UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BeiGene USA, Inc. and BeiGene, LTD.,

Petitioner,

v.

Pharmacyclics LLC,

Patent Owner.

PGR2024-00009

Patent 11,672,803

Virtual Deposition of STEVEN ROSEN, M.D.

Monday, June 17, 2024

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Pharmacyclics LLC
Exhibit 2021
BeiGene v. Pharmacyclics
PGR2024-00009
EX2021.0001

Virtual deposition of STEVEN ROSEN, M.D., pursuant to notice, before Tiffany M. Pietrzyk, a Certified Shorthand Reporter in the States of Illinois, Texas, and California, Registered Professional Reporter, Certified Realtime Reporter, and a Notary Public in and for the State of Illinois.

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P R O C E E D I N G S

(Witness sworn.)

MS. PATEL: Can I just note, I understand that this is all being recorded and you stated that it's for backup. Can we confirm no one is really going to be ordering the video or intending to use it for anything for the board in terms of video or recorded testimony; is that right?

MS. DANEK: That's correct. The video is just for backup and confirmation of record purposes.

MS. PATEL: Okay. Got it.

WHEREUPON:

STEVEN ROSEN, M.D.,

called as a witness herein, having been first duly sworn, was examined and testified as follows:

EXAMINATION

BY MS. DANEK:

Q. Good morning, Dr. Rosen.

A. Good morning.

Do I refer to you as Brenda or what's the proper term?

Q. Brenda works fine.

A. Brenda? Okay. Good morning, Brenda.

Q. As we, sort of, noted a little bit before we started recording here, my name is Brenda Danek. I represent Pharmacyclics in this proceeding. I'm going to be asking you some questions today regarding the declaration that you submitted on behalf of BeiGene in relation to U.S. Patent Number 11,672,803.

If I refer to that patent as the '803 patent or just the patent, will you understand what I mean?

A. I will.

Q. Okay. And if you have any questions, obviously, please ask for clarification.

Can you please state your full name for the record?

A. Steven Rosen.

Q. Have you ever been deposed before?

A. I have.

Q. How many times?

A. Many. I can't tell you the exact number, but they've all been in medical legal cases while I was at Northwestern.

Q. By "medical legal cases," do you mean medical malpractice cases?

A. Yes.

Q. Okay. So you've not testified before in connection with a patent litigation?

A. Not that I recall.

Q. Have you ever testified at trial before?

A. I have.

Q. And was that also in connection with a medical malpractice case?

A. It was.

Q. Okay. So I want to take a few minutes to review some ground rules so we all are, sort of, working from the same playbook for today's proceeding. Just to make sure that everything goes smoothly.

As I noted, I will be asking you some questions. My questions and your answers are going to be recorded by the court reporter. The court reporter can't record physical gestures, like nods or shrugs or shaking of your head, so all of your answers must be oral.

Do you understand?

A. I do.

Q. And the court reporter is going to be doing her best to make sure that she is accurately getting down everything that we are saying. But it's going to be really important that we don't speak over one another. So I will do my very best to wait for you to complete your answer to a question before asking another question if you will do your very best to wait for me to complete my question before starting to answer it.

Is that fair?

A. That's fair.

Q. If I ask you a question and you don't understand it for any reason, please let me know, and I will try to rephrase or clarify.

Is that okay?

A. It's okay.

Q. But if you do answer my question, I'm going to assume that you understood my question and are responding to it from that assumption.

A. I understand.

Q. Okay. Now, if you need to take a break at any time for any reason, please just let me know, and we can, you know, accommodate that. We talked about the need for potentially responding to patient calls, and we'll absolutely respond to those promptly. Absent the patient needs, you know, if there is a pending question, I just ask that you complete your answer to any question before we take a break.

Is that okay?

A. That's okay.

Q. Now, during the deposition, your counsel may make objections to my questions. Now, unless your counsel instructs you not to answer a question, you must respond to my questions.

Do you understand that?

A. I do.

Q. Okay. You understand that you're under oath today and obligated to testify truthfully; right?

A. Yes.

Q. And that's the same as if you were testifying before a court of law; right?

A. Right.

Q. Okay. Is there any reason that you can't provide full and complete or accurate answers to my questions today?

A. Not that I'm aware of.

Q. And as I noted earlier, if you need any clarification for any of my questions, please ask for it. Also, if at any time it occurs to you that you need to clarify an answer that you've previously given, please let me know so we can make sure that the transcript includes your complete and accurate testimony. Okay?

A. Yes.

Q. What did you do to prepare for today's deposition?

A. I reviewed my declaration. I reviewed Dr. Showalter's declaration. I reviewed the '803 patent. And I reviewed the appeal board's decision and discussion document.

Q. The decision and discussion document you just referenced, is that the institution decision from the patent trademark and appeal board?

A. Correct.
Q. Other than the institution decision, did you review any materials that were not cited in your declaration in preparation for your deposition today?
A. Not that I'm aware of.
MS. PATEL: Objection. Vague.
Objection. Vague.
Q. Okay. So you have a copy of your declaration that was submitted in this proceeding that's been labeled Exhibit 1005.
You have that in front of you?
(Exhibit 1005, previously marked, is attached to the transcript.)
A. I do.
Q. And I believe that the technician is going to put it on the screen just so we can all, kind of, follow along, but I know you have a hard copy and will be referring to the hard copy; right?
A. Yes.
Q. Okay. So Exhibit 1005, is this -- does this accurately reflect the declaration that you signed

and submitted in support of the petition that BeiGene filed?

A. Yes.

Q. Okay. And if we turn to the very last page of your declaration.

A. Yes.

Q. And there's a signature on this page, page 144 of the exhibit.

Do you see that?

A. I do.

Q. Is that your signature?

A. It is.

Q. Okay. And in preparing -- and before signing your declaration, you reviewed the text of the declaration to make sure that everything was accurate and complete?

A. I did.

Q. Okay. Now, in paragraph 2 of your declaration, it states that this declaration -- and this is at page 7 of the document -- [As read] This declaration sets forth my analyses and opinions based on my knowledge, experience, and the materials

I have considered.

Do you see that?

A. I see it.

Q. And so all of the opinions that you offer in this proceeding are contained within this declaration; right?

A. Right.

Q. And you indicate that you considered materials.

Are the materials that you considered in forming your opinion the materials that are cited in the declaration?

A. Yes.

MS. PATEL: Objection. Vague.

Q. And so your opinions aren't based on any references that you haven't cited in your declaration.

MS. PATEL: Objection. Asked and answered.

A. My opinions, I believe, are all contained within the information provided.

Q. Okay. And in preparing your declaration, you tried your best to get the evidence -- all the

evidence that you could to support your analysis; right?

A. Right.

Q. Okay. You wanted to make sure that your analysis was complete and to identify all of the references that supported your opinions?

MS. PATEL: Objection. Form.

A. Can you restate that so that I better understand what you're driving at?

Q. Sure.

I just wanted to confirm the, sort of, process that you underwent in preparing your declaration, that you looked for all of the references you could that would support and corroborate the opinions and analysis that you performed in writing your declaration.

MS. PATEL: Same objection.

A. I looked at all the information available that would allow me to render opinion regarding the issues that were given to me.

Q. And all of the information available, did that include performing searches of the literature

to identify articles and publications concerning this, you know, subject matter that you were looking for?

A. I did look for articles that were relevant to Imbruvica and zanubrutinib.

Q. Was that the limit of the searches that you did for relevant publications, just limited to Imbruvica and zanubrutinib?

MS. PATEL: Objection. Form.

A. The only other articles related to the consequences of atrial fibrillation, which you -- as you know, is a significant effect of Imbruvica.

Q. Okay. I just -- I think maybe we got a little bit -- we're talking past one another. Let me try to reframe my question.

I just wanted to confirm in your analysis, related to the claims of the '803 patent and the methods for treating CLL and SLL, in performing your analysis of those claims, you searched for literature references that you could find related the opinions you were forming concerning those method patent claims; is that right?

MS. PATEL: Object -- objection. Asked and answered.

A. So I believe I've answered the question.

Q. And the answer is that you did search for references related to the subject matter of the claims.

MS. PATEL: Objection. Asked and answered.

A. As I said, I provided all the information in my declaration, and I feel that that really gives you the totality.

Q. Okay. And you tried to cite all of the examples that you were aware of in your declaration that would support your opinions; right?

MS. PATEL: Objection. Vague.

A. Can you be a little bit more precise?

Q. Sure. You didn't hold anything back in citing the materials that supported your opinions in your declaration?

MS. PATEL: Objection. Asked and answered.

A. I believe I've answered the question.

Q. Please do so again.

MS. PATEL: Same objections.

A. There are no articles I reviewed that I excluded because they didn't favor my opinion.
Q. Okay. And you're a medical doctor; correct?
MS. PATEL: Objection.
A. Correct.
Q. And so you're not an expert in chemistry; right?
A. Correct.
Q. You're not an expert in medicinal chemistry?
A. Correct.
Q. You're not an expert in chemical structures?
A. Correct.
Q. You're not an expert in protein structures?
A. Correct.
Q. You're not an expert in kinase structures?
A. Correct.
Q. You're not an expert in the chemical structure of small molecule drugs?
A. Correct.
Q. You're not an expert in structural interactions between small molecule drugs and proteins?

A. Correct.

Q. And you're not an expert in structural interactions between small molecule drugs and kinases?

A. Correct.

Q. And you don't have any other specialized training in the field of protein kinase structures?

A. Correct.

Q. And you don't have any expertise in the structure function relationship between BTK and BTK inhibitors?

A. Correct.

Q. And you don't have any expertise in the structure or function relationship of protein kinases generally?

A. Correct.

Q. So any details about how a compound would be expected to interact with BTK, you would need to rely on someone else with that specialized training in kinase structure and inhibitor design?

A. I would.

Q. And you're not personally involved in

studying the structural mechanism of kinase inhibition?

A. Only in an abstract way.

Q. What do you mean by an abstract way?

A. I've developed therapeutics that are inhibitors of kinases, but I'm not a medicinal chemist and I am not the one who would decide or formulate the structures.

Q. In your experience in developing therapeutics that are kinase inhibitors, your experience is on the clinical side; is that right?

A. Both pre-clinical and clinical.

Q. And what is your pre-clinical experience in the development of kinase inhibitors?

A. My laboratory would be involved in some of the in vitro cellular analyses and pre-clinical animal testing. And then I would be also involved in the clinical therapeutics.

Q. And in the testing, the in vitro cellular testing and animal testing that you've done, you've not been involved in correlating the testing results with the structure of the compounds that you were

testing; is that right?

MS. PATEL: Objection. Vague. Form.

A. Can you be a little bit more specific?

Q. Sure. So you said that you have experience in pre-clinical testing, including in vitro cellular testing and animal testing; is that right?

A. That's right.

Q. And in your experience in running those sorts of tests, those pre-clinical tests, you've not then yet -- you have not taken the step of associating the testing results to how the structure of the drug you were testing affected those results; is that right?

MS. PATEL: Objection. Form. Vague.

A. I don't quite understand the question. I'm sorry.

Q. That's okay. I think maybe it will become clearer if we do more specific questions later.

A. Okay.

Q. In running the tests that you've done, your experience running pre-clinical tests, you wouldn't be able to look at the structure of a compound and

understand what kind of activity it would have; is that fair?

MS. PATEL: Objection. Form.

A. It would be fair to say I'm not a medicinal chemist, and I work with medicinal chemists on these analyses.

Q. But they're not analyses you perform in looking at a structure and understanding what that -- what kind of function that structure may have; is that right?

MS. PATEL: Objection. Asked and answered.

A. I believe I have given you the answer of what my expertise is.

Q. So I understand that your counsel is making objections, but you do still need to answer my question regardless of whether or not you think you've answered it before. So I'll just ask it again. Okay?

The -- you said that you are not a medicinal chemist and you work with medicinal chemists who work on analyses related to understanding how a structure of a compound may have particular

activity; is that right?

A. Correct.

Q. Okay. But you yourself do not perform those analyses of understanding how a structure of a compound may have particular function; is that right?

MS. PATEL: Objection. Vague. Asked and answered.

A. It is vague. If you could be more specific, I'm happy to answer the question.

Q. Okay. The medicinal chemists that you work with perform analyses where they look to understand how the structure of a compound relates to its particular functions; is that right?

A. Correct.

Q. But you yourself do not perform analyses correlating the structure of a compound to particular functions; is that right?

MS. PATEL: Objection. Vague. Asked and answered.

A. I don't want to misspeak, and so I'm not comfortable answering in the way you frame the

question. I apologize.

Q. What about my question is confusing to you?

A. So a medicinal chemist may look at the structure of a molecule. We would have a dialogue about the structure of that molecule and what it's targeting on a particular protein. I'm capable of understanding those conceptual aspects. I'm not a medicinal chemist in being able to construct a therapeutic. And I would say a medicinal chemist would have a skill set much broader than me in terms of how to manipulate a specific structure in its broadest sense.

Q. And how to manipulate a chemical structure to affect its function is not one of the skills in your skill set; is that right?

MS. PATEL: Objection. Asked and answered. Vague.

A. That would be correct.

Q. Okay. And in particular, in this case, you are not able to opine on whether any structure irreversibly inhibits BTK; right?

MS. PATEL: Objection. Form.

A. Can you be, again, more specific?

Q. What is unspecific about my question? Do you need me to repeat it?

A. No, I mean, it's contextual. If you gave me a molecule that I knew wouldn't bind to BTK, then I would be able to say it won't bind to BTK. But if you're asking me in the context of something that's a structural BTK inhibitor in all the permutations, that is correct, I would rely on Dr. Showalter.

Q. In the context, you stated that -- in the context of something that's a structural BTK inhibitor in all the permutations, you would rely on Dr. Showalter as to whether or not it would inhibit BTK; is that right?

MS. PATEL: Objection. Vague. Asked and answered.

A. It's correct, for structural issues related to BTK inhibitors, Dr. Showalter is an expert.

Q. And you would need to rely on someone like Dr. Showalter to understand permutations of structure and its effect on BTK inhibition; is that right?

A. Again, it's a little bit vague for me because there are conceptual aspects and then there are scientific aspects. So you could have a molecule that binds to BTK but not inhibit the BTK, as an example.

Q. And how do you -- sorry. I didn't mean to interrupt you if you still had --

A. No, that's all right.

Q. And are you able to identify a molecule that binds to BTK but does not inhibit BTK?

A. Well, I think, in advance, a structural or medicinal chemist could make an assertion, but it's really only through experimentation that you could verify. So the theoretical would often come from a medicinal chemist. The experimentation my lab would be involved with as well, but I would not be involved in the construction of the molecule.

Q. And in not being involved in the construction of the molecule, you're not involved in designing molecules intended to be BTK inhibitors; right?

A. Yes. A medicinal chemist would have

predictions, but experimentation is essential in order to know what will work and not work.

Q. And you're not an expert in assessing the physiochemical properties of a compound; is that right?

A. Correct.

Q. And those include things like the molecular weight of the compound?

A. Correct.

Q. The size of the compound?

A. Correct.

Q. The pKa of a compound?

A. Correct.

Q. The C log P of a compound?

A. Correct.

Q. The partition coefficient of a compound?

A. Correct.

MS. PATEL: Objection. Vague.

Q. The solubility of the compound?

MS. PATEL: Objection. Vague. Form.

A. Correct.

Q. And you don't have any expertise in

understanding how different structures may affect these physiochemical properties?

MS. PATEL: Objection. Form. Vague.

A. I would say not at the level of a true expert.

Q. And you're not offering opinions in this proceeding about how the structure of a BTK inhibitor affects its physiochemical properties; correct?

MS. PATEL: Objection. Vague. Form.

A. That is a little bit vague for me.

Q. So for example, you're not offering opinions of how modifications in structure would be understood to affect the physiochemical properties of BTK inhibitors in this proceeding; correct?

MS. PATEL: Same objections.

A. Can you be a little bit more specific? I don't want to misstate anything.

Q. Sure.

What specificity do you need?

A. So I'm not expert in the structure of the molecule, potentially, that should be tried. My lab

would look at does it have an impact, recognizing that in most instances, what may be predicted when you do experimentation isn't what's seen. And so I'm not sure that I understand specifically what your question was related to the molecule itself versus its interaction with a, in this case, BTK versus what the effect is. Because as Dr. Showalter states in his declaration, there was a billion perturbations, and the structure, obviously, of all these billion molecules is different. But it's only when you get to experimentation that you say, this is something that looks exciting and works.

Q. And you mentioned in your response there that there are predictions that are made with respect to the physiochemical properties of a compound; is that right?

MS. PATEL: Objection. Mischaracterizes prior testimony.

A. Can you restate it? I apologize.

Q. Sure.

You mentioned in your previous response that there may be -- they may be predicted -- let me --

let me strike that. Let me start over.

You said you're not an expert in the structure of the molecule that potentially should be tried, that your lab would look at does it have an impact, recognizing that you do experimentation -- that in most instances, what may be predicted when you do experimentation isn't what's seen.

Is that roughly about what you testified?

A. Yes.

Q. Okay. And so in that testimony, you're recognizing that there are predictions that are made about the types of physiochemical properties that a structure may have; is that right?

MS. PATEL: Objection. Mischaracterizes prior testimony. Asked and answered.

A. What's not covered in what I responded?

Q. I'm -- so Dr. Rosen, I'm asking questions to try to clarify some of your testimony and to understand what your opinions, your expertise, and bases are. I understand that your counsel is making quite a few objections, and you seem to be responding to that. I just would like you to

respond to my questions.

So what I'm trying to understand is your testimony, and so I'm asking you some additional questions. Okay?

A. Okay.

Q. Okay. Do you recognize that there are predictions that are made about the types of physiochemical properties that a chemical structure may have?

MS. PATEL: Objection. Asked and answered.

A. I believe I've answered it, but yes.

Q. And you are not an expert in making those predictions about what physiochemical properties a particular chemical structure may have; is that right?

MS. PATEL: Objection. Vague. Asked and answered.

A. Again, I believe I have answered it, but yes.

Q. And you're not a structural biologist; right?

A. Correct.

Q. You have no specialized training in the field of structural biology?
A. Correct.
Q. And you understand here that we're talking about a class of compounds that have a component that's been designated Z prime.
Do you recall that?
MS. PATEL: Objection. Lacks foundation.
A. I do recall the figure that has the Z-prime structure.
Q. And you don't have any specialized training that allows you to opine on how the structure of Z prime impacts the activity of the compound; is that right?
MS. PATEL: Objection. Vague.
A. I'm not a medicinal chemist.
Q. So no, you don't have that training?
A. I do not --
MS. PATEL: Objection. Asked and answered.
Sorry.
A. I do not have that training.
Q. And your understanding about the impact of

the Z-prime component on activity is based on Dr. Showalter's analysis; correct?

MS. PATEL: Objection. Vague. Lacks foundation.

A. I think Dr. Showalter is an expert in that domain, and I didn't rely on his opinion.

Q. And you haven't conducted a separate analysis or formed a separate opinion on the way that Z prime can affect activity; right?

MS. PATEL: Objection. Vague. Asked and answered.

A. I am not a medicinal chemist. I don't have that level of expertise.

Q. All right. But you are an expert in clinical oncology; right?

A. I am.

Q. Okay. And you're an expert in the treatment of CLL and SLL and other lymphomas?

A. I am.

Q. Okay. And you treat CLL and SLL patients?

A. I do.

Q. And you use BTK inhibitors to treat CLL and

SLL patients?

A. I do.

Q. And you've -- you have used ibrutinib and zanubrutinib to treat CLL and SLL patients?

A. I have.

Q. And ibrutinib and zanubrutinib treat CLL and SLL patients by irreversibly inhibiting BTK?

A. Yes.

Q. And they irreversibly inhibit BTK by binding to a cysteine residue in BTK?

MS. PATEL: Objection. Outside the scope of expertise.

A. That's what's reported.

Q. And in inhibiting BTK, BTK inhibitors inhibit B-cell proliferation and reduce tumor growth?

MS. PATEL: Objection. Form. Vague. Lacks foundation.

A. Please restate the question.

Q. BTK inhibitors inhibit BTK and thereby inhibