

to determine the comparison of affinity between aprepitant and netupitant in the prior art?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: It was out of scope. I didn't look it up.

BY MR. ASHKENAZI:

Q. I want to make sure we're clear. You did not evaluate any data to compare aprepitant to -- withdrawn.

Let me ask a different question.

Did you evaluate any data comparing aprepitant and netupitant that's in the prior art?

MR. TORCZON: Same objection.

THE DEPONENT: Let me think about that a little bit.

Specific data, some of the tables may -- in the back here might have data, but not in the prior art.

BY MR. ASHKENAZI:

Q. With respect to -- is it your opinion that a person of ordinary skill in the art would have a reasonable expectation that putting netupitant in a triple therapy would treat nausea in patients receiving cancer chemotherapy?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: I would say yes, based on the numerical differences seen with other similar agents.

BY MR. ASHKENAZI:
Q. When you say other similar agents, what agents are you referring to?
A. Aprepitant and casopitant.
Q. So you have not provided any data for casopitant for treating nausea, have you?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Casopitant?
MR. ASHKENAZI: Yes.
THE DEPONENT: We have one reference. Do you want to look at that? I'd have to refresh and look at it.
BY MR. ASHKENAZI:
Q. I'm asking you, have you provided -- have you analyzed in your declaration any data for casopitant asserting that it can be used to treat nausea in patients receiving cancer chemotherapy?
MR. TORCZON: Objection. Relevance. Scope.
THE DEPONENT: I did review casopitant data, and I just would have to refresh by looking back at it and seeing what it says. And, yeah, I didn't memorize it.
BY MR. ASHKENAZI:
Q. I'm not asking whether you've memorized it or whether you've reviewed the data. I'm asking: Have you provided an opinion in your declaration that casopitant

can be used to treat nausea in patients receiving cancer chemotherapy?

MR. TORCZON: Same objections.

THE DEPONENT: I would have to go through this whole thing and see if casopitant is summarized anywhere.

BY MR. ASHKENAZI:

Q. Sitting here right now, to the best of your recollection, given that that's 700-and-something pages in your declaration, can you recall providing an opinion that casopitant is effective for treating nausea in patients receiving cancer and chemotherapy?

MR. TORCZON: Same objections. Asked and answered.

THE DEPONENT: An opinion, I don't recall.

BY MR. ASHKENAZI:

Q. Okay. So the only data that you're referring to that you believe that shows an NK-1 receptor antagonist can be used to treat cancer chemotherapy -- withdrawn.

The only data that you were referring to when you said that aprepitant can be -- show numerical benefits -- withdrawn.

With respect -- knowing that you've said that now with respect to casopitant, is it still your opinion that a POSA would have had a reasonable expectation that

using netupitant in triple therapy would treat nausea in patients receiving cancer chemotherapy?
A. Yes.
Q. And why is that?
A. Well, again, the total response -- not the complete response but, whatever that term was, total response, where there was a benefit where nausea was included. Two, the data that I mentioned from Campos. And I know your objections to that, but when you look at the curve from other studies looking at the nausea, there's almost always a superiority, and I think if powered properly, you would get a statistical. I have total confidence that if you looked at the data, looked at the effect size on nausea of the other agents, and then you did a study with the appropriate number of patients, it would -- you could easily reach statistical significance. 49 to -- what was it? 49 to 39, you know, that's -- that's a big difference if you had more patients.
Q. You're aware that out of all of the articles that we've reviewed, a number of the authors have said that aprepitant is not effective for treating nausea in patients receiving cancer chemotherapy, correct?
MR. TORCZON: Objection. Misstates relevance.
THE DEPONENT: I disagree. You're focusing on

the no nausea. But if you read the two ones we talked about earlier in the amend, both Poli-Bigelli and -- was it Hes -- Hesketh, they both say it treats chemotherapy-induced nausea and vomiting.

MR. ASHKENAZI: Okay.

THE DEPONENT: In the article -- so if I can finish. Number 1, the authors of those two key pivotal phase 3s of netupitant say it, then almost assuredly they went through peer review in the journals they were in. They say it. Then number 3 -- I'll wait until you can listen. Number 3, the FDA agreed and said this drug treats chemotherapy-induced nausea and vomiting.

So you're focused on this one line of a exploratory and/or secondary endpoint with inadequate statistical power to show a statistical difference, but there is numerical and you've got authors, reviewers, and the FDA itself agreeing.

BY MR. ASHKENAZI:

Q. So let's go through what you have here. I want to make sure that I understand this correctly.

What you're relying upon are the netupitant studies that we reviewed, the four phase 3 clinical trials that you and I have discussed and Campos. Is that accurate?

A. Mainly the two pivotals, because that's what the

FDA reviewed.

Q. Okay. So your focus on the expectation that netupitant can treat nausea is the two pivotal studies that the FDA reviewed that are included in the FDA label. Is that accurate?

A. The FDA label says that, yes.

Q. That's accurate, right?

A. Yes.

Q. And that's -- that and Campos, that's your basis for saying netupitant treats nausea, correct?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: Well, the graph in Campos, taken that the dose is different, but also -- I'm trying to remember what -- it had the one -- the median was one for the overall, or it shows four different time points.

BY MR. ASHKENAZI:

Q. I'm sorry. I just want to make sure that I'm clear.

Your opinion that netupitant treats nausea is based on, essentially, just so we're clear, the two pivotal studies that are referenced in the aprepitant label and Campos. Is that accurate?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: No. There's Herrington.

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BY MR. ASHKENAZI:
Q. And Herrington. So we've got four references. I just want to make sure I have the totality, that I understand what you're basing your expectation that aprepitant can treat nausea. It's those four references?
MR. TORCZON: Objection. Misstates.
THE DEPONENT: Yeah. I -- I have to go through, but those are the four main ones.
BY MR. ASHKENAZI:
Q. Those are the ones that you're relying upon, aprepitant -- let's be totally clear. The four references that you rely upon to say that aprepitant can treat nausea are the two that are included in the FDA label, Campos, and Herrington. Is that accurate?
MR. TORCZON: Objection. Form. Misstates.
THE DEPONENT: Yes, those are the four main.
BY MR. ASHKENAZI:
Q. Okay. Now, other than that, you will agree with me that nausea as of 2009 still remained a significant issue for patients receiving cancer chemotherapy, correct?
MR. TORCZON: Objection. Objection. Foundation. Relevance.
THE DEPONENT: For a subset of patients.

BY MR. ASHKENAZI:
Q. For a subset of patients. Even though netupitant regimen using a 5HT3 and dexamethasone was already known in the art and being used for years, correct?
MR. TORCZON: Objection. Form.
THE DEPONENT: Used for years. Well, yeah, a few years. There was still room to go. We've talked about this. So you've run a mile and, you know, you're eight-tenths, nine-tenths done, you're not there yet to finish. The goal is the complete total response literally, the term that we're using differently, with no nausea, meaning ideally less than five, second best would be no significant, and then no emesis and no rescue.
MR. ASHKENAZI: Okay.
THE DEPONENT: So there was room to improve.
BY MR. ASHKENAZI:
Q. All right. And you will agree with me that you did not do a comparison.
With respect to Campos, what conclusion can be drawn -- well, withdrawn.
You would agree with me that despite having the data in Campos, Merck did not seek or receive FDA approval for the dosing regimen included in Campos,

correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: We discussed this. I don't know what they filed and didn't file.

BY MR. ASHKENAZI:

Q. Either they -- either Merck didn't file for approval for the dosing regimen in Campos or the FDA did not approve of the dosing regimen in Campos if Merck had filed it. Is that accurate?

MR. TORCZON: Objection. Scope. Relevance. Asked and answered.

A. Yes.

Q. Okay. Now, and just so we're clear, your belief that netupitant can be used for treating nausea is based on your assertion that aprepitant can be used for treating nausea in patients receiving cancer chemotherapy, correct?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: In part.

BY MR. ASHKENAZI:

Q. When you say in part, what's the in part?

A. Well, we reviewed this. The CNS penetration, if oral bioavailability, the NK-1 antagonism.

Q. So maybe just so my question is clear.

Your belief that netupitant can be used for

treating nausea relies on the fact that -- and is dependent on the fact that, according to you, aprepitant can be used to treat nausea in patients receiving cancer chemotherapy, correct?

MR. TORCZON: Objection. Misstates. Asked and answered.

THE DEPONENT: In part. Do you want me to repeat everything again? It's the same answer I just gave.

BY MR. ASHKENAZI:

Q. Well, no. You see -- okay. Let's break it up. Aside -- so the reason why you think netupitant can be used for treating nausea in patients receiving cancer chemotherapy is because the data that's contained in Hoffmann and Bös, and aprepitant, according to you, can be used to treat patients receiving cancer chemotherapy for nausea.

Is that accurate?

A. For CINV, yes, in part. But there's also the -- the casopitant data and there's also the fact that we know netupitant gets into the brain, at least in gerbils.

Q. And you provided no opinions on any casopitant data that you could recall in your expert declaration, correct?

MR. TORCZON: Objection. Scope. Relevance. Asked and answered.

THE DEPONENT: It is -- it is back here, and it's -- I vaguely remember it being in the text here, but I can't find it this second.

BY MR. ASHKENAZI:

Q. Well, let me ask you this question: Have you provided any analysis of comparison of that molecule for casopitant and netupitant?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: No, I haven't provided that.

BY MR. ASHKENAZI:

Q. Okay. And you haven't compared the molecules casopitant, netupitant, and aprepitant in terms of the molecular structural properties, correct?

MR. TORCZON: Same objection.

THE DEPONENT: Yes. That's beyond on the scope. I'm not a medicinal chemist.

BY MR. ASHKENAZI:

Q. And you haven't analyzed how casopitant, netupitant, or aprepitant bind with the NK-1 receptor antagonist, correct?

MR. TORCZON: Same objections.

THE DEPONENT: That was not in the scope.

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BY MR. ASHKENAZI:
Q. And you have not provided any data whatsoever comparing how casopitant, netupitant, or aprepitant, how long they remain bound or interact with the NK-1 receptor, correct?
MR. TORCZON: Same objections.
THE DEPONENT: Well, how long they're bound is a measure of affinity. Basically, the tighter you bind, the higher affinity you're going to have, so. But specifically, no, I did not find that in the scope.
BY MR. ASHKENAZI:
Q. You did not. So let's be clear. You did not analyze the affinity between casopitant, netupitant, and aprepitant for the NK-1 receptor, right?
MR. TORCZON: Same objections. Asked and answered.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. And you did not analyze, with respect to any other NK-1 receptor antagonist, the affinity that that NK-1 receptor antagonist could have compared to casopitant or netupitant, right?
MR. TORCZON: Objection.
BY MR. ASHKENAZI:
Q. Or aprepitant?

MR. TORCZON: Objection. Asked and answered. Scope.

THE DEPONENT: Correct.

MR. TORCZON: And relevance.

THE DEPONENT: Oh, sorry. I thought you were done.

Correct.

BY MR. ASHKENAZI:

Q. And you did not analyze, with respect to any other NK-1 receptor antagonist, the similarity of structure between those and casopitant, aprepitant, or netupitant, right?

MR. TORCZON: Same objections.

THE DEPONENT: You already asked me that, but correct.

BY MR. ASHKENAZI:

Q. And to be clear, with respect to any property whatsoever for any other NK-1 receptor -- NK-1 receptor antagonist, casopitant, aprepitant, netupitant, you haven't analyzed that?

MR. TORCZON: Objection. Form.

BY MR. ASHKENAZI:

Q. That question was a little messy. I'm going to repeat that again.

For any other property of the following

molecules, you haven't analyzed -- well, withdrawn.

With respect to any property of aprepitant, netupitant, casopitant, and any other NK-1 receptor antagonist, you have not provided any such analysis in your declaration?

MR. TORCZON: Objection. Scope. Relevance. Asked and answered.

THE DEPONENT: Well, the pharmacological profile NK-1 antagonism, they all have that. They're all orally bioavailable. And two have shown efficacy in CINV clinically, and casopitant and netupitant. And the third, netupitant had preclinical data, which was supportive of CNS entry, which was believed to be a predictor and a necessity to have in your profile as a drug.

BY MR. ASHKENAZI:

Q. Okay. Let's --

A. For CINV.

Q. I meant to cover something a little different in my question, so I'm going to try to rephrase it and maybe I can capture it.

With respect to NK-1 receptor antagonists that are in the prior art, other than casopitant and aprepitant, did you evaluate their -- any of their properties other than the fact that they -- withdrawn.

I'm sorry. I'm --

THE DEPONENT: Can we do a bio break real quick?

MR. ASHKENAZI: Yeah. Why don't we take a short bio break.

(A recess transpires.)

BY MR. ASHKENAZI:

Q. Dr. Peroutka, during the breaks, have you spoken to your counsel about the substance of any of your testimony?

A. Not really.

Q. Okay. When you say not really?

A. Well, he said -- he said hour and a half, and so he said I could text my wife.

Q. Okay. Yeah, no. I meant about the substance that we've been discussing.

Have you discussed that with your counsel during the breaks?

A. Nothing specific. Or like -- like we're going to go another hour and a half.

Q. Other than timing, did you discuss the substance of your testimony with your counsel during the break?

A. I'm trying to -- honestly, let me think. Just the general of how's it going, like the time.

Q. Other than time, did you discuss the substance of your testimony with your counsel during the break?

A. No, nothing specific.
Q. When you say nothing specific --
A. I mean, like how much longer and talking to my wife at the time.
Q. Other than how much longer and talking to your wife, did you discuss the substance of your testimony with your counsel during the break?
A. Let me think, because I was -- if I did any offhand. There is something I think, but let me get exactly what my question was. It was just an offhand comment.
I think I mentioned I thought that the complete response was a really good measure.
Q. What did your counsel say when you said that to him?
A. Nothing, really.
Q. When you say nothing really, did he say anything in response?
A. I don't even think he nodded.
Q. Okay.
A. He was on a computer.
Q. Did your counsel say anything to you that addressed the substance of your testimony during any of the breaks?
A. Not that I recall.

Q. Okay. Dr. Peroutka, is it your opinion that a POSA would have understood that as long as netupitant can penetrate into the CNS or the brain, it will treat nausea?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: It would treat CINV, would be the understanding of a POSA.

BY MR. ASHKENAZI:

Q. Okay. A POSA would not have an expectation that netupitant would be able to treat nausea if it could penetrate into the CNS or the brain, correct?

A. Same thing. There's like three things.

MR. TORCZON: Same objection and form.

MR. ASHKENAZI: I'll ask my question again.

Is it your opinion that a POSA would have understood that as long as netupitant can penetrate into the CNS or the brain, it will treat nausea from cancer chemotherapy?

