UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS, INC., WOCKHARDT BIO AG and TEVA PHARMACEUTICALS USA, INC.,

Petitioners,

v.

ASTRAZENECA AB,

Patent Owner.

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IPR2015-01340

Patent RE44,186

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CROSS-EXAMINATION OF ANN E. WEBER, Ph.D.

Washington, D.C

October 27, 2016

Cross-Examination of ANN E. WEBER, Ph.D., a witness herein, called for examination by counsel for Petitioners in the above-entitled matter, was taken on Thursday, October 27, 2016, commencing at 8:07 a.m. at the law offices of Wilson Sonsini Goodrich & Rosati, 1700 K Street, N.W., Fifth Floor, Washington, D.C. 20006 before Cappy Hallock, Registered Professional Reporter, Certified Realtime Reporter, Certified Livenote Reporter and Notary Public in and for the District of Columbia.

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C O N T E N T S

Deposition of ANN E. WEBER, Ph.D.

October 27, 2016



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E X H I B I T S

PREVIOUSLY MARKED EXHIBITS



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E X H I B I T S (Continued)

PREVIOUSLY MARKED EXHIBITS



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E X H I B I T S (Continued)

PREVIOUSLY MARKED EXHIBITS



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P R O C E E D I N G S

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WHEREUPON,

ANN E. WEBER, Ph.D.,

A Witness called for examination, having been first duly sworn, was examined and testified as follows:

EXAMINATION

BY MR. CARSTEN:

Q Good morning, Dr. Weber.

A Good morning.

Q It's very nice to see you again.

A Nice to see you.

Q So we met before.

A Yes, we have.

Q I had the great pleasure of conducting your cross examination at trial in a district court action pertaining to saxagliptin.

Now, when we last had occasion to talk we were talking about invalidity of a particular patent, correct, the RE'186 patent?

A Correct.

Q And we were discussing it in the context of an opinion or series of opinions by Dr. Powers, correct?
A Correct.
Q You understand that today we are going to be talking also about the validity or invalidity of the RE'186 patent, right?
A Yes.
Q But this time we will be focused on a slightly different set of opinions relating to the alleged invalidity of that patent, right?
A That's my understanding.
Q And those are the ones that have been tendered by Dr. Rotella, correct?
A Yes.
Q You understand that you took an oath here today to tell the truth, correct?
A Yes.
Q And there is no reason you would have any difficulty in testifying completely and accurately and truthfully today; is that fair?
A That's correct.

MR. LIVINGSTONE: I don't want to interrupt the examination. Did you take an oath?

THE WITNESS: Yes.

MR. LIVINGSTONE: Sorry. I was over here writing something down. My apologies. It's early morning.

Q Dr. Weber, I have tons of materials here. So, as you know, Dr. Rotella had a declaration that had a bunch of exhibits, right?

A Yes.

Q And you had a declaration that had a bunch of exhibits; is that fair?

A There were exhibits, yes.

Q Sure.

I have done my level best to have at our fingertips, should you need them, the lion's share of the exhibits. If for some reason there is something else that you want to look at that I don't have here, just ask and we can take a quick break and I can get whatever you need to look at printed. This isn't designed to be a memory test. It's not designed to trick you in any way. If you

need to see something in order to fully and completely answer a question, just feel free to ask. Okay?

A Okay.

Q What I would like to do as the first order of business, though, is put your declaration in front of you.

MR. CARSTEN: This has been marked previously as AstraZeneca Exhibit 2056.

(Previously marked AstraZeneca Exhibit No. 2056, first referral.)

BY MR. CARSTEN:

Q If I could trouble you to look at that document and make sure it is accurate to the best of your knowledge.

A Yes, this looks like my report.

Q Okay.

It's a declaration, correct?

A Excuse me, my declaration.

Q And your declaration, if you turn to -- there are two series of pages at the bottom. There is a set that actually has the page number

of the document, so I, II, and then 1, 2, et cetera. And there is another series that says Page X of 129. We might have some difficulties here. I will do my best to make clear which I am referring to.

If you turn to Page 126 of the document. It's the last page. It's also 129 of 129.

A So 126 of 129 -- no, 129 of 129.

Q Yup, the very last page.

A Yes.

Q And that's your signature?

A It is.

Q Okay, and you say, "In signing this declaration," reading from Paragraph 1265, "I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent & Trademark Office."

Have I read that correctly?

A Yes.

Q And you say, "I acknowledge I may be

subject to cross-examination in the case, and that cross-examination will take place within the United States." Correct?

A Correct.

Q And, "If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination." Correct?

A Correct.

Q And then Paragraph 264 says, "I declare under penalty of perjury that the foregoing is true and correct." Right?

A Correct.

Q Are there any corrections you would like to make to this declaration?

A No.

Q To the best of your knowledge, it is truthful and accurate?

A Yes.

Q Let's turn to some of the legal standards that you were asked to apply in this document. So I'm looking at, starting at Page 14

of 129. And there there is a Section V called Legal Standards.

Do you see that?

A I do.

Q You said that you've relied upon AstraZeneca's counsel for the applicable legal standards governing your analysis and opinions, right?

A That's correct.

Q And if you turn to the following page, Paragraph 41, there you say, "I understand that for a prima facie case of obviousness, structural similarity between the claimed compound and the prior art compound is not enough. The prior art must also have suggested making the specific modifications necessary to achieve the claimed invention."

Have I read that correctly?

A You have.

Q Is that the legal standard that you were directed by AstraZeneca's counsel to apply in this case?

A That is part of the legal standard, yes.

Q And you did use that legal standard in forming your opinions with respect to the opinions you have tendered in this case?

A I did.

Q The next paragraph, Paragraph 42 says, "I understand that a 'lead' compound is one that is most promising to modify and that selection of a lead compound is guided by all of the compound's pertinent properties."

I have read that correctly?

A You have.

Q Is that a legal standard that you were asked to rely upon by AstraZeneca's counsel?

A Yes, it is.

Q And is that a -- is that a legal standard that you did apply in forming your opinions in this case?

A I did.

Q On the Paragraph 40, which bridges the two pages we have been discussing here, Pages 14

of 129 and 15 of 129, the bridging sentence says, "I have been told by AstraZeneca's counsel to assume the 'time of the invention' mentioned above to be no later than October 2000."

Is that an instruction that you received from AstraZeneca's counsel with respect to your opinions in this matter?

A It is.

Q You further say, "My opinion would not differ, however, if the filing date of February 16, 2001 applied." Correct?

A That's correct.

Q You didn't do any independent analysis to determine what the appropriate date to frame your analysis was. Instead you rather relied solely upon what AstraZeneca's counsel told you; is that correct?

A That's correct. I relied on these dates.

Q So you didn't look at provisional applications, et cetera, to determine when saxagliptin compound was first included in any of

those preliminary applications and so forth, correct?

A I'm aware of the preliminary applications, and I certainly had access to them, but I did not do that particular analysis.

Q Okay.

We will come back from time to time over the course of the day to Exhibit 2056, your declaration. I put it in front of you early, sort the first thing out of the gate, so you would have it handy in the event you wanted to look at it for any purpose over the course of the day as well. Okay?

A Okay.

MR. CARSTEN: So I would like to hand to you what has been marked as Exhibit 1001.

(Previously marked Mylan Exhibit No. 1001, first referral.)

MR. CARSTEN: I have copies for you as well.

MR. LIVINGSTONE: Thank you.

BY MR. CARSTEN:

Q I hope and trust this is a document that looks familiar to you.

A Yes, it does.

Q This is the re-issue '186 patent; is that correct?

A Yes, that's correct.

Q Okay.

And you considered this document and reviewed it carefully in connection with rendering your opinions in this case; is that fair?

A Yes, I considered this document and reviewed it in the case.

Q You reviewed it carefully.

A Yes, I read it and I reviewed it. I guess it depends on what you mean by carefully.

Q Well --

A But yes, I read it.

Q You're tendering opinions --

A Yes.

Q -- relating to the validity of the claims of the patent, correct?

A Yes.
Q You wouldn't do that if you hadn't read the document carefully, I presume; is that fair?
A If that's your definition, yes.
Q Let's turn to Column 88, if we could. That's towards the back. It's in the claims section.
Now, if we look at -- have you got claim 8?
A I do.
Q Now, if you look at claim 8 there are one, two, three, four, five, six, seven, eight different compounds identified in claim 8 plus pharmaceutically acceptable salts; is that correct?
A That is correct.
Q Now, with respect to the first compound depicted under claim 8, so that's Column 88 starting around Lines 45 to 52 or so. Have you got that compound?
A I have.

Q In this patent there's no data presented for this compound relating to potency against DPP-4, correct?

A I would have to go back and just --

Q Feel free.

A -- glance.

Q Sure.

A I believe that is correct. Again, there is likely, for example, mass spec data. There may be -- so if you're referring to biological data --

Q The question was there is no data relating to potency of that compound as the DPP-4?

A That is correct.

Q And by potency you understand I'm referring to in vitro data; is that correct?

A That's correct. I would assume that you are referring to an IC50 or a Ki at DPP-4 enzyme.

Q And those would be in vitro measures of potency?

A Ki and IC50 are in vitro measures of

potency.

Q With respect to the compound we have been discussing, the first one under claim 8 in Column 88, there is no data presented relating to activity in any in vivo studies; is that correct?

A Actually, let me just -- can I just have a minute to check something?

Q Absolutely. Again, as I said, it's not intended to be a memory contest. Feel free.

A So that is correct. There is no in vivo data.

Q Okay.

And there is no information presented here in the patent relating to the activity of any metabolites of that compound against DPP-4, correct?

A I think there would be not enough information in the patent to definitively say that there was no metabolite of this particular compound that may have been covered by the patent.

Q I'm asking about whether there is any data presented relating to data --

A If you are referring to in vitro potency data, then that would be correct.

Q And if I'm describing in vivo activity of a metabolite of that compound, that is also correct, right?

A That would be correct. There is no in vivo data for any potential metabolite of that compound.

Q Okay.

And there is no data provided regarding the interaction of this compound with the DPP-4 enzyme in the patent, correct?

A That is correct.

Q And there is no data relating to the safety of this compound, correct?

A There is no safety data in the patent, that is correct.

Q There is no efficacy data relating to this compound in the patent, correct?

A That's correct. There is no efficacy data for that compound in the patent.

Q And this compound, to your knowledge,

was never advanced to any clinical trials, correct?

A I'm not aware of any clinical trials that were conducted with that compound.

Q And this compound was never FDA approved, correct?

A That's correct.

Q So under your analysis in this case, and we will get to some of this a little later, but this compound would be a failure, exhibit a failure of others in connection with your work in this case, correct?

A So this compound by virtue of the fact that it was not FDA approved, and that was the standard I used for failure of others, yes, this would be a failure.

Q So just to be clear, the standard you applied for your assessment of failure of others was FDA approval, correct?

A That is correct.

Q And was that a legal standard that you were asked to apply by AstraZeneca's counsel in

connection with forming your opinions in this case?

A That -- can I have a minute, please?

Q Sure.

A So the legal standard that I was asked to apply, this is for the objective evidence of obviousness, was the failure of others in the prior art to fill -- to fill the need. And so the standard I applied was whether the compounds were in the prior art and whether they were able to fill the need for a diabetes medication in the United States. So that was FDA approval of compounds that were in the prior art prior to that, to the date of October 2000.

Q And that legal standard that you just described, was that provided to you by Astra's counsel?

A Yes. Yes, it was.

Q So they are the ones that selected the threshold question or the litmus test of FDA approval as indicative of failure or nonfailure; is that fair?

A Well, they provided me with the understanding that the failure of others in the prior art to fill the need. And so if you were talking about, if I was talking about filling the need for a compound to treat diabetes in the U.S., then that would be FDA approval.

Q Now, as of the priority date there had been no FDA approved DPP-4 treatment for diabetes; is that fair?

A There were no FDA approved -- FDA approved DPP-4 inhibitors for the treatment of type 2 diabetes as of the priority date?

Q Yes, that is correct.

A That is correct.

Q In fact, the first FDA approved diabetes treatment was sitagliptin; is that correct?

A If you are referring to the first FDA approved DPP-4 inhibitor for the treatment of type 2 diabetes and not a compound in the prior art, yes, the first one to be approved was sitagliptin that wasn't in the prior art.

Q And sitagliptin is your compound?
A Sitagliptin is Merck's compound, and I did work on that, yes.
Q Your team won what I think you referred to at trial as the Nobel Prize of medicinal chemistry for your work on sitagliptin, correct?
A Yes, we did.
Q You are a member of the Medicinal Chemistry Hall of Fame in part because of your work on sitagliptin?
A I would imagine, yes.
Q By any measure you would consider sitagliptin a success?
A So if you're referring to sitagliptin as a success because it is FDA approved, yes. It would be a success.
Q Well, even taking it away from that framework, you yourself, you consider sitagliptin to be a success in your career, don't you?
A Well, I would consider sitagliptin to be a compound that I worked on that achieved FDA

approval and is being used to treat patients with type 2 diabetes.

Q You are aware that it's the biggest selling of the four FDA approved gliptin compounds, correct?

A That's correct.

Q And you are aware that it's the biggest selling of the ten worldwide approved gliptin compounds, correct?

A That's correct.

Q Let me just ask. Is there any way in which you think sitagliptin is not successful?

A Not if you are referring to success in the marketplace or success in treating patients with type 2 diabetes, but no. No.

Q Now, vildagliptin, you are aware of the compound vildagliptin, correct?

A I am.

Q I don't want to quibble with you about terminology here. I understand that the compound that is now known as vildagliptin is a prior art compound to saxagliptin; is that correct?

A That is correct.

Q Now, I recognize that at the time, October 2000, vildagliptin was not known commonly as vildagliptin but rather the structure of the compound itself was known at that point, correct?

A That is correct.

Q Okay.

Vildagliptin, under your standard in this case, is a failure, correct?

A That is correct.

Q Now, vildagliptin is approved in Europe for treatment of type 2 diabetes as a DPP-4 inhibitor, correct?

A Vildagliptin is approved in Europe.

Q Okay.

Going back to the patent, you were talking about Exhibit 1001. We were talking about the compounds listed under claim 8. We had just finished discussing the first compound under claim 8. I would like to ask the same series of questions with regard to the second compound.

So with respect to the second

compound, the one that has the cyclobutane ring in it, do you have that, Dr. Weber?

A I do.

Q Is there any data presented in the specification of the RE'186 patent pertaining to potency data for that compound against DPP-4?

A No. There is no specific IC50 or Ki for this compound.

Q Is there any data presented with respect to that second compound under claim 8 with respect to in vivo data against DPP-4 or type 2 diabetes?

A That's correct. No in vivo data presented in the patent.

Q And there is no data presented regarding activity of a metabolite of that compound against DPP-4?

A That's correct.

Q And there is no data about the safety of that compound?

A No data about the safety of the compound in the patent.

Q No data about the efficacy of the compound in the patent?
A No data about the efficacy in the patent.
Q To your knowledge, it's never advanced to clinical trials?
A To the best of my knowledge, this compound has not advanced to clinical trials.
Q And it is not FDA approved?
A It is not FDA approved.
Q And under your analysis in this case that compound is also a failure?
A That's correct.
Q Okay.
With respect to the third compound under claim 8, the one at the bottom of Column 88 that has got the cyclohexyl group, do you see that?
A I do.
Q There is no data in the patent pertaining to in vitro activity against DPP-4?
A That's correct. No IC50 or Ki.

Q And no data presented relating to in vivo activity of that compound?
A No in vivo activity.
Q No information provided relating to interaction of that compound with the DPP-4 enzyme?
A That's correct.
Q No information provided regarding activity of a metabolite of that compound against DPP-4?
A No information about metabolites of this compound.
Q No information provided relating to safety of this compound in the patent?
A No information on safety.
Q No information about efficacy of this compound in the patent?
A That's correct. No efficacy data.
Q Under your analysis in this case that compound is also a failure, correct?
A This compound was not approved by the FDA and is a failure.

Q Okay.

There are five compounds at the top of Column 89 which is also part of claim 8, correct?

A That is correct.

Q Okay.

Now, one of the five compounds is saxagliptin; is that correct?

A That's correct.

Q With respect to the four compounds that are not saxagliptin, I'm just going to ask the same series of questions for expediency sake.

With respect to those four compounds, is there any data presented in the specification of the RE'186 patent relating to in vivo -- excuse me, in vitro activity against DPP-4?

A There is no specific in vitro data presented.

Q With respect to the four compounds that are not saxagliptin on the top of Column 89, is there any in vivo activity information presented in the specification?

A There is no data regarding in vivo

activity.

Q With respect to those four compounds at the top of Column 89, is there any information in the patent relating to activity of any metabolites of these compounds against DPP-4?

A No, there is no information on metabolites.

Q Is there any data in the patent with respect to those four compounds at the top of Column 89, not including saxagliptin, regarding interaction with the DPP-4 enzyme of those compounds?

A No data on interaction with the enzyme.

Q With respect to the four compounds at the top of Column 89, not including saxagliptin, is there any data on the safety of those compounds?

A There is no data on the safety of these compounds.

Q With respect to the four compounds at the top of Column 89, not including saxagliptin,

is there any information in the patent about the efficacy of those compounds?

A No, there is no efficacy information in the patent on these compounds.

Q Are you aware that any of the four compounds at the top of Column 89, not including saxagliptin, were ever advanced to clinical trials?

A My understanding is that these compounds were not advanced to clinical trials.

Q And are any of the four compounds we have been discussing FDA approved?

A No, none of these are FDA approved.

Q And under your analysis in this case the four compounds at the top of Column 89, not including saxagliptin, are failures, correct?

A That's correct. These would be failures.

Q With respect to claim 10, Column 89, have you got that, Dr. Weber?

A I do.

Q Okay.

There are a group of compounds identified here with respect to variations in R1.

Do you see that?

A I do.

Q But, generally speaking, there are two, if you will have it, classes of compounds identified here, and the difference between the two classes of compounds is the location of the cyclopropane ring on that five-membered ring containing a nitrogen.

Do you see that?

A I do see that, yes.

Q And is my loose terminology, would you agree with that, that the difference between those two sets of compounds has to do with the location of the cyclopropane ring in that area of the molecule?

A Yes. These two structures differ by the location of the cyclopropyl ring.

Q And the one on top has a 4,5-cyclopropane ring where the one on the bottom has a 3,4-cyclopropane ring?

A Actually that doesn't look to be numbered that way in this particular patent. But in general the terminology we have been using on the case, yes. This is the 4,5- -- the upper one is the 4,5- and the lower one is the 3,4-.

Q Thank you.

Now, with respect to the class of compounds at the bottom, what we have called the 3,4-cyclopropane compounds, there is no data in the patent relating to in vitro activity of that class of compounds relating to DPP-4, correct?

A That's correct. There is no specific in vitro data on these compounds.

Q No Ki, no IC50?

A No Ki, no IC50 on any of these compounds.

Q With respect to -- with respect to in vivo data, there is no in vivo data on these compounds in the patent?

A That's right. No in vivo data in the patent on these compounds.

Q And there is no information relating

to potential activity of potential metabolite of any of these compounds in the patent?

A That's correct, no metabolite information for these compounds.

Q And there is no data provided in the patent relating to interaction of any of those compounds with the DPP-4 enzyme, correct?

A That's correct.

Q And there is no data relating to safety of those compounds?

A That's correct. No safety data on these compounds in the patent.

Q No efficacy data in the patent about these compounds?

A There is no efficacy data in the patent on these compounds.

Q Under your analysis those compounds would be a failure, correct?

A None of these are FDA approved, thus a failure.

Q Let's talk about saxagliptin for a moment. In terms of the saxagliptin molecule,

there is no data in the patent relating to in vivo activity of saxagliptin against DPP-4, is there?

A No, there is no in vivo data on saxagliptin in the patent.

Q And there is no information in the patent relating to in vivo activity of saxagliptin, correct?

A That is correct. No in vivo data on saxagliptin is reported in the patent.

Q And there is no information regarding the activity of any metabolite of saxagliptin against DPP-4?

A That's correct. There is no metabolite --

Q And there is no data -- I'm sorry, did I interrupt you?

A Yes, you did.

Q I'm sorry. Please finish your answer.

A As I was saying, there is no metabolite data for the compound in the patent.

Q Thank you. If I ever do that again, feel free -- I will try my best not to interrupt

you.

A Thank you.

Q There is no data in the patent relating to the interaction of saxagliptin with the DPP-4 enzyme, correct?

A That's correct. No data about how saxagliptin interacts with the enzyme as presented in the patent.

Q And there is no safety data related to saxagliptin in the patent?

A Correct.

Q And there is no efficacy data on saxagliptin in the patent?

A That's correct, no efficacy data on saxagliptin in the patent.

Q And under your analysis in this case, saxagliptin is a success?

A So saxagliptin is FDA approved and thus a success, yes.

Q Now, as of 2000, Dr. Weber, DPP-4 was a feasible approach to developing a type 2 diabetes treatment, correct?

A So as of 2000 while there were many issues that still remained to be answered, people were looking at DPP-4 as a potential treatment for type 2 diabetes.

Q In fact, you yourself was spearheading a group at Merck that was targeting DPP-4 as a type 2 diabetes treatment, correct?

A Starting in 2000, yes, that's correct.

Q And as of 2000 potent DPP-4 inhibitors were known in the art, correct?

A Yes. There were many DPP-4 inhibitors that were known in the art.

Q Now, your work at Merck on the DPP-4 program, that was the project that led to the development of sitagliptin, correct?

A That is correct.

Q And I think we established that sitagliptin was the first marketed DPP-4 inhibitor for type 2 diabetes in the U.S., correct?

A That's correct. It was the first FDA approved DPP-4 inhibitor.

Q Now, even after sitagliptin had been

discovered, that wasn't the end of your work at Merck on that program, was it?

A No. We continued working on that program.

Q And, in fact, that work continued for probably ten years or more following the discovery of sitagliptin, correct?

A Some -- so that would be roughly the time frame, yes.

Q And as of 2000 you understood that other companies were actively developing DPP-4 inhibitors to treat type 2 diabetes, right?

A So I had reviewed the literature, so I was aware, for example, that Novartis had a program.

Q And Probiodrug had a program?

A I was aware of Probiodrug's program also.

Q And you were aware also of some academic groups that were prospecting the DPP-4 space as well?

A There were a number of publications

from academic groups on DPP-4.

Q Now, you disagree with Dr. Rotella's opinions in this case; is that fair?

A That's correct.

Q Okay.

And you disagree with Dr. Rotella's selection of a lead compound in this case; is that correct?

A That's correct. I do not agree with his selection of a lead compound.

Q Now, Dr. Rotella has identified a particular compound from one of Dr. Ashworth's publications as the lead compound; is that correct?

A That's correct.

Q Okay.

MR. CARSTEN: I'm going to mark this, or put it in front of you just so you have it. I will give you what is marked as Exhibit 1007.

(Previously marked Mylan Exhibit No. 1007, first referral.)

MR. LIVINGSTONE: Thank you.

BY MR. CARSTEN:

Q This is the Ashworth publication from which Dr. Rotella selects his lead compound; is that correct?

A That is correct.

Q And you reviewed this article back in the 2000s when you were working in this space, correct?

A Correct. That is one of the articles that I reviewed when I first started working on the DPP-4 program.

Q And you know that Dr. Rotella was also, as of 2000, was working in the DPP-4 space, correct?

A I'm not aware of the exact dates that he worked on DPP-4, but I am aware that he works for BMS and did work on the DPP-4 project.

Q Now, when you started working in the DPP-4 space at Merck, you had to start somewhere, right?

A That's correct. We had to start somewhere.

Q And among the first things you did was to in-license two compounds from Probiodrug, correct?

A That's correct.

Q And those are the P3298 compound and its alloisomer, correct?

A That's correct. We in-licensed P3298 and the alloisomer from Probiodrug.

Q Now, you've worked with a large number of medicinal chemists over the course of your career; is that correct?

A Again, it depends on what you mean by large, but yes, I have worked with many medicinal chemists over the course of my career.

Q And you understand that medicinal chemists can choose different starting points for their project, correct?

A I understand that there may be more than one starting points and medicinal chemists may choose different starting points.

Q In fact, you yourself in the Merck program chose both P3298 and its alloisomer to

carry forward, correct?

A We chose P3298 and we also in-licensed the allo compound.

Q And you were developing or working with the allo compound as well in tandem with P3298?

A It depends on what you mean by in tandem, but P3298 was our lead compound and the alloisomer was further behind.

Q But you were also actively developing that, too, correct?

A We had -- so again, by actively developing you mean were we doing clinical trials with that compound, no. But we were doing some preclinical studies on that compound.

Q Right.

And while you were working with the P3298 and its alloisomer, you also looked at the literature and tried to determine what the most potent compounds were, correct?

A When I initiated the, or when I started working on the program, yes. I surveyed

the literature not necessarily to understand what the most potent compounds were, but I did acquire that information as I surveyed the literature.

Q You are familiar with a publication co-written by you and Nancy Thornberry?

A Yes, I'm quite familiar with that publication.

Q And --

A Well, I guess it depends on which one you are referring to. But I assume you are going to show it to me.

Q I'm going to show it to you right now.

MR. CARSTEN: Exhibit 2161.

(Previously marked AstraZeneca Exhibit No. 2161, first referral.)

A Yes, I'm familiar with this publication as I co-wrote it.

BY MR. CARSTEN:

Q Now, I'm looking -- and this is a document that you considered in connection with your opinions in this case?

A This certainly is a document that I

re-reviewed as part of my opinion, but obviously this was my opinion when I wrote -- I mean, this was a document I wrote, yes. It was not in the prior art so it wasn't considered as part of my opinion of obviousness.

Q Okay.

And looking at Page 4 of 12 in the left-hand column you wrote -- I'm in the second paragraph up from the bottom -- "While we were waiting for results from our internal screening efforts we identified, we initiated SAR studies based on the known alpha amino acid derived inhibitors. The most potent inhibitor recorded in the literature that did not contain an electrophile was cyclohexylglycyl thiazolidide (7, Table 1) discovered by chemists at Ferring."

Do you see that?

A Yes, I see that.

Q Have I read that correctly?

A You have read that correctly.

Q And the Ferring group that you are referring to there is the one that resulted in the

Ashworth line of publications that we talked about in connection with this case; is that correct?

A So reference 27 is the Ashworth I publication, yes.

Q Okay.

Now --

MR. LIVINGSTONE: By Ashworth I you mean --

THE WITNESS: Exhibit 1007.

MR. LIVINGSTONE: Thank you.

BY MR. CARSTEN:

Q If you look at Table 2, which is also on Page 4 of 12 on Exhibit 2161, there is a series of compounds there. Correct?

A That's correct.

Q The first four of those have a sulphur in the ring, correct?

A That's correct.

Q The following three compounds do not have a sulphur in the ring. Instead they have a methylene unit where there is an X in the ring, correct?

A That is correct.
Q Now, this information that you are reporting here, this is all Merck information, correct?
A So as we discussed at trial, this sentence actually has a number of mistakes in it.
Q I'm not talking about the sentence. I'm talking about the table.
A Right, and so the table, these compounds we synthesized at Merck. So -- can you just repeat your question because I thought you said that these were Merck compounds.
Q The data that is reported -- let me change the question then.
The data that is reported in Table 2 were data that were generated at Merck in connection with its DPP-4 program?
A That is correct. These are our data, the IC50 data from our assay tests.
Q And the compounds that are being described here, compounds 7 through 16, those were compounds prepared at Merck in connection with its

DPP-4 program?

A That is correct. We prepared these compounds for our DPP-4 program.

Q Right, and these compounds were modeled off of or analogs of some of the compounds that were disclosed by the Ashworth group from Ferring, correct?

A I wouldn't characterize it as that. As we indicated in the paper, P3298 was our lead compound. It contained the key thiazolidine P1 substituent. And we incorporated the teachings from this Exhibit 1007 into that P3298 lead, and that is how we ended up with compound 7. Then we analogued compound 7 and then later went back and made the -- which those are compounds, for example, 8, 9, 10, those are three of the many compounds that we made. Based on that, and then we went back later and made the pyrrolidine analogs.

Q So you went back later and took out the sulphur and replaced it with a methylene for that series of compounds; is that correct?

A That's correct.

Q Now, one of your criticisms of Dr. Rotella's selection of a lead compound is that a person of ordinary skill in the art would not have chosen the Ashworth compound 25 from Exhibit 1007 for fear that it may liberate a cyanide moiety; is that fair?

A No.

Q Well, if we turn to your report at Paragraph 117 -- let me know when you have that.

A I have it.

Q So am I incorrect when I say that one of your criticisms of Dr. Rotella's selection of the cyano-containing compound is concern about the potential for toxic cyanide release?

A So the reason why I -- why I had issues with his selection of a compound had do with the fact that there were two compounds known at the time that had advanced into clinical studies where there was human clinical data, and that there was very limited data on compound 25 including just stability and in vitro data.

Q So let me make sure I understand. So you do not criticize Dr. Rotella's selection of Ashworth compound 25 for fear of toxic cyanide release; is that your testimony?

A So when I was talking about the toxic cyanide release I was actually describing our program at Merck, and really explaining why we had elected not to have a nitrile in the molecule.

Q And that is a concern that -- that doesn't have anything to do with your criticisms about Dr. Rotella's selection of compound 25 from Exhibit 1007; is that your testimony?

A So there was no information -- there was no information. This was a hypothetical concern. And so my selection of a lead compound was really based on the data that was known in the prior art, which included clinical data on P3298 and NVP-DPP728 and very limited data on the hundreds, probably thousands of other molecules that have been reported in the literature, among which compound 25 was one.

Q Well, if you turn to Page 69 of your

report, Paragraph 155, that shows the structure of NVP-DPP728, correct?

A That's correct.

Q And NVP-DPP728 was one of the compounds that you identified as being a suitable lead compound that a person of skill in the art would have selected instead of Ashworth compound 25, correct?

A That's correct. DPP728 had been advanced to clinical trials, and that is why I chose this as one of the two that would have been selected over compound 25.

Q Now, the same concerns that you had expressed about potential for toxic cyanide release also apply to NVP-DPP728, correct?

A As I mentioned, that was a hypothetical concern. However, it was known in the prior art that NVP-DPP728 had advanced to clinical trials. So I think it was safe to assume that Novartis was not seeing cyanide release with this compound.

Q So the potential for toxic cyanide

release of a nitrile-containing compound on the P1 moiety, that's not a reason why somebody would have gravitated away from choosing Ashworth compound 25 as a lead compound, correct?

A So, as I said, my choice of a lead compound was based solely on the fact that two compounds had advanced into clinical studies. So as a medicinal chemist of ordinary skill in the art, it would be safe for me to assume that those compounds had sufficient safety data, sufficient efficacy data, sufficient in vitro potencies, stability, et cetera, in order for them to be developed as potential treatment for type 2 diabetes.

Q And the portion of the molecule we are talking about here, the P1 portion, that is the same as the P1 portion in Ashworth compound 25, correct?

A So NVP-DPP728 has the same P1 substituent as Ashworth 25.

Q Now, when you elected to initiate structure activity relationship studies with the

compounds such as those described in Table 2 of Exhibit 2161 --

A I think, I believe I said that we initiated structure activity relationship studies with P3298 and that led to the compounds in Table 2.

Q So you say in this article, "we initiated SAR studies based on the known alpha amino acid derived inhibitors. The most potent inhibitor reported in the literature which did not contain an electrophile was cyclohexylglycyl thiazolidide," right?

A I think you're missing the part in the paragraph before where I said, "we focused initially on identifying the 'Best in Class' compound by improving on the potency of isoleucyl thiazolidide," and we did that by incorporating the teachings of the Ashworth I paper.

Q Right.

So if a person of skill in the art relied upon Ashworth I to inform their development of a DPP-4 compound in the year 2000 time frame

that would not be unreasonable, would it?

A I think the reliance on Ashworth I that's a hypothetical question, and the reliance on Ashworth I would really depend on the context in which the person was developing their program.

Q But you yourself relied on the Ashworth publications in 2000 to inform your own development at Merck of a DPP-4 inhibitor, correct?

A We started with P3298 as our lead, and so that was an alpha amino acid reversible inhibitor. So I think in that case it was proven of us to rely on Ashworth I. However, if you would have started with NVP-DPP728, which is an N-linked DPP-4 inhibitor, then I don't think there is anything in Ashworth I, which are C-linked compounds, that's going to inform upon --

THE REPORTER: I'm sorry. I need you to slow down. Too many syllables. Thank you.

MR. LIVINGSTONE: You've got the hardest job here.

MR. CARSTEN: I'll second that.

THE REPORTER: I beg your pardon. I just can't keep up.

THE WITNESS: Okay.

THE REPORTER: Thank you.

A We started with P3298, which is a C-linked reversible DPP-4 inhibitor. And in that case it made sense for us to turn to Ashworth I to understand the teachings of Ashworth I because she also describes C-linked reversible DPP-4 inhibitors.

However, if one had started with NVP-DPP728 as a lead compound, that compound is N-linked and so in that case you wouldn't turn to Ashworth I for guidance.

Q And just for clarity, Ashworth I is itself C-linked, correct?

A The compounds in Ashworth I are C-linked reversible DPP-4 inhibitors.

Q Now, you are familiar with a 1993 paper to the Mentlein group?

A Yes.

Q And just for clarity, let me put that

in front of you.

(Previously marked AstraZeneca Exhibit No. 2096, first referral.)

MR. CARSTEN: It has been marked as Exhibit 2096.

MR. LIVINGSTONE: I'm sorry.

BY MR. CARSTEN:

Q You recognize this one?

A I do.

Q Now, so 1993, that's about seven years ahead of where the time period that we are talking about in connection with the time of invention or the priority date as you are applying it here, correct?

A That's correct.

Q And Mentlein is a discussion of inhibitors of DPP-4 enzyme, correct?

A That's not correct. He is discussing substrates in this paper.

Q And by substrates you're talking about things that DPP-4 will cut naturally, correct?

A If by -- well, if by naturally you

mean in vitro substrates?

Q Sure.

A He's discussing substrates or peptides which DPP-4 will cleave in vitro.

Q And if you look at the abstract on Page 1 of 7, the last line, it says, "The relevance of this finding for their inactivation and their determination by immunoassays is discussed." Correct?

A That is correct. He's talking about cleavage of the substrates to give inactive forms.

Q Figure 4 of Mentlein -- that's Page 5. Let me know when you have that, Dr. Weber.

A Yes.

Q So Figure 4 is a schematic that represents in sort of a cartoon fashion the binding pocket of DPP-4, correct?

A This is correct, and he's representing substrate binding in this scheme.

Q And in Figure 4, the legend, it says, "Proline and alanine fit in the hydrophobic P1 substrate binding pocket," right?

A That's correct.
Q "Whereas serine appears to be too hydrophilic to yield appreciable binding." Correct?
A That's correct.
Q It goes on to say, "In the P2 position bulky ammino acids with an obligate free amino group are preferred"?
A Yes, bulky amino acids are preferred for substrates.
Q You agree with me that an adamantyl group is bulky, right?
A I would imagine that most medicinal chemists would consider adamantyl a bulky group, yes.
Q And hydroxy adamantyl is also a bulky group to most medicinal chemists in October of 2000?
A Yes.
Q And just to clarify the question before, put some time frame on that, as of October 2000 most medicinal chemists would have considered

adamantyl to be a bulky group, correct?
A That is correct.
Q Now, proline has a five-membered ring containing nitrogen within it, correct?
A That's correct.
Q And you've seen, in the course of both your work at the time as well as the work that you've done in connection with this case, a number of references which discuss a preference in the P1 position for a five-membered ring; is that fair?
A Yes. They are both in terms of substrates and inhibitors, a five-membered ring is preferred.
Q Okay.
MR. CARSTEN: Want to take a short break? We have been going about an hour.
(Recess taken -- 9:07 a.m.)
(After recess -- 9:21 a.m.)
BY MR. CARSTEN:
Q Welcome back, Dr. Weber.
A Thank you.
Q So now we were discussing the Mentlein

article, Exhibit 2096, when we broke. In terms of the Figure 4 legend, you don't disagree with what the Mentlein group is reporting here about proline and alanine fitting within the hydrophobic P1 substrate binding pocket, do you?

A No. Again, they are talking about substrates, and substrates with proline and alanine at P1 are known substrates of DPP-4.

Q And you don't disagree that, "In the P2 position, bulky amino acids with an obligate free amino group are preferred," either? That's all correct?

A That's what they report and I have no reason to doubt that.

Q Okay.

Now, you are also aware that in the prior art there was a use in connection with a DPP-4 inhibitor compound of an adamantyl hydroxy substituent, right?

MR. LIVINGSTONE: Objection, form.

A So I'm sorry, can you --

Q I will rephrase it.

A Yes.
Q You are aware in the prior art there is an example of a DPP-4 inhibitor compound that contained hydroxy adamantyl moiety, correct?
A Yes, I'm aware of the patent literature and there were patents -- there was a Villhauer patent, for example, that contained a hydroxy adamantyl moiety.
MR. CARSTEN: And just for the record, I will put in front of you Exhibit 2013.
(Previously marked AstraZeneca Exhibit No. 2013, first referral.)
MR. LIVINGSTONE: Thank you.
BY MR. CARSTEN:
Q And is this the -- this is the Villhauer '063 patent; is that correct?
A That's correct.
Q And this is a document that you considered in connection with your work in this case?
A So this is a document that I was well aware of when, at the time and that I also

considered in this case.

Q And if you turn to Column 7 there is an Example 1?

A Yes.

Q And that, is the compound depicted there is the compound that subsequently became known as vidagliptin, correct?

A That's correct.

Q And that contains a hydroxy adamantyl moiety?

A That's correct, Example 1 contains an hydroxy adamantyl moiety.

Q Okay, thank you.

Now, you are aware of a work by Dr. Augustyns and his group in connection with DPP-4 inhibitors, correct?

A That's correct.

MR. CARSTEN: I will hand you document Exhibit Number 2151.

(Previously marked AstraZeneca Exhibit No. 2151, first referral.)

BY MR. CARSTEN:

Q I think we discussed this when we were together last time at trial. Is this a document that you reviewed both at the time in connection with your work then and also in connection with your work relating to the case?

A Yes, it is.

Q And this is the 1997 Augustyns reference, correct?

A That's correct.

Q There is a second Augustyns publication as well that we discussed at trial, and this is Exhibit 2007.

(Previously marked AstraZeneca Exhibit No. 2007, first referral.)

MR. LIVINGSTONE: Thank you.

BY MR. CARSTEN:

Q I think we spent some quality time discussing this one as well when last we spoke, correct?

A I wouldn't phrase it like that, but yes. This came up at trial as well.

MR. LIVINGSTONE: I wasn't going to object but ...

Q This is a document that you were aware of back during your time on the DPP-4 project at Merck, and then again reviewed in connection with your work in this case, correct?

A That's correct.

Q Now, this Augustyns reference, if I can frame it this way, this is a review article?

A Yes. The Augustyns '99 reference is a review article.

Q Right, and when I'm talking about this one, I'm talking about -- let's call Exhibit 2007 the Augustyns '99 article if we might. Is that all right?

A Absolutely.

Q Now, there is a section in the Augustyns 1999 review article describing competitive reversible inhibitors.

Do you see that?

A I do.

Q And in the section on competitive

reversible inhibitors there are about ten compounds identified as exemplars of competitive reversible inhibitors for DPP-4, correct?

A I believe that is correct.

Yes, compounds 1 through 10.

Q And there is also a much longer HIV-1 Tat protein that is discussed in the competitive inhibitor, competitive reversible inhibitor section, but that's a different approach to inhibiting DPP-4 all together in terms of using a protein, correct?

A So that -- I think that it's fair to say that a protein would be a different approach from a small molecule, yes.

Q And what we are talking about here is the small molecule approach in connection with this case, correct?

A That's correct.

Q All right.

So of compounds 1 through 10, they are depicted in Figure 4 on Page 5 of 17 of the Augustyns 1999 review article, correct?

A That's correct.
Q And in terms of the P1 position, each of the compounds 1 through 10 contains a five-membered ring containing a nitrogen; is that fair?
A That's not correct.
Q I apologize. Compound 10 does not. Thank you.
So compounds 1 through 9 all have the five-membered ring containing a nitrogen, correct?
A That's correct.
Q And even compound 10 has a five-membered ring, it just isn't a nitrogen containing five-membered ring; is that correct?
A That is correct.
Q Two of the ten compounds have a five-membered ring that has a cyano group attached to it, correct?
A Compound 9 has a cyanoproline, and as we said, compound 10 without a nitrogen also has a nitrile.
Q And the Augustyns reference in 1999

was referencing what had been, what the state of the art at that time was with respect to competitive reversible inhibitors that had been published, correct?

A This paper describes his view of the DPP-4 world in 1999, yes.

Q And you have no reason to disagree with his assessment of the DPP-4 world as of 1999, right?

A No, and I think, I guess, one clarification is it is not really clear exactly when he wrote this paper and submitted it, so it could be prior to 1999. It was published in '99.

Q Now, some of the, compounds 3 and compound 5, they include sulphur in the five-membered ring, correct?

A That's correct. So compound 3 is P3298 and compound 5 is an analog.

Q And in fact some of the compounds here are similar to those that had been worked upon at the Ferring group as well, correct?

A Compound -- yes. So compound I think

4, compound 6, 8 and 9 were from the Ashworth publications.

Q Okay.

Compounds 1 through 10, can you tell me which of those are primary amines?

A All of compounds 1 through 10 contain primary amines.

Q And the compound, the first compound that you -- strike that.

The sitagliptin compound that you developed, that contains a primary amine as well; is that correct?

A That's correct.

Q Now, as of 2000 a number of the known DPP-4 inhibitors were known in the art to be susceptible to intramolecular cyclization; is that correct?

A It was known that compounds, DPP-4 inhibitors that contained electrophiles were prone to cyclization because of the requirement for the amine.

Q And you are aware that as of 2000 one

approach for flattening a five-membered ring would be to add a cyclopropane moiety to it; is that fair?

MR. LIVINGSTONE: Objection, form.

A If you are referring to the approach described in the context of ACE inhibitors, there was a paper by Hanessian that described flattening of a pyrrolidine by the addition of a cyclopropyl in the context of inhibitors of a different enzyme and attempt to convert an enzyme.

MR. CARSTEN: I'm going to hand to you Exhibit 1010.

(Previously marked Mylan Exhibit No. 1010, first referral.)

BY MR. CARSTEN:

Q This is a paper by Hanessian, correct?

A That is correct.

Q And this is prior art; is that correct?

A This is published in 1997 so this is prior art.

Q And the Hanessian reference on the

first page in the second paragraph down says, "Conformationally constrained analogs of proline have been used extensively in connection with peptidomimetic research."

Do you see that?

A I see that.

Q What is peptidomimetic research?

A Peptidomimetics was an approach to converting peptides, and these would be typically very large peptides, into more small molecule-like inhibitors in an effort to make them orally bioavailable and efficacious when given orally.

Q And peptidomimetic research would also include an approach to designing a small molecule that competitively inhibits an enzyme, correct?

A If the enzyme had a peptide as a natural inhibitor, for example, then you could use peptidomimetic research to mimic that peptide in an effort to convert it to a small molecule.

Q And I want to make sure that I'm not hung up on nomenclature with you, Dr. Weber.

A Okay.

Q You said something in your answer and I would like to confirm that I understood it correctly. Okay?

A Um-hmm.

Q Is that a yes?

A That's a yes.

Q You can also apply peptidomimetic research strategies where an enzyme has as its natural substrate a peptide, and you are designing something to competitively inhibit that enzyme, correct?

A So if you're suggesting that you could start with a substrate and apply peptidomimetic approaches to make an enzyme inhibitor, for example by converting the scissile amide bond to a peptidomimetic-like structure, yes, that would be one approach that somebody might choose to use in the context of an enzyme inhibitor program.

Q And this Hanessian paper is not specific to ACE inhibitors, is it?

A I believe this one is not specific to ACE inhibitors. He had some additional papers

that or at least one paper where he applied this approach to the context of ACE inhibitors.

Q As part of a peptidomimetic research approach to ACE inhibitors?

A I would have to look at that paper. I don't believe I would exactly -- that was not a -- he wasn't starting with a peptide. He was starting with a small molecule. So I wouldn't say that he was applying peptidomimetic research in that case because he already had a small molecule.

Q Now, in connection with the Augustyns 1999 paper, I think we identified two compounds that had a five-membered ring but also contained a sulphur in the ring?

A If you're referring to --

Q The review article.

A The Augustyns 1999, we had discussed compound 3 and compound 5 which contained sulphur in the five-membered ring, yes.

Q And both of those five-membered ring compounds that contained the sulphur had reportedly good potency; is that fair?

A I don't believe that he reports potency in this particular publication.

Q I don't believe he does. I'm asking just if you, if that's consistent with your recollection that the five-membered rings containing the sulphur exhibited reasonable or good potency?

A I think it would depend on what you meant by reasonable or good potency because I believe in the Hanessian -- at least compound 3 is reported in the Augustyns 1997 paper, and he's talking about for most of his data is IC50s which is different from a Ki. So I think his IC50 numbers are micromolar, but I think it would be fair to say that compound 3, which is P3298. Had sufficient potency. Obviously that compound advanced into human clinical trials so I would say that compound had sufficient potency to advance to the clinic.

Q Well, you are aware also that Dr. Ashworth reported some either Ki or IC50 values on compounds that had the five-membered

ring structure with a sulphur in it as well, correct?

A She reported data on that nitrile, cyanothiazolidide.

MR. CARSTEN: I will hand you a document identified as 2001, Exhibit 2001.

(Previously marked AstraZeneca Exhibit No. 2001, first referral.)

MR. LIVINGSTONE: Thank you.

BY MR. CARSTEN:

Q And is this the paper that you were just referring to about Dr. Ashworth reporting on the cyano compounds that also contained a sulphur moiety?

A That is correct.

Q And the fact that a sulphur-containing five-membered ring exhibited a Ki hero, 0.41 nanomolar, that is good potency, right, for compound 3?

A Again, good is kind of a loose term but I would imagine that most medicinal chemists would consider a Ki of less than 1 nanomolar as

being good potency.

Q Subnanomolar is pretty good potency generally, all things being equal, correct?

A I would agree with that.

Q And sulphur is larger than a methylene group, right?

A Well, I think what we can say about sulphur is that the sulphur-carbon bond is longer so that if you have -- so a methylene group actually contains three atoms, carbon attached to hydrogens as opposed to just a sulphur atom. I wouldn't want to comment on the overall structure of a methylene group compared to a sulphur, but I think your point is that a sulphur-carbon bond is longer than a carbon-carbon bond.

Q So this type of Ki value suggests to a person of skill in the art that there is tolerance for bigger groups within the five-membered ring; is that fair?

A I think what this would suggest is that a sulphur in that particular location in the five-membered ring is tolerated. The data taken

as a whole suggests that it's -- it doesn't really have to do with the actual size of the ring because she presents data on another compound that doesn't show any change in potency.

Q And which compound are you talking about there?

A I'm talking about compound 4 which within the error of the assay is identical to the pyrrolidine analog 5.

Q And that's the 3-position, correct?

A So compound 4 contains sulphur in the 3-position. And compound 3 contains sulphur in the 4-position.

Q Okay.

Now, you are aware that -- we could go to an article, but it's probably easier to go to your declaration at Page 55 of 129.

THE REPORTER: I'm going to have to ask you to please take a break.

MR. CARSTEN: Okay.

(Recess taken -- 9:42 a.m.)

(After recess -- 10:01 a.m.)

BY MR. CARSTEN:

Q So Dr. Weber, right before we broke I was about to direct you to a portion of your report, and that's at Page 55 of 129.

A I got it.

Q There is a series of compounds here depicted. There is compound 3 which is sort of the starting point, and then from there you've got a number of analogs, each of which have a substituent at the 3-position of the cyclopropane ring, correct?

A That's correct.

Q Okay.

Now, these compounds, if I'm not mistaken, are taken from -- and the data presented on these compounds is taken from the Augustyns 1997 article that I handed you before; is that right?

A That is correct.

Q Okay. I would like to -- and, to the best of your knowledge, the data and the compound structures that I presented here are correct?

A Yes.
Q Okay.
You've done a very nice service here and you depicted all the compounds instead of, you know, the Augustyns paper. In every case a substituent in the 3-position, perhaps with the exception of fluorine, demonstrates a reduction in IC50; is that correct?
A That is correct.
Q And with respect to the fluorine substituent at the 3-position, it's a difference of 27 micromolar versus 21 micromolar with fluorine exhibiting 27 micromolar IC50?
A I would need to check the paper for the exact number.
Q If you would like to. I did hand that to you previously, and that's Exhibit 2151. And feel free to do that.
A So Augustyns presents two compounds with, it looks like two compounds with fluorine. I think that's -- is that a fluorine? This is a very poor copy but I'm pretty sure it's -- let me

just double-check. So compound 17b is definitely a fluorine, and it looks like it's the 2 epimers. And so for that compound, and I can't see for 18c which may be a single isomer of fluorine but it's hard to tell from this reproduction.

So for compound 17b it's 27 micromolar, which is similar to the unsubstituted compound 3 with the EC50 -- excuse me, an IC50 of 21 micromolar.

Q Okay.

Now, staying within the Augustyns 1997 reference at Page 3 of 9, Dr. Augustyns and his group report at Page 3 of 9 in the right-hand column, second paragraph down, "Introduction of a substituent at 3-position of the pyrrolidine ring, (fig 3, (16B through 23B), generally decreased the inhibitory activity (Table 1)." Correct?

A That is correct.

Q And he goes on to say, "Only a small substituent such as fluorine, isosteric to hydrogen, is allowed." Correct?

A Correct.

Q And that conclusion, as far as you can tell, is premised upon consideration of the compounds and the resulting data that we just discussed as depicted in your Page 55 of 129 in your declaration.

A Yes.

Q Okay.

Now, I would like to talk to you a little bit about one of the changes that Dr. Rotella suggests a person of ordinary skill in the art would have made to the Ashworth compound 25, lead compound. I understand you disagree with Dr. Rotella's selection of a lead compound. Okay?

A Yes.

Q So I'm asking you to put that behind you and assume for the line of questions that a person of skill in the art for some reason would have gotten to Ashworth 25 as a lead. Do you understand that?

A I do understand it.

Q Okay. And by answering these questions you're not suggesting that you agree

with that. I understand you disagree; is that fair?

A That is fair.

Q Okay.

Dr. Rotella suggests that a person of skill in the art would choose to make the five-membered ring portion of the Ashworth 25 lead compound into a bicyclic structure. Do you understand that?

A He suggests that you would fuse a cyclopropyl to the pyrrolidine ring which would give you a bicyclic.

Q Thank you.

If a person were interested in making a bicyclic ring on that section of the Ashworth 25 lead compound, the smallest possible bicyclic structure would necessarily include appending a cyclopropane ring onto that structure; is that correct?

A If you were going to maintain the five-membered ring pyrrolidine and make a bicycle then appending a cyclopropyl ring would be the

smallest.

Q And you agree with me that the literature contained directives suggesting that maintaining a five-membered ring structure would be important to maintaining potency; is that fair?

A I believe that, in fact, Augustyns suggested that a saturated five-membered ring compound was preferred.

Q And in terms of substrates, Mentlein, even as far back as 1993, was saying in the context of substrates that proline was something that fit well in the binding pocket, correct?

A What he was saying in terms of substrates that a proline containing substrate was cleaved efficiently by the enzyme.

Q Now, if you were going to append a cyclopropane to the ring structure of Ashworth 25, there are five possible configurations in which you could append that cyclopropane ring, correct?

A If you were assuming that we are going to keep the nitrile in the same position, then there are five different ways that you could

append a cyclopropyl ring to the pyrrolidine.

Q Now, if you were also taking the Augustyns 1997 work and applying the conclusion that Dr. Augustyns and the Augustyns group reported in 1997 that for position 3 you prefer a hydrogen or an isostere of hydrogen, that eliminates three of the possible configurations upon which you would append the cyclopropane ring, correct?

A I would not agree with that. As we discussed at trial, the -- what Augustyns -- how a medicinal chemist would view this is that these five-membered rings could sample -- he's suggesting that you cannot attach an appendage to a carbon that is not attached to the nitrogen. In other words, while his compounds are 3 substituted, the enzyme actually samples two configurations of that compound, of these compounds because the ring can flip over, so essentially you're sampling the 3- and the 4-position.

So a medicinal chemist would view

these data and would understand that Augustyns was suggesting that putting an appendage, substituting at one of the two carbons that is not attached to nitrogen would not be preferred.

Q So is it your -- let me see if I understand this. Is it your testimony that the 3- and the 4- positions are impacted by the Augustyn series of compounds testing the 3-position that we just discussed in your report at Page 55 of 129?

A I don't think I would phrase it exactly that way. What I'm suggesting is that Augustyns is showing that you cannot substitute on the carbon that is not attached to nitrogen. And so because you have two configurations of that pyrrolidine ring, if you flip it over and keep the numbering the same it's actually the 4-position. It's a little bit confusing because it's really based on how you number the ring, but the enzyme samples both configurations of the molecule.

Q With respect to the Ashworth series of compounds, Ashworth discloses, as Villhauer discloses, a preference for one orientation of the

cyano nitrile substituent, correct?

A I think it's generally understood in the art that there is a preferred -- well, obviously it was generally understood in the art that there was a preferred configuration for the nitrile, yes.

Q And if you have a nitrile in one configuration, would you agree with me that a person of skill in the art would understand that the enzyme was preferentially sampling that substrate or that molecule in one orientation?

A That is correct. These compounds lack the nitrile so the enzyme can sample both configurations.

Q Right. What I'm suggesting or what I'm asking you, though, is in the compound that's premised upon Ashworth compound 25 which has a nitrile in a preferred configuration, does Augustyns teaching apply to both carbons 3 and 4?

A Yes. It -- yes, it does. With the nitrile being at position 2, just so we are clear how we are numbering it.

Q So notwithstanding the fact that Augustyns group reports introduction of a substituent at 3-position of the pyrrolidine ring, your testimony and opinion is that a person of ordinary skill in the art applying this to the Ashworth series of compounds would read that as applying to both carbons 3 and 4?

A That is correct. It's a convention of how a chemist numbered it. So a medicinal chemist would understand that what the data suggests is that you cannot substitute on those two carbons that are not attached to nitrogen. And we are not talking about nitriles, just to be perfectly clear. The cyano group is a different story. That is at the 2-position. I'm not referring to the cyano group in this analysis.

Q I thought the question did require you to consider the nitrile group.

A What I'm saying is that Augustyns is not saying that you can't have a nitrile at the 2-position. So when I say that you cannot substitute, make a substitution at the carbons

that are not attached to nitrogen I'm not meaning to imply that you -- I'm not meaning to imply that you cannot have a nitro at the 2-position. Certainly you can have a nitrile at the 2-position.

Q Well, Dr. Augustyns, Page 3 in the paragraph above says, "Therefore, we believe that the S-1 subsite of DPP-4 ideally fits a five-membered saturated ring."

Do you see that?

A Yes.

Q Now, the five-membered ring that contains a nitrile substituent is not a saturated ring, is it?

A Oh, it absolutely is a saturated ring.

Q So a saturated ring can still have a substituent?

A Absolutely.

Q So a cyclopropane appended five-membered ring is still a saturated five-membered ring?

A A cyclopropane appended ring is a

saturated ring with a substituent, and -- at those -- with a substituent that would be at the 3-position, yes.

Q Okay.

Or at the 4,5-position?

A As I said, you're sampling those -- it depends on where you put the cyclopropyl ring. But for the purposes of the Augustyns analysis, what Augustyns is saying is that it's not preferred to have a substituent at one of those two carbons that are not attached to nitrogen.

And all of the five-membered rings that you would be -- all of the cyclopropyl fusions contain a substituent at one of those two carbons. You cannot make a five-membered -- you cannot fuse a cyclopropyl to this five-membered ring without adding a substituent to one of the two carbons, which these data suggest would not be preferred.

Q I understand your opinion.

A Okay.

Q And in the same spirit of fairness

that I offered you, I don't agree with you but I understand it now.

A Okay, thank you.

Q Now, in your declaration you talked about some of the six-membered rings that were tested in the prior art and conclude that the six-membered rings exhibited potency that was less than those exhibited in the five-membered rings, generally speaking, correct?

A The six-membered rings containing inhibitors were generally less potent, yes.

Q And you understand that a cyclopropionated five-membered ring would have a different space and shape than a six-membered ring, correct?

A Well, it certainly is a six-membered ring, but by virtue of the two carbons being fused together it would have a slightly different overall shape.

Q So it would have a different shape in space, correct?

A It would have a slightly different

shape, yes.

Q What do you mean by slightly?

A It would still be a six-membered ring. You can draw a six-membered ring, but because the two carbons are fused, the two carbons are not exactly in the same location as in the six-membered ring. They would have a different, a slightly different shape.

Q They would be closer together and have a bond between them, correct?

A They would have a bond between them, yes.

Q And they would be closer together?

A Because of the virtue of the bond. In a six-membered ring there is no bond between those two carbons, so they would be slightly farther apart.

Q In the bicyclic context they would be closer together, those two bonds?

A Yes.

Q Thank you.

Now, one of your criticisms of

Dr. Rotella is found in the Magnin reference; is that fair?

A So I used the Magnin reference in the secondary considerations but I did not use it in forming my obviousness argument or my lack of obviousness argument.

Q Well, if you turn to Paragraph 184 of your declaration, you site to Magnin there, don't you?

A I'm using Magnin here just to confirm the unexpected results -- or it's just to confirm the expected results that one would -- can I rephrase that?

I'm using Magnin here not to form the basis of my opinion, but just to confirm, in a confirmatory way, for my opinion.

Q Well, we agree that a hypothetical person of ordinary skill in the art as of the date that you were asked to provide opinions about obviousness would have had no information whatsoever that is disclosed in the Magnin reference.

A The Magnin reference was not in the prior art. I would agree with that.

Q Okay.

And if you actually look at your report, your declaration, the secondary considerations analysis begins at Page 106, which in the alternative numbering is Page 109 of 129, correct?

A That is correct.

Q And so when you cited Magnin previously, that was in the section that was dedicated to obviousness, correct?

A The citation is in that section but that in no way implies that I'm using Magnin to support my -- when I -- to argue the -- let me start again.

I in no way used the Magnin paper in my opinion about obviousness. I'm solely using the Magnin paper for confirmation. For example, in here I had stated that based on the Augustyns paper one would have expected that if you fused a ring, essentially adding a substituent to the

carbons that were not attached to nitrogen, then you would expect a decrease in potency, and this is shown in the Magnin paper.

Q If you turn to Paragraph 194, which is also in the obviousness section of your report and not the secondary consideration section, you there cite to Magnin as well, correct?

A Yes. Again, confirmatory, not as part of my considerations for obviousness in this section, the prima facie section.

Q In terms of what you were entitled to consider with respect to unexpected results and the like, were you instructed that you were able to consider post filing date information that was not available in the prior art?

A So I was instructed that for the prima facie case that I was to only consider information that was in the prior art, but with respect to secondary considerations that by necessity I was able to cite information that was not in the prior art.

Q What do you mean by necessity?

A Well, if you're going to show unexpected results, those unexpected results would not be in the prior art because the compound was not in the prior art.

Q So, for example, at Pages 115 and 116 -- and by 115 and 116 I'm referring to the actual page number, so it would be Pages 118 and 119 of 129 -- there you talk about saxagliptin's active metabolite?

A Yes.

Q And you refer to a reference with a lead author of Su. Paragraph 239, "Su reported concentration"?

A Yes.

Q You see that?

A I do.

Q None of that was in the prior art, correct?

A Absolutely not because saxagliptin was not in the prior art.

Q And there is nothing in the patent specification that talks about the activity of a

metabolite, correct?

A That is correct.

Q And similarly, if we flip the page to 121 of 129 you're talking here about the X-ray crystal structure showing covalent attachment. Paragraph 243.

A Yes.

Q This X-ray data was not available in the prior art, correct?

A Again, that's correct, because saxagliptin was not in the prior art.

Q Well, the DPP-4 crystal data was not available as of 2000 as well, was it?

A I believe that is also correct.

Q Now, with respect to -- so the metabolite information, the X-ray information, the information about favorable binding interactions and so forth, none of that was available to a person of ordinary skill in the art as of the priority date, correct?

A So none of the information on saxagliptin, as I said, was available to a person

of ordinary skill in the art as of the date.

Q Okay.

Now, you also referred to some internal BMS documentation; is that correct?

A That is correct.

Q And that information was confidential to BMS?

A That is correct.

Q And a person of ordinary skill in the art as of the date that you are applying your obviousness analysis would have no way of knowing, correct?

A That is correct.

Q Are you testifying that a person of ordinary skill in the art as of 2000 would never have considered a bicyclic ring structure in connection with developing a DPP-4 inhibitor?

MR. LIVINGSTONE: Objection, form.

A I am -- that is not my testimony.

Q All right. In fact, sitagliptin contains a bicyclic ring structure moiety, correct?

A Sitagliptin, which was not in the prior art, does contain a bicyclic ring system.

Q Now, in the years following your development of sitagliptin, your discovery of sitagliptin, you also determined a second gliptin compound that is approved in Japan, correct?

A I'm sorry, can you repeat that?

Q Sure.

In the years following your work at Merck and your discovery of sitagliptin, you discovered a second gliptin compound that is now approved in Japan, correct?

A That is correct.

Q And that's omarigliptin?

A That is correct.

Q And you consider omarigliptin to be the best in class of the gliptins, correct?

A At the time that we were bringing omarigliptin into development, we used the term at Merck best in class inhibitor. That was our goal, yes.

Q And you use that to describe

omarigliptin?

A We use that to describe omarigliptin. Let me just take a step back. At the time when we were discovering or working on the omarigliptin program our goal was to identify a best in class inhibitor.

Q Now, the omarigliptin, I think you just said something along the lines of the program to determine or discover omarigliptin. It's the same program that had initially determined sitagliptin, correct?

A If you mean by the same program, if you're talking about DPP-4 inhibition as a general program, yes, it is also a DPP-4 inhibitor.

Q And omarigliptin is not approved in the United States, correct?

A That is correct.

Q And so under your analysis in this case omarigliptin would be a failure?

A That is correct.

Q Now, you're aware that there are lots of reasons why a company might elect not to pursue

FDA approval of a compound that have nothing to do with the safety or efficacy of a compound, correct?

A As we discussed at trial, pharmaceutical companies make science-based business decisions, and those, the business decisions are based in science which would take into consideration a whole host of factors, including safety and efficacy, but other factors as well.

Q There is no question in your mind about the safety and efficacy of omarigliptin, right?

A I have no reason to doubt the safety and efficacy of omarigliptin.

Q And outside of the context of this case you would consider omarigliptin to be a success, wouldn't you?

A Again, it depends on how you define success. I consider omarigliptin to be a compound that I worked on that was approved in Japan and is being used in Japan to treat patients with type 2

diabetes.

Q I'm going to read a passage from a Merck press release, which I think at trial you testified you were generally aware of.

A Yes.

Q It says, "This decision did not result from concerns about the efficacy or safety of omarigliptin. Instead, the company has for business reasons decided to focus its development resources on a promising pipeline of late stage compounds and in early development new approaches to diabetes control while continuing to emphasize its existing portfolio of Januvia, the most prescribed DPP-4 inhibitor worldwide, and Janumet."

Is that consistent with your understanding of the reasons why Merck decided not to pursue FDA approval of omarigliptin in the U.S.?

A Yes.

MR. CARSTEN: If I may have five minutes to confer with my brain trust, we may well

be done. I may have a handful of mop-up questions from my side. I think your counsel would like to have some questions for you, but if we could take a short break I think that would be beneficial for me.

MR. LIVINGSTONE: Great. Thanks.

(Recess taken -- 10:31 a.m.)

(After recess -- 10:45 a.m.)

MR. CARSTEN: We are back on the record.

Thank you so much for your time. I do appreciate it.

Mr. Livingstone, I pass the witness to you.

MR. LIVINGSTONE: Thank you very much.

EXAMINATION

BY MR. LIVINGSTONE:

Q Let's start, Dr. Weber, there has been some suggestion, both at trial and I think through some of the questioning today, that there might be a sweet spot at the P1 group in between, for instance, the favored five-membered saturated ring

that Augustyns describes and the six-membered ring that Augustyns shows as disfavored.

In your review of the prior art what, if any, support for such a sweet spot argument is there?

A I didn't find any support for such a sweet spot argument. And in particular I would point to Augustyns 2 which clearly shows that while the thiazolidine slightly larger ring is preferred in one position it is not preferred in a second position, indicating that something other than size is contributing to the greater potency of that compound.

Q We talked, you talked briefly this morning about sitagliptin and that it has a bicyclic ring system. Is that bicyclic ring system in the P2 or in the P1 position?

A Sitagliptin's bicyclic ring binds in the P2 position.

Q We also just discussed omarigliptin and a press release discussing Merck's discontinuation of omarigliptin in the United

States. Do you remember that?

A Yes.

Q In your opinion, what are the science-based business decisions related to omarigliptin being approved for use in Japan versus the United States?

A So when we started the omarigliptin program we were looking for a once weekly inhibitor that could be used to treat diabetes. And the reason we considered this best in class is that if patients were taking a medication once a week that would result in better compliance and better compliance would then result in better outcomes.

What we were expecting was that by the time omarigliptin was ready to be approved that DPP-4 inhibitors would be used as first class therapy in the U.S. That, however, has not happened and Metformin continues to be used as first line therapy in the U.S.

That's not the case in Japan. The diabetes in the Japanese population is slightly

different and there is -- which makes it really actually ideal as -- which makes the DPP-4 inhibitor ideal for treating patients with type 2 diabetes in Japan. And in Japan DPP-4 inhibitors are used first line. So in Japan it makes sense to have a once-weekly treatment because these patients are newly diagnosed and not on a lot of medication.

That's in contrast to the situation that we had, that we currently have in the U.S. where patients who are newly diagnosed typically start on Metformin, and when their disease progresses then doctors would typically add a DPP-4 inhibitor. So DPP-4 inhibitors are used as second line therapy in the United States. And in this case it makes more sense, because patients are taking Metformin every day, to treat them with Janumet which is a fixed dose combination of Metformin and sitagliptin, and that combination then lowers their pill burden.

MR. LIVINGSTONE: I'm going to hand you a document that's been identified as

AstraZeneca 2210.

MR. CARSTEN: Thank you.

(Previously marked AstraZeneca Exhibit No. 2210, first referral.)

BY MR. LIVINGSTONE:

Q And can you identify Exhibit 2210 for us, please?

A This is my CV from earlier this year.

Q Okay. And is this CV accurate and complete, to the best of your knowledge?

A No. There are a number of changes. I started a full-time job last week so while I am still consulting, I'm also senior vice president of drug discovery at Kallyope in New York City.

In addition, I believe this CV has a mistake in -- no, it looks like we corrected this mistake, so the mistake to my timeline of employment with Merck has been corrected. And there are a number of -- there is certainly at least one additional award and a number of additional papers.

Q With those corrections is it okay to

rely on what is here in your CV, Exhibit 2210?

A Yes.

Q Could you summarize your educational background, please?

A I have a Bachelor of Science degree from the University of Notre Dame in chemistry and a Ph.D. from Harvard in organic chemistry.

Q Where in your class did you finish at Notre Dame?

A I finished first in my class with a 4.0.

Q If you look at Page 1 it indicates you worked at Merck and Company. How long did you work at Merck?

A I worked at Merck for over 28 years.

Q And did there come a time in your work at Merck when you began working on DPP-4 inhibitors?

A There did. About 13 years after I started, I started working on DPP-4 in January of 2000.

Q And before you started on the DPP-4

program, did you view yourself as an experienced medicinal chemist?

A By that time, yes.

Q And how long did you continue to work on DPP-4 inhibitors?

A My involvement with the program lasted until the merger with Schering-Plough. So that would have been I believe in November -- actually it was right before the merger so sometime, 2008-2009. Then the program was reinitiated with the Legacy Schering-Plough group for a couple of years. But I was not directly involved with that part of the program.

Q Did you generally keep abreast of the DPP-4 field in the years after 2008 until you left Merck?

A I did.

Q If I can direct your attention to Page 3 of 17, you identified a number of awards on that page. About midway down in 2007 there is an award called the Prix Galien award for Januvia. Can you identify what that award is?

A The Prix Galien award is considered the Nobel prize of the pharmaceutical industry.

Q You also received the Merck directors award. Can you tell us a little bit about that?

A The Merck directors award is the highest award that Merck bestows on its employees.

Q I think you mentioned in your discussion with Mr. Carsten that you were recently inducted into the American Chemical Society Hall of Fame; is that right?

A The American Chemical Society Medicinal Chemistry Hall of Fame. Yes, that happened earlier this summer.

Q Did you have occasion to publish your scientific work?

A I did.

Q Approximately how many scientific publications do you have?

A I'm a co-author on over 80 scientific publications, author or co-author.

Q Approximately how many of those relate to DPP-4 inhibitors?

A I believe it's around 35.

Q And if we look at Page 10 of your CV, there are identified a number of patents, and I have taken the liberty to count that there are approximately 31 patents in this list. My question is how many of these patents relate to DPP-4 inhibitors?

A That's correct, there are 31 U.S. issued patents, and I believe about 25 of them relate to DPP-4 inhibitors.

Q Okay.

Now, you had testified that you came into the DPP-4 field, inhibitor field around 2000 at Merck. To get your arms around the state of the art, what was the first thing you did?

A The first thing I did was survey the literature, both the journals and the patent literature, collect all the prior art. Review and study it.

Q We can go to your declaration, which Mr. Carsten was kind enough to provide you, and look at pages, actual pages 39 to 44. There is a

table here, and my question will be can you describe to us what is included in this table.

A So you are referring to the document page 39, correct?

Q I apologize.

A Yes. So this table, in this table I have summarized some of the examples of DPP-4 inhibitors which were known in the prior art which were not ultimately approved by the FDA, and this is also a summary of the literature that I reviewed as I started the program.

Q At Merck in 2000?

A At Merck in 2000.

Q Have you attempted in this figure that spans from Pages 39 to 44 to depict all of the DPP-4 prior art?

A I believe this depicts, this generally depicts the prior art. What I have not done is depict all of the structures that were disclosed in the prior art.

Q All right.

In your opinion, how would a person of

ordinary skill in the art sitting down with the goal of developing a useful DPP-4 inhibitor in the year 2000 or early 2001, how would that person have viewed the prior art that is illustrated here in your declaration on Pages 39 to 44?

A So a person starting a DPP-4 inhibitor program, a person of ordinary skill in the art, would have realized that there was a morass of different structural types and literally millions of compounds that had been disclosed, both in the patent literature and in journals. And they would have realized that out of this very large and structurally diverse set of DPP-4 inhibitors, by that time there had emerged two compounds, P3298 and NVP-DPP728, that were in human clinical trials.

Q That brings us to another point.

When reviewing the prior art in or around 2000 I suspect you saw studies that had in vitro data and studies that had in vivo animal data and studies that had human data; is that fair?

A There were studies that had in vitro, in vivo and human data, yes. The human data was reported in 2000, in the middle of 2000.

Q Thank you.

As a medicinal chemist is there a typical hierarchy to ascribe an importance to that type of data, and if so what is it?

MR. CARSTEN: I object to the extent it's beyond the declaration testimony.

Q You can answer.

A Absolutely. A medicinal chemist would understand that in vivo data would trump in vitro data and that human clinical data, so data in humans would trump any preclinical in vivo data.

Q In the course of your work familiarizing yourself with the state of the art in 2000, did you ultimately publish on the conclusions that you drew at that time?

A I did.

(Previously marked AstraZeneca Exhibit No. 2098, first referral.)

BY MR. LIVINGSTONE:

Q I'm going to hand you what has been identified or marked as AstraZeneca Exhibit 2098. And by reference to the third page of this document can you tell me what this is?

A This is a miniperspective that I wrote on DPP-4 inhibitors for the treatment of type 2 diabetes for the Journal of Medicinal Chemistry.

Q If I can direct you to Page 4, the first paragraph in the top left column. If you could read into the record the middle two sentences starting with, "Replacement of the pyrrolidine"?

A "Replacement of the pyrrolidine with thiazolidine gives derivatives with increased potency. However, larger rings, (e.g. piperidine, homopiperidine) or those containing other heteroatoms, (e.g. oxazolidine) are less potent. With the exception of fluorine, substituents on the pyrrolidine ring are not well tolerated."

Q I see you have a reference there, 15. What article did you site there for reference 15?

A I think reference 15 cites the Ashworth and Augustyns -- it's Ashworth II and Augustyns 1997.

Q And was this a conclusion that you newly drew in 2004 or a conclusion that you came back to in around 2000?

A This was a conclusion that I based on those earlier references. And I drew this conclusion when I initiated the program in 2000, and I'm just reiterating it here several years later.

Q In your opinion, with the body of art that you reviewed at that time including, for instance, Augustyns 1997 reference and the Ashworth II publication, what would that body of art have taught the person of ordinary skill in the art in 2001 about adding a cyclopropyl group to the cyanopyrrolidine ring in a reversible DPP-4 inhibitor?

A That information would have taught a person of ordinary skill that adding a cyclopropyl ring would be a bad idea. It would not lead to

compounds with increased potency. And if one had decided to add a cyclopropyl ring one would not have anticipated success in doing so.

Q In the course of your work in developing DPP-4 inhibitors at Merck, did you or any of your colleagues consider adding a cyclopropyl group at the P1 position of your DPP-4 compounds?

A No, we never did, and to the best of my knowledge nobody other than the chemists at BMS ever did that.

Q What was your reaction when you first learned that saxagliptin had a cyclopropyl group on the pyrrolidine ring?

MR. CARSTEN: Again, object as beyond the scope of the declaration.

A I was very surprised when I saw the patent when it was first published. I was first surprised that they had actually tried it, and I was even more surprised that it worked.

Q Now, at that time being surprised, did you have any access at that time to BMS

confidential information?

A I did not.

Q And not to be Captain Obvious, but you didn't have any access to the Magnin publication, did you?

A No.

Q And you didn't have access to, for instance, the post invention publications that we talked about earlier, Su and Wang?

A No.

Q In your work on DPP-4 inhibitors at Merck did you or your colleagues look to any of the ACE inhibitor art for guidance?

A No, we absolutely never did that.

Q And did you have any specific ACE expertise in your group?

A I had no personal expertise on ACE, but one of my managers was the chemist that actually synthesized Enalapril, which is Merck's ACE inhibitor. So there was a lot of expertise on ACE at Merck, and specifically involved with the program.

Q And to your recollection that colleague never looked at ACE inhibitor art for guidance in the DPP-4 inhibitor space?

A He never did, nor did he ever suggest we do that.

MR. CARSTEN: I object to those questions as beyond the scope.

Q I think you might have Exhibit 2161 in front of you. I may have a hard time finding mine. Maybe you can find yours.

A Which one is that?

MR. CARSTEN: It's the Thornberry and Weber article.

MR. LIVINGSTONE: I have an extra copy if you need it.

MR. CARSTEN: I've got it.

THE WITNESS: Okay.

BY MR. LIVINGSTONE:

Q Looking at Exhibit 2161, I think you identified earlier, but just for the sake of the record, can you please tell me what this is?

A This is a paper that I wrote with

Nancy Thornberry that covers the discovery of Januvia, which is Merck's DPP-4 inhibitor.

Q This paper is dated 2007, but were you attempting to relate events that occurred earlier in time?

A I was.

Q If we can go to Page 2, please. And if you look at the left column there is a heading that says Probiodrug Licensing Experience.

Do you see that?

A I do.

Q And can you read those first two sentences slowly, please, into the record?

A "When we initiated our internal screening and medicinal chemistry program, two compounds were already advancing through human clinical trials, Probiodrug's isoleucyl thiazolidine (1) and NVP-DPP728 (3) from Novartis (Figure 1). Thus, in order to jump start our internal program, in late 2000 we elected to in-license L-threo-isoleucyl-thiazolidide, P3298, and it's allo stereoisomer

(L-allo-isoleucyl-thiazolidide 2)."

Q And in looking at Figure 1 is compound 1 there P3298 that you have chosen in this case as one of your potential lead compounds?

A Yes, it is.

Q And is compound 3, NVP-DPP728, another compound that you have chosen as a potential lead in this case?

A It is.

Q In forming your nonobviousness opinion in this case, have you relied on post invention or nonpublic evidence for your opinions?

A No.

Q Earlier, the beginning of my questioning, we were talking about the sweet spot argument and you had said -- we think you might have said, we can't tell on LiveNote -- that Augustyns 2 taught away from the sweet spot. I guess my question is were you speaking about Ashworth II or Augustyns -- or an Augustyns reference?

A I'm sorry, I thought I said

Ashworth II.

Q Right.

MR. LIVINGSTONE: That's it for us.

MR. CARSTEN: Let me have a, just a look.

Nothing here.

MR. LIVINGSTONE: All right.

MR. CARSTEN: I think we are done.

MR. LIVINGSTONE: Thank you for your time.

THE REPORTER: Signature?

MR. LIVINGSTONE: Reserve for signature.

THE REPORTER: And do you want rough draft?

MR. LIVINGSTONE: We do, please.

And really, I mean this honestly. Your LiveNote was great. You did a great job. Considering all the issues we had with the transcript at trial, we could have used you there.

MR. TORCZON: We definitely want rough draft.

THE REPORTER: How soon do you want it?

MR. CARSTEN: Monday is great.

(Thereupon, signature having not been waived, the examination of ANN E. WEBER, Ph.D. was concluded at 11:12 a.m.)

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CERTIFICATE OF SHORTHAND REPORTER - NOTARY PUBLIC

I, Cappy Hallock, a Registered Professional Reporter (NCRA #6006), and Notary Public in and for the District of Columbia, do hereby certify:

That ANN E. WEBER, Ph.D., the witness whose deposition is hereinbefore set forth, was duly sworn by me before the commencement of such deposition and that such deposition was taken before me and is a true record of the testimony given by such witness.

I further certify that the adverse party, ASTRAZENECA AB, was represented by counsel at the deposition.

I further certify that the deposition of ANN E. WEBER, Ph.D. occurred at the offices of WILSON SONSINI GOODRICH & ROSATI, 1700 K Street, NW, Fifth Floor, Washington, D.C. on Thursday,

October 27, 2016, commencing at 8:07 a.m. to 11:08 a.m.

I further certify that I am not related to any of the parties to this action by blood or marriage, I am not employed by or an attorney to any of the parties in this action, and that I am in no way interested, financially or otherwise, in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 31st day of October, 2016.

My Commission expires September 30, 2017

_____

Cappy Hallock, RPR, CRR, CLR
Notary Public, District of Columbia

J U R A T

I, ANN E. WEBER, Ph.D., do hereby certify under penalty of perjury that I have read the foregoing transcript of my deposition taken on Thursday, October 27, 2016; that I have made such corrections as appear noted herein in ink, initialed by me; that my testimony as contained herein, as corrected, is true and correct.

Dated this _____ day of _____, 2016, at _____.

_____

ANN E. WEBER, Ph.D.

ERRATA SHEET

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I, the undersigned, ANN E. WEBER, Ph.D., do hereby certify that I have read the foregoing deposition, and that to the best of my knowledge, said deposition is true and accurate (with the exception of the following corrections listed below):

Global: change from "P3298" to "P32/98"

Page 43, line 16: change from "works" to "worked"

Page 50, lines 14: change from "back and" to "back -- and"

Page 50, lines 15: change from "-- which those are" to "thiazolidine"

Page 56, lines 12: change from "proven" to "prudent"

Page 71, lines 9: change from "enzyme" to "enzyme,"

Page 71, lines 10: change from "and attempt to convert an" to "angiotensin converting"

Page 75, lines 15: change from "P3298. Had" to "P32/98, had"

Page 111, lines 18: change from "art. Review" to "art, review"

Dated: 09-NOV-2016 Signature: Ann E Weber

Ann E. Weber, Ph.D.