A. It would treat CINV as defined by the field.

Q. And I'm not -- that's not my question. So let's focus to my question.

Is it your opinion that a POSA would have understood that as long as netupitant can penetrate into the CNS or the brain, it will treat nausea caused by cancer chemotherapy?

A. To the ex --

MR. TORCZON: Misstates.

THE DEPONENT: To the exclusion of emesis?

MR. ASHKENAZI: No. I'm just -- you can answer my question because it's really related to nausea. I'm not asking about emesis.

THE DEPONENT: I'll go back to the fact that I think the numerical directionality of the superiority of the nausea was real, and I think that given the proper powering, that it would. And I think a POSA looking at all the data, seeing that it was always better, if not statistically better, would be enough evidence to move forward and do a properly powered nausea study.

BY MR. ASHKENAZI:

Q. So I want to make sure that my question -- listen to my question, then, carefully.

Is it your opinion that a POSA would have understood that as long as an NK-1 receptor antagonist can penetrate into the CNS or brain, it will treat nausea for patients receiving cancer chemotherapy?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: I think there would be a high likelihood that they would think that, based on the data.

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BY MR. ASHKENAZI:
Q. So any NK-1 receptor antagonist that can penetrate into the CNS or the brain, according to you, can be used to treat nausea for -- as a result of cancer chemotherapy, correct?
MR. TORCZON: Again, that mis -- objection. Misstates.
THE DEPONENT: I think they would think it would have a high chance if properly powered.
BY MR. ASHKENAZI:
Q. And that's your opinion, that that's what a POSA would understand in 2009, correct?
A. If they reviewed the data, yes.
Q. And it's your belief that any NK-1 receptor antagonist that showed efficacy in preclinical studies, preclinical models for -- similar to foot tapping -- withdrawn.
Let me ask the question again?
It's your belief -- it's your opinion in this case that a POSA in 2009 would understand that any NK-1 receptor antagonist that showed efficacy in preclinical models like that of the foot tapping would be understood to be effective for treating nausea in patients receiving cancer chemotherapy?
MR. TORCZON: Objection. Misstates. Scope.

THE DEPONENT: I think a POSA would look at the foot tapping data as evidence of CNS penetration, and I think that based on the literature of the time, the prior art, they would think that essentially active NK-1 antagonists should be effective in the treatment of nausea if properly studied.

BY MR. ASHKENAZI:

Q. And it's your belief that a POSA in two thousand -- that it would be obvious for a POSA to use any NK-1 receptor antagonists that showed CNS penetration in preclinical data for the treatment of nausea in patients receiving cancer chemotherapy. Is that correct?

MR. TORCZON: Objection. Scope. Misstates.

THE DEPONENT: There was, like, three things, so if you could --

BY MR. ASHKENAZI:

Q. Let's take them one at a time. We're focused on 2009. Okay?

A. (Moves head up and down.)

Q. Yeah, if you say yes, then it's easier --

A. Yes.

Q. -- to break down the question.

So okay. It's your understanding that a POSA in 2009 would find it obvious to use any NK-1 receptor

antagonist that showed CNS penetration in preclinical data for the -- and that NK-1 receptor antagonist could be used for the treatment of nausea in patients receiving cancer chemotherapy, correct?

MR. TORCZON: Objection. Scope. Relevance. Misstates.

THE DEPONENT: Correct. If studied properly.

BY MR. ASHKENAZI:

Q. And it's your belief that a POSA would have the resources to evaluate any NK-1 receptor antagonist and identify netupitant as one to be used in the triple therapy identified by you in your reports as of 2009, correct?

MR. TORCZON: Objection. Scope. Relevance. Misstates. Asked and answered.

THE DEPONENT: It depends on your definition of resources, meaning, you know, intellectual resources to say, I want to mimic netupitant to the best of my ability and hope that maybe mine is better or come up with a different regimen, those resources, or are you talking financial resources?

BY MR. ASHKENAZI:

Q. I am -- I want to sort of understand what different tests -- do you think a POSA would be testing all NK-1 receptor antagonists to determine which ones

would be able to be used if they had CNS penetration from preclinical data for treating patients for nausea after receiving cancer chemotherapy.

MR. TORCZON: Objection. Form. Asked and answered.

THE DEPONENT: They would have interest, but whether they would have access and resources to actually do it is major impediment.

BY MR. ASHKENAZI:

Q. Okay. Now, so just so I understand correctly, when we look at the data that you had for netupitant in the prior art, you're focused on CNS penetration, which is evidenced from the foot tapping study. Is -- did I understand that correctly?

A. Correct.

Q. Okay. And that's really what you're focused on with respect to netupitant in terms of its ability to treat patients for nausea, correct?

A. Well, the affinity of it was good. The selectivity was stated to be good. So what was in the public domain, mostly Bös --

Q. Okay.

A. -- seemed like it would be a -- the next up, if you will, in line to be studied.

Q. And you evaluate it. But the only NK-1 receptor

antagonist other than aprepitant and casopitant that you evaluated was netupitant, correct?
A. I looked at the others, but I didn't see as much data with them.
Q. You didn't discuss that anywhere in your report, though?
A. Correct.
Q. And you didn't identify or go through any other NK-1 receptor antagonist in your report, other than casopitant and netupitant, right?
MR. TORCZON: Object.
BY MR. ASHKENAZI:
Q. And netupitant?
MR. TORCZON: Objection. Relevance. Scope.
BY MR. ASHKENAZI:
Q. I'm rephrase -- restate the question, because it got broken up there.
You didn't identify or go through any other NK-1 receptor antagonist in your report other than casopitant, aprepitant, and netupitant, correct?
MR. TORCZON: Same objections.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. Now, it's your opinion that you did evaluate the other NK-1 receptor antagonist, you just

didn't put it in your report, right?
A. I looked for information on others.
Q. Okay. Because that's something a POSA would have done, right?
A. Yes.
Q. Okay. Because a POSA would have considered the other NK-1 receptor antagonists that would have been available other than casopitant and aprepitant, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: They would have considered them, yes.
BY MR. ASHKENAZI:
Q. Yeah. And a POSA doesn't have unlimited resources in terms of time, money, or ability to conduct experiments, correct?
MR. TORCZON: Same objections. Asked and answered.
THE DEPONENT: As well as access to the molecules.
BY MR. ASHKENAZI:
Q. Okay. Now, and you said according to you, there were only a handful of other NK-1 receptor antagonists that were available that you considered. Is that accurate?
A. Only a couple two or three more that were out

there around that time, but at earlier stages.
Q. Okay. That's based on your review of the literature that you conducted for the declaration that you submitted in these IPRs, right?
MR. TORCZON: Objection. Asked and answered.
THE DEPONENT: Yeah.
BY MR. ASHKENAZI:
Q. Okay. Now I want to look at Hoffmann if we can, so I'm going to hand you Hoffmann. It's Exhibit 1011.
(Exhibit No. 1011 marked for identification.)
BY MR. ASHKENAZI:
Q. And this is one of the references that you have discussed related to netupitant, correct?
A. Correct.
Q. Okay. And do you have Exhibit 1011 in front of you?
A. Yes.
Q. Okay. And this is the Hoffmann reference that's titled "Design and Synthesis of a Novel Achiral Class of Highly Potent and Selective Orally Active Neurokinin-1 Receptor Antagonists," right?
A. Correct.
Q. Okay. Now, you will agree with me that Hoffmann is actually discussing a new class of compounds, which they refer to as a novel achiral class of highly potent

and selective orally active NK-1 receptor antagonists, right?

A. Correct.

Q. Okay. And you could see here on the first page that aprepitant does have a different chemical structure than those of the compounds that are being discussed in this article, Hoffmann, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Yeah. I mean, I'm not a medicinal chemist and, you know, they are obviously different because they're different molecules, but how different from a medicinal chemist point, I don't -- I am not able to opine.

BY MR. ASHKENAZI:

Q. Okay. Now, just to be clear, Hoffmann does say -- let's look at the abstract. Tell me when you're there. Hoffmann states:

"The evaluation of this class is briefly outlined, leading to the identification of netupitant, 21, befupitant, 29, and two new proprietary chemical entities with high affinity and excellent CNS penetration."

Do you see that?

A. Yes.

Q. And is it your belief that every one of those

four compounds would be effective for treating nausea in patients receiving cancer chemotherapy?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Well, it's possible, but there are the other factors of oral bioavailability, metabolism, et cetera.

BY MR. ASHKENAZI:

Q. Well, this is providing -- this is discussing high affinity and excellent CNS penetration, and that these are orally NK-1 receptor antagonists, correct?

A. Correct.

Q. Okay. So I want to make sure. I'll my question again.

Is it your belief that the four compounds identified in the abstract would all be effective for treating patients for nausea -- for nausea after receiving cancer chemotherapy?

MR. TORCZON: Object -- same objections.

THE DEPONENT: Yeah. There's a high likelihood.

BY MR. ASHKENAZI:

Q. High likelihood, at least 80 percent, as you referenced earlier, right?

A. Roughly, yes.

Q. And high likelihood that these would be FDA approved, correct?

MR. TORCZON: Objection. Relevance. Scope.

THE DEPONENT: As long as they were safe and effective.

BY MR. ASHKENAZI:

Q. And you believe there's no reason to believe they wouldn't be safe and effective, right?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: No. I said 80 percent drugs can always hit a speed bump of toxicity, metabolism, drug-drug interactions.

BY MR. ASHKENAZI:

Q. You think there's an 80 percent likelihood that these four drugs would all be able to be approved by the FDA -- withdrawn.

You believe that there's -- that a POSA in 2009 would believe there's an 80 percent likelihood that these four drugs that had preclinical data identified in the Hoffmann article would be able to be FDA approved for treating nausea in patients receiving cancer chemotherapy, correct?

MR. TORCZON: Objection. Form. Foundation. Scope. Relevance.

THE DEPONENT: I believe there -- there's a high probability that I estimated as a guesstimate 80 percent, roughly.

BY MR. ASHKENAZI:
Q. Okay. Now, you do agree with me that this article is discussing a class of compounds and they identified 31 compounds in here that are selective orally active NK-1 receptor antagonists, right?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Yeah, I see 31.
BY MR. ASHKENAZI:
Q. I'm sorry?
A. I do see 31 different ones.
Q. Okay. You haven't provided any reason to identify netupitant or to select netupitant other than -- withdrawn.
You haven't provided us with any reason to select netupitant or the other NK-1 receptor antagonists identified in this article, correct?
MR. TORCZON: Objection. Misstates. Foundation.
THE DEPONENT: Correct. It is not my expertise.
BY MR. ASHKENAZI:
Q. Okay. I should put something at the end of that, so I'm just going to.
You haven't provided us with any reason to select netupitant over the other NK-1 receptor antagonists identified in this article for treating

nausea, patients with nausea, as a result of cancer chemotherapy, correct?

MR. TORCZON: Same objections.

THE DEPONENT: Let me read here what I wrote.

Yeah. The ones that they identified as good oral availability, which we discussed, and CNS penetration would be higher up on the list, and then in the pharmaceutical world, there is going to be other factors, such as synthesis ease, how hard it is to make the molecules, solubility, formulation issues, et cetera. But the things we've already discussed, oral bioavailability and CNS penetration.

Q. Okay. I want to make sure we're clear. But you, in your declaration, have not provided us any analysis of a reason to select netupitant over the other NK-1 receptor antagonists identified in Hoffmann, Exhibit 1011, for treating patients for nausea as a result of cancer chemotherapy, correct?

MR. TORCZON: Objection. Foundation. Misstates.

THE DEPONENT: You're going to have to repeat that whole thing again because you're down the road and...

BY MR. ASHKENAZI:

Q. In your declaration, you have not provided --

A. Yeah.
Q. -- an analysis to select netupitant over the other NK-1 receptor antagonists discussed in Hoffmann for treating patients for nausea as a result of cancer chemotherapy, correct?
A. Correct.
MR. TORCZON: Same objections.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. And you did not evaluate the other pharmaceutical considerations that you say a POSA would put into place, like ease of synthesis, solubility, formulation issues, for netupitant and the other 31 -- other 30 NK-1 receptor antagonists identified in Hoffmann, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. And to be clear, Hoffmann doesn't have any human clinical data, correct?
A. Not that I'm aware of.
Q. And the only data that's provided in Hoffmann is an animal model studying in parables and in vitro CHO cells that are derived from hamsters, correct?
A. I would have to reread it to make sure that

that's correct.
Q. Is that correct to the best of your understanding right now, of your recollection?
A. Let me find it. Yes.
Q. Okay. Now, you'll agree with me that foot tapping only shows that the compounds is engaging with the receptor, correct?
A. No. Well, the way they do the study shows in the -- in the brain through an oral -- they inject agonist into the brain itself so that it gets -- the drug given orally goes up there.
Q. Okay. What we do know is that the studies that are provided in Hoffmann don't actually evaluate the ability to treat emesis in a patient, correct?
A. Correct.
Q. And they don't evaluate the ability to treat nausea in a patient, correct?
A. Correct.
Q. Okay. And you will agree with me that the data that's included in Hoffmann, Exhibit 1011, doesn't provide any information on adverse events that a compound can have, correct?
A. Correct.
Q. And we also know that we mentioned earlier that NK-1 receptor antagonists can have an adverse event

for -- of nausea, correct?

MR. TORCZON: Objection. Scope. Asked and answered.

THE DEPONENT: I don't believe we've really dove into that in great detail.

BY MR. ASHKENAZI:

Q. We did reference it, though, did we not?

A. We did.

Q. And you'll agree with me that NK-1 receptor antagonists can have an adverse event of nausea, correct?

A. Possibly.

MR. TORCZON: Same objections.

THE DEPONENT: Possibly, I said.

BY MR. ASHKENAZI:

Q. But none of the data that's contained in Hoffmann would provide any information on the adverse events of nausea for the compounds that's included in Hoffmann, right?

A. Correct.

Q. Okay. So if we could go to Bös, that's the -- you have that in front of you. It's Exhibit 1014.

A. I got it.

Q. Do you have that, Doctor?

A. Yes.

Q. Okay. Great. And the Bös patents which we have been referring to is US Patent No. 6,297,375. Is that accurate?
A. Yes.
Q. And this was published in October of 2001, right?
A. Correct.
Q. Okay. And the group that did this is from Hoffmann-La Roche, right?
MR. TORCZON: Objection. Relevance.
THE DEPONENT: Correct.
Q. That's the same group that is the author of the Hoffmann article, Exhibit 1011, correct?
MR. TORCZON: Same objection.
THE DEPONENT: Well, there's overlap, yes.
BY MR. ASHKENAZI:
Q. Now, if we look at the abstract of the Bös patent, it indicates that the compounds of the invention are related to a 4-phenylpyridine derivatives connected by a bridge-connecting oxygen or nitrogen to a phenyl derivative.
Do you see that?
A. Yes.
Q. Okay. And -- and, really, this is talking about a class of -- of compounds, correct? Or group of

compounds?
A. Correct.
Q. Okay. And if we turn to the summary of the invention, which is on the second page, column 2 of the Bös patent, you will see there that there's a formula 1, correct?
A. Correct.
Q. Now, the patent lists a number of different substitutions that can be substituted into the general formula, correct?
MR. TORCZON: Objection. Relevance. Scope.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. And you haven't done anything to evaluate the number of permutations or different molecules that could be made as a result of the formula contained in the summary of the invention of the Bös patent, right?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. I want to turn to column 18, line 42, if we can. It says the compounds of formula 1B is a pu -- withdrawn.
It says:
"The compound of formula 1B is a potent

selective antagonist at recombinant human neurokinin (NK-1) receptors expressed in CHO cells."
do you see that?
A. Yes.
Q. And you understand that's talking about the class of compounds that are in formula 1B, right?
A. No. Formula 1B is a specific compound, netupitant. It's not a class.
Q. Right. I'm sorry. I misspoke. Formula 1B is what's contained in column 14, right?
A. Yes.
Q. Okay. Now, if we look at column 18, line 64, you will agree with me that Bös includes data for a number of different compounds, correct?
A. Correct.
Q. And you haven't provided us an opinion to pick one compound over another with respect to the NK-1 affinity or activity, correct?
MR. TORCZON: Objection. Scope. Relevance.
MR. ASHKENAZI: I will ask my question a little differently.
With respect to Hoffmann, you did not evaluate or compare or provide us with an analysis of why you would select only netupitant over any of the other NK-1 receptor antagonists identified in Hoffmann, correct?

MR. TORCZON: Objection. Scope. Relevance. Asked and answered.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. And -- but it's your opinion that any of the compounds that are in Hoffmann that's showed efficacy in the in vivo studies for foot tapping would be effect -- would be expected to be effective for treating patients for nausea after receiving cancer chemotherapy, correct?

MR. TORCZON: Objection. Scope. Relevance. Misstates.

THE DEPONENT: The -- with the criteria we said, you know, selective NK-1, oral bioavailable, CNS active. That would be the criteria set that would be predicted, and the in Vivo, with the in Vivo, foot tapping.

BY MR. ASHKENAZI:

Q. So oral bioavailability just means that you could take it and it goes into the patient. It has some NK-1 receptor activity, and it's CNS -- it's able to penetrate to CNS. Those are your three criteria, correct?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: Those are three main ones that give a high probability of technical success.

BY MR. ASHKENAZI:
Q. And any NK-1 receptor antagonist that has those criteria would be expected to be able to treat patients for nausea after receiving cancer chemotherapy, right?
MR. TORCZON: Objection. Relevance. Scope. And asked and answered.
THE DEPONENT: They would have a high probability of technical success.
BY MR. ASHKENAZI:
Q. And that's based on the aprepitant data that you have identified for us from the clinical studies that we referenced earlier today, those two main pivotal phase 3 clinical trials and casopitant. Is that accurate?
A. Correct.
Q. And when I see the two phase 2 clinical trials, those are the -- phase 3 clinical --
A. Three.
Q. -- trials, those are the phase 3 clinical trials reported in the aprepitant label, correct?
A. Correct.
Q. Okay. And for the NK-1 receptor antagonist discussed in Hoffmann or Bös, you haven't provided any comparison of those to the properties of aprepitant, other than the fact that they are considered NK-1 receptor antagonists, right?

MR. TORCZON: Objection. Scope. Relevance. Misstates.

THE DEPONENT: No. I haven't provided.

MR. ASHKENAZI: Okay.

THE DEPONENT: It was not in my purview.

BY MR. ASHKENAZI:

Q. We had that problem again the negative with the no, so I will ask the question --

A. I'm sorry.

Q. -- again.

For the NK-1 receptor antagonist discussed in Hoffmann and Bös, you -- you have not provided any comparison of the property of those compounds with aprepitant other than to say they are considered NK-1 receptor antagonists, right?

MR. TORCZON: Same objections.

THE DEPONENT: I have not provided that analysis.

BY MR. ASHKENAZI:

Q. Okay. Now, have you provided us with any articles or references that connect CNS penetration to efficacy?

A. No. But it was sort of common knowledge that the area post stream is in the brain, and that the injections of this agonist to induce the foot tapping,

for example, had to go into the brain. So the location of the neurokinin antagonist had -- was assumed in the field, would be by a POSA, was a central site.

Q. Okay. So CNS penetration doesn't actually tell you anything about efficacy, but it does tell you that the compound can get to the brain. Is that accurate?

A. Correct.

Q. Okay. And you haven't provided -- well, withdrawn.

Okay. I want to shift gears for a moment and...

MR. ASHKENAZI: So, Doctor, I know we're not going to be able to finish the full hour. Do you want to take a short five-minute break now?

THE DEPONENT: Let's go.

MR. ASHKENAZI: Let's keep going? All right.

So I'm going to hand to you what's been marked as Exhibit 1001, but specifically for the patent 8,623,826.

(Exhibit No. 1001 marked for identification.)

BY MR. ASHKENAZI:

Q. And, Doctor, I just want to make sure we're on the same page.

As far as you're concerned, all the patents at issue in the IPR that are the subject of the IPRs, they all have the same specification essentially, but the

claims are different, right?
A. Well, they're different patents with different claims.
Q. But the specification is --
A. Similar.
Q. Similar. So if I refer to one of the specifications, that will be good enough for you?
A. Well, let's start and see.
Q. All right.
A. And then we can double-check.
Q. All right. Can we turn to example 5?
A. Column?
Q. It starts on column 16. It's the clinical efficacy study in the '826 patent.
A. Okay.
Q. And you reviewed this portion of the patent, correct?
A. Yes.
Q. And that includes Table 5?
A. Yes.
Q. Okay. Now, is it your belief that -- that -- just to make sure we're clear, looking at the data that we have in Table 5, you will agree with me that netupitant does have a statistically significant effect with respect to the endpoints considered when eval --

when you look at netupitant at 300 -- at 300 milligrams?

MR. TORCZON: Objection. Form. The one, two three -- the fourth column you're referring to was P listed 05 for each of the three, CR overall phase, clear response acute, and clear response delayed. Significant, PO5. So CR -- overall, CR acute phase, and CR delayed phase.

MR. ASHKENAZI: Can we go off the record?

(A recess transpires.)

BY MR. ASHKENAZI:

Q. Dr. Peroutka, are you ready to move on?

A. Yes. Yes.

Q. So in the '826 patent and all the patents since, you -- you will agree with me that they represent or provide data for the combination of palonosetron/netupitant for treating a number of endpoints for patients receiving cancer chemotherapy, correct?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. And you will agree with me that, as we see in example 5 from the data that's shown in Table 5, but also the data that's contained in Table 6, that the netupitant plus palo -- palonosetron, where netupitant

is 300 milligrams in its dose, provides a statistically significant difference for patients with respect to no emesis, correct?

MR. TORCZON: Objection. Foundation. Relevance.

THE DEPONENT: Okay. Wait. We're on Table 6, right?

BY MR. ASHKENAZI:

Q. Yes.

A. And no -- let me find it. No emesis. Oh, right at the top line. Okay. Now that I found it, say --

Q. All right. Let's start again.

A. Yeah, yeah. 300 milligrams shows --

Q. I want to focus -- I want to focus on palonosetron --

A. Right.

Q. -- and netupitant at 300 milligrams.

A. Right.

Q. And you'll see 300 milligrams of netupitant at -- given orally is considered a therapeutically effective amount, right?

A. Yes.

Q. Okay. And what we see here is that for palonosetron/netupitant at 300 milligrams, there's a statistically significant difference with respect to no

emesis, overall acute and delayed, correct?
A. Correct.
Q. And you will agree with me that when it comes to nausea for overall acute and delayed, that same regimen, palo plus netupitant at 300 milligrams shows a statistically significant difference, correct?
A. For no nausea?
Q. Yes. I'm sorry. No significant nausea.
A. Okay. Wait. Yes.
Q. Okay. And you will agree with me that for complete protection, netupitant at 300 milligrams and palonosetron showed a statistically significant difference for overall, acute, and delayed, correct?
A. Correct.
Q. Okay. In other words, it's your belief, and you would agree with me, that palonosetron/netupitant at 300 milligrams is effective for patients for treating nausea and vomiting, correct?
A. Compared to palo alone.
Q. Yes.
A. Well, it's better, so yeah. I mean, they're all good, but you're comparing -- the statistics is against palo alone, which is steroids.
Q. Okay. And you will agree with me that the palo plus aprepitant arm did not show statistical

significance for the data that's provided in Table 6, correct?

MR. TORCZON: Objection. Foundation. Relevance.

THE DEPONENT: Palo versus -- say which column again?

BY MR. ASHKENAZI:

Q. The last column, palo plus aprepitant at 285 milligrams, compared to palo alone did not show a statistically significant difference with respect to no significant nausea and complete protection, correct?

A. No, because that's a completely different study that -- you can't compare column 6 to column 1.

Q. Okay. So you can't compare between studies, is your point, right?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: It -- not when they're radically different.

BY MR. ASHKENAZI:

Q. Okay. So when we look at the Grunberg study, right, you will agree with me that Grunberg was evaluating palo plus aprepitant at 285 milligrams, right?

A. I have to double-check.

Q. Okay.

A. Can you give me Grunberg?
Q. I'm going to go get that.
Handing you Exhibit 1035, which is a copy of the Grunberg reference. Do you have that in front of you?
A. I do.
(Exhibit No. 1035 marked for identification.)
BY MR. ASHKENAZI:
Q. And the title of this article is "Effectiveness of a Single-Day Three-Drug Regimen of Dexamethasone, Palonosetron, and Aprepitant for the Prevention of Acute and Delayed Nausea and Vomiting Caused By Moderately Mutagenic Cancer Chemotherapy."
Is that right?
A. Correct.
Q. Okay. Now, you have that, but I'm going to ask you some other questions. I just want to make sure we had it.
Let's keep focus on the '826 patent and Table 6 for a moment. You're not disputing here that palonosetron/netupitant are effective when netupitant is given at 300 milligrams for treating patients for nausea and vomiting, right?
A. I'm looking for the -- well, the no nausea, there was no significant difference in overall and acute, but for the no significant nausea, it was

significantly better than palo alone. So triple was better than palo for no significant nausea, but only one of the three reached it for no nausea.

Q. Right. Now, based on the data you've seen here with numerical differences, it's your belief, at a minimum, that netupitant at 300 milligrams and palonosetron would be effective for treating patients for both nausea and vomiting, correct, as a result of cancer chemotherapy?

A. Correct. Correct. CINV.

Q. Just to be clear, because I want to make sure we are specific, it's both nausea and vomiting, correct?

A. It's vomiting. Where is -- let me see the vomiting data. No emesis. 300 was clearly significantly better than palo alone, and for no nausea, delayed but not overall, and for no significant, it was effective.

Q. All right. Just taking all the data that you have available to you, you would agree with me, not just Table 6, but all the data you have available, that it's your belief that netupitant plus palonosetron can be effective -- withdrawn. I'll ask the question again.

Taking all the data that you have available to you that you reviewed in this case, you believe that palonosetron plus netupitant at 300 milligrams would be

effective for treating both nausea and vomiting for patients receiving cancer chemotherapy, correct?

MR. TORCZON: Objection. Form. Relevance.

THE DEPONENT: Well, have these been Bonferroni corrected for multiplicity?

BY MR. ASHKENAZI:

Q. Is there -- so my question is: Based on all the data you have available to you, it's an opinion and you can say I don't know, but based on all the available -- the data that you have available to you that you've reviewed in this case, is it your opinion that palonosetron plus netupitant at 300 milligrams would be effective for treating both nausea and vomiting for patients receiving cancer chemotherapy?

MR. TORCZON: Objection. Form. Relevance.

THE DEPONENT: As the FDA did, I would want to say the multiplicity adjustment.

BY MR. ASHKENAZI:

Q. So it's your opinion that without evaluating the statistics for the data that we have in Table 6, you cannot make a determination on whether netupitant can -- would be considered effective for treating both nausea and vomiting when given at 300 milligrams with palonosetron?

MR. TORCZON: Objection. Scope. And -- I'm

sorry, I'm blanking here. Go on.

THE DEPONENT: Without the multiplicity correction, I can't say statistically. Numerically, yes, it looks effective.

BY MR. ASHKENAZI:

Q. I'm asking you your opinion right now.

Do you believe that based on all the data that you have reviewed in this case, that palonosetron plus netupitant given at 300 milligrams is effective for treating patients for both nausea and vomiting as a result of cancer chemotherapy?

A. Can -- C --

MR. TORCZON: Objection. Form. Scope. Relevance.

THE DEPONENT: For CINV, yes, the data --

BY MR. ASHKENAZI:

Q. I'm -- you keep putting in for CINV, and I'm saying for both nausea and vomiting, so I want to make sure we're clear. I don't know what the distinction you're drawing, so I'm going to ask the question again.

Is it your opinion based on all the data that you have had available, that you have reviewed in this case, that palonosetron plus netupitant given at 300 milligrams is effective for treating patients for both nausea and vomiting as a result of cancer

chemotherapy?

MR. TORCZON: Same objections.

THE DEPONENT: With both nausea and vomiting?

MR. ASHKENAZI: Yes.

THE DEPONENT: Yes.

BY MR. ASHKENAZI:

Q. Okay. Now, you did talk about the Grunberg reference in your declaration, correct?

A. Correct.

Q. Is one of your criticisms that you can't compare 300 milligrams of netupitant to 285 milligrams of aprepitant?

A. I'm sorry. That I can't compare 300 milligrams...

I don't know. That's a separate issue. My main complaint is that the patient population in the sample size was so small in the Grunberg paper.

Q. So your issue with the Grunberg paper is not really with the study design or with the doses that were provided, but rather the fact that the number of patients that were studied was too low. Is that accurate?

A. The patient --

MR. TORCZON: Objection. Form.

THE DEPONENT: I'm sorry.

MR. TORCZON: Misstates.

THE DEPONENT: Was the patient population. This -- this was moderately emetogenic therapy, and I'm trying to look up -- I would have to compare, and I'll take the time if you'd like, to go through exactly what these patients got, versus these patients.

For example -- can I say something?

MR. ASHKENAZI: Sure?

THE DEPONENT: So the Grunberg people, they can continue to get chemo for those five days, and that's unusual and that's probably why the numbers look relatively low. But I have to do a strict comparison of the dosing regimens and patient populations, the ages, if any of that's in here.

BY MR. ASHKENAZI:

Q. Okay. Doctor, let me ask you a question. Just I'm going to take a step back, if I can.

A. Mm-hmm.

Q. You would agree with me that a doctor would not change the aprepitant triple therapy unless they believed that the change would provide at least similar or better patient outcome, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Correct.

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BY MR. ASHKENAZI:
Q. Okay. And I'm going to broaden that out now to a POSA.
You would agree with me that a POSA would not be changing the aprepitant triple therapy unless they believe that the change would provide similar or better patient outcomes, correct?
MR. TORCZON: Objection. Scope. Relevance. Foundation.
THE DEPONENT: Correct.
BY MR. ASHKENAZI:
Q. Okay. And you would agree with me that a doctor would need to see clinical data for the proposed change to the triple therapy before administering that altered therapy to patients, correct?
MR. TORCZON: Objection. Scope. Relevance.
THE DEPONENT: It depends if it's a research physician working on aprepitant versus netupitant.
BY MR. ASHKENAZI:
Q. Okay. Let's broaden this out to a POSA right now.
A POSA would need to see clinical data for a proposed change to the triple therapy before administering the altered therapy to patients, right?
MR. TORCZON: Objection. Scope. Relevance.

Foundation.

THE DEPONENT: No, not necessarily.

BY MR. ASHKENAZI:

Q. That your -- it's your belief that a POSA would believe that it would be proper to treat patients with modifications to the triple therapy even though there was no data showing that that triple therapy would be effective in patients?

MR. TORCZON: Same objections.

THE DEPONENT: If there was a high likelihood of success, as there was in this case with the topics we discussed, CNS penetration, affinity, oral availability, then given that these numbers are not all 100 percent across the board, which is the ultimate therapeutic goal, maybe unrealistic, but that is the goal, and you've improved here from the double therapy, palo alone, column 1, then I'd be willing to try something new.

BY MR. ASHKENAZI:

Q. Okay. Let's make sure we're -- I want to make sure we're framing things right.

You said you would be willing to try something new, meaning a POSA would take a chance to try something new because the patient doesn't -- that the no therapy is 100 percent effective. Is that your position?

MR. TORCZON: Objection. Misstates.
THE DEPONENT: No standard of care was available that got to 100 percent.
BY MR. ASHKENAZI:
Q. And, therefore, a POSA would be willing to try something new, right?
A. If it had a high chance of success to match or succeed the existing standard of care.
Q. So the standard we're applying here is that a POSA would need to have a high chance of success that the resulting therapy would match or exceed the existing care, which was aprepitant in the triple therapy, correct?
A. Correct.
Q. Okay. Now, I -- just so we're clear on the -- just so we're clear on the -- what chemo cancer -- sorry, CINV is, the patient who is receiving CINV is being treated for cancer, correct?
A. Correct.
Q. The main drug that they are receiving to solve their ailments is the chemotherapy, correct?
A. In chemotherapy-induced nausea and vomiting, correct.
Q. In other words, the patient -- chemotherapy is what's being given to the patient to allow them to

treat -- to be treated for their cancer, right?
A. Correct.
Q. A side effect of the chemo -- the chemotherapy is nausea and vomiting, correct?
A. With certain agents, it -- I mean, it varies, but yes, a common side effect.
Q. Right. In other words, the chemotherapy -- I'm sorry. Withdrawn.
In other words, the drugs that are being used to treat chemotherapy-induced nausea and vomiting, those are to help treat the symptoms that are a result of the chemotherapy itself. Is that fair?
A. Correct. The adverse events.
Q. The adverse events. Thank you.
A. Adverse side effects.
Q. Okay. In other words, this is about the drugs that are being used at -- to treat CINV or chemotherapy-induced nausea and vomiting. Those are to allow the patient to receive their cancer treatment, right?
A. To make -- no. I would disagree with that. That maybe at one point in time was true, but nowadays it's more to make them feel as best they can.
Q. Okay.
A. So --

Q. Let's focus on 2009. As of 2009, the goal of the CINV treatments was not to actually treat the patient for the cancer, but, rather, to make it easier for them to undergo the cancer treatment. Is that fair?
A. Right, so they would feel better and not suffer from the adverse events.
Q. Right. And, therefore, the threshold for providing the drug to a patient that is suffering from CINV -- well, withdrawn.
With respect to netupitant and palonosetron, you have reviewed the data that was provided in the declaration showing that there's a synergistic effect between palonosetron and netupitant with respect to substance P. Is that accurate?
A. I've reviewed data --
MR. TORCZON: Objection to form.
THE DEPONENT: I'm sorry.
I reviewed data on the combination, and we can discuss this, quote, synergy.
BY MR. ASHKENAZI:
Q. Okay. Do you believe that there's a synergistic effect between netupitant and palonosetron with respect to the ability to inhibit substance P -- I mean, the ability to ask act as an -- to affect substance P?
A. I -- we can look at the data. I know what

you're talking about. It's a complicated situation because you're looking at EC50s, effective doses, and I would have to do much more due diligence on understanding if you have two different receptors in this assay system, which is not a standard assay system, if it's true synergy or just two different mechanisms, and in terms of EC50. See, they're not showing -- they're showing a shift of the curve, right? So do you multiply the two numbers or do you add them? So if you multiply them, you know, then it may not be any, quote, synergy, meaning synergy, you have to define. I would define it as 1 plus 1 equals greater than two.

Q. Okay. So I just want to make sure that I'm clear.

What you're saying is, you have reviewed the data that was provided to the patent office related to the alleged synergistic effect between netupitant and palonosetron, correct?

A. Correct.

Q. But you have not done the analysis to determine whether or not that synergistic effect is real. Is that accurate?

A. No. I -- I will accept the data as the data. You want to go to it, and we can maybe be more clear?

Q. Why don't you finish your answer, please. I'm a

little confused when you say -- well, withdrawn.

Let me just ask one question.

You said that you will accept the data as the data, but earlier you were questioning how you analyze the data. Is that right?

A. Correct. In terms of the word "synergy."

Q. Okay. Have you provided an analysis in your declaration on whether or not there truly is a synergistic effect between netupitant and palonosetron?

MR. TORCZON: Objection. Scope.

THE DEPONENT: Page 782.

MR. TORCZON: And relevance.

BY MR. ASHKENAZI:

Q. I'm sorry. I was asking you -- I had a question pending.

A. Yeah.

Q. Have you provided an analysis in your declaration on whether or not there is truly a synergistic effect between netupitant and palonosetron with respect to substance P?

MR. TORCZON: Same objections.

THE DEPONENT: I provided comments on what I think of the claim that there was synergy.

BY MR. ASHKENAZI:

Q. And is it your assertion that there is no

synergistic effect between netupitant and palonosetron with respect to substance P?

MR. TORCZON: Same objections.

THE DEPONENT: There are data with the two. Whether that's true synergy or not, I don't think can be determined from the provided data.

BY MR. ASHKENAZI:

Q. Okay. So you -- you have not provided an opinion one way or the other on whether there is a true synergistic effect with respect to palonosetron and netupitant related to substance P, correct?

MR. TORCZON: Objection. Scope. Relevance.

THE DEPONENT: Not on that narrow specific topic, no.

BY MR. ASHKENAZI:

Q. In other words, you would -- okay. Withdrawn.

You do agree with me -- you're not disputing the numerical values that are included in the declaration with respect to the EC50 values for netupitant and palonosetron, correct?

A. Correct.

Q. Okay. And I'm going to hand to you -- I'm going to hand to you what's an excerpt of Exhibit 1005. That's the prosecution history, and this is going to be a portion of the declaration that you referenced. Okay?

MR. ASHKENAZI: And, specifically, it's pages 341 through 349 from the prosecution history of the '826 patent.

MR. TORCZON: Can we just -- just for clarification, is the pagination our pagination?

MR. FLEISCHACKER: Yes.

MR. TORCZON: Okay. We don't have to mark it, then.

THE REPORTER: So don't mark it.

BY MR. ASHKENAZI:

Q. Doctor, so you have the data now in front of you, correct?

A. Correct.

Q. Okay. Now, when we're looking at Table 1, it is your assertion that you don't truly understand how the EC50 value -- EC50 data was evaluated in this table, correct?

MR. TORCZON: Objection. Misstates.

THE DEPONENT: Yeah, misstates. So I understand how it was generated.

MR. ASHKENAZI: Okay.

THE DEPONENT: But what's not clear, and additional data are needed, is a couple of things. One is, when you have -- EC50 is the effective concentration. If you block one class of receptors in

the case with 30 nanomolar netupitant, it goes 20-fold different, 40, right? You see that? It goes from two EC50 to 40. So it increases by a factor of 20, correct?

I'm asking you. Sorry.

And then plus palonosetron, it's a 30, which is 15. So drugs work differently. Drugs, first off, they work on logarithmic scales, not numerical scales. So pharmacology of receptor drug interaction. So in terms of -- for example, two is twice one, two is half of four, but in the log scale, one is considered -- three is considered half of ten on a log scale. I don't know if you're familiar with this, but. So that's one issue.

I don't know. I did not opine on all this we're adding here.

BY MR. ASHKENAZI:

Q. Well, okay. So let me ask you this question, though. I just want to make sure we have an understanding.

You haven't provided an opinion on whether or not a synergistic effect can be determined from Table 1 of the declaration that was submitted during the prosecution, which is Exhibit 1005, pages 341 to 350. Is that correct?

A. Well, in that specific question, I have not.

Q. Okay. Now, you do agree with me that at least

numerically, when you use -- for the EC50 values as being reported, the benefit of netupitant at 1 nanomolar and palonosetron at 2 nanomolar provides a 120 -- EC50 of 120 micromolar, correct?

A. Correct. That's what the table shows.

Q. And when you look at -- for that same dosage of netupitant, you had two as the EC50 value, correct?

A. Correct.

Q. For the same dosage of palonosetron, you had two at the EC50 value, correct?

A. Correct.

Q. Okay. Now, just so we understand correctly, it's your position that oral antiemetics are better than IV antiemetics, correct?

MR. TORCZON: Objection. Form. Foundation.

THE DEPONENT: Well, better in which way? Patient --

MR. TORCZON: Sorry. Scope. I'm done.

THE DEPONENT: Patient preference is always oral.

BY MR. ASHKENAZI:

Q. Okay. Let me break it down.

From your perspective, a POSA in 2009 would be focused on using antiemetics that were oral as opposed to IV, if they could, correct?

A. There's a patient preference for that. You would want the highest efficacy. So patients, for example, with triptans for migraine, IV sumatriptan is 96 percent, injectables 76, oral 56, roughly. So you -- as long as you don't lose potency, or efficacy, I should say, sorry, efficacy, my mistake, patients prefer oral.
Q. So while patients prefer oral, you will agree with me that a patient suffering from chemotherapy-induced nausea and vomiting, or potentially suffering from it, would prefer to take an IV drug over an oral drug. Isn't that right?
A. With the same efficacy?
Q. Yes.
A. I think they -- they can -- I mean, they can swallow.
Q. They can swallow, but you don't know if they vomit if that drug stays in their system, correct?
MR. TORCZON: Objection. Scope. Relevance.
BY MR. ASHKENAZI:
Q. I'm sorry. Is that correct?
A. If they vomit, you don't know they got absorbed.
Q. So developing an antiemetic in the 2009 time period, a POSA would be focused on developing an IV drug over an oral drug. You will agree with me on that?
A. Well, either would work. IV has certain

advantages and oral has certain advantages. It depends on when they're given. Like the predose, you don't need an IV for that. So --

Q. The predose, you don't know an IV, but the predose also requires you to get -- take on days two and three oral as -- I mean, the drug orally as well, correct?

MR. TORCZON: Objection. Foundation. Scope. Relevance.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. So let's make sure that we're clear.

A POSA in 2009 looking to develop a regimen for treating patients for CINV would prefer to give drugs that are IV as opposed to oral, correct?

A. I'm not sure I would agree with that.

Q. How --

A. I mean, you --

Q. Have you done that analysis?

A. No.

Q. For this case?

A. No. I'm giving my opinion.

Q. I'm sorry?

A. That's my opinion. I -- I'm not sure that's true. You have to ask the patients.

Q. You haven't done the analysis, looking at the literature, on whether a POSA would have focused on making an IV versus an oral antiemetic in 2009, correct?

MR. TORCZON: Objection. Asked and answered.

THE DEPONENT: Correct.

BY MR. ASHKENAZI:

Q. Okay. Now -- I'm sorry. One second, Doctor.

You haven't provided any evidence in the prior art that any 5HT3 receptor antagonist has an impact on substance P, correct?

MR. TORCZON: Objection. Form.

THE DEPONENT: What type of an effect?

BY MR. ASHKENAZI:

Q. I -- let's -- 5HT3 receptor antagonists do not work on the NK-1 receptor, correct?

A. Correct.

Q. Okay. So you haven't provided an opinion in this case that a POSA would have expected any 5HT3 antagonist as of 2009 to have an impact on substance P, correct?

MR. TORCZON: Objection. Form. Scope. Relevance.

THE DEPONENT: You have to define impact.

BY MR. ASHKENAZI:

Q. Okay. Do you believe -- did you provide an

opinion that any 5HT3 antagonist would have been expected as of 2009 to buy into the NK-1 receptor?

MR. TORCZON: Objection. Relevance.

THE DEPONENT: Well, they were most likely screened. So in the one patent we discussed, they talked about 50 other receptors. There's usually general screens across the panel.

BY MR. ASHKENAZI:

Q. I'm sorry. I just want to be clear. I'm asking what opinions you provided in your declaration. Okay?

A. Okay.

Q. Have you provided an opinion in your declaration that any 5HT3 receptor antagonist would reduce the binding of substance P or antagonize substance P as of 2009?

A. No.

MR. TORCZON: Same objection.

MR. ASHKENAZI: Doctor, I know you do have to get out of here soon, so I will pass the witness. No further questions at this time, although I reserve the right if you submit further declaration to ask further questions.

MR. TORCZON: Okay. Can we take a quick break off record?

(A recess transpires.)

MR. TORCZON: Back on the record.

Okay. We have no questions. Thank you very much for your time, Dr. Peroutka.

THE DEPONENT: Thank you, thank you, thank you, thank you, thank you.

MR. ASHKENAZI: Thank you. Why don't we go off the record.

(Proceeding Concludes at 5:48 p.m.)

REPORTER'S CERTIFICATE

STATE OF CALIFORNIA) ss.

I, DEREK L. HOAGLAND, CSR #13445, State of California, do hereby certify:

That prior to being examined, the witness named in the foregoing proceeding was by me sworn to testify to the truth, the whole truth and nothing but the truth;

That said proceeding was taken down by me by stenotype at the time and place therein stated and thereafter transcribed under my direction into computerized transcription.

I further certify that I am not of counsel nor attorney for nor related to the parties hereto, nor am I in any way interested in the outcome of this action.

In compliance with section 8016 of the Business and Professions Code, I certify under penalty of perjury that I am a certified shorthand reporter with license number 13445 in full force and effect.

Witness my hand this 16th of January, 2026.

_____
DEREK L. HOAGLAND, CSR #13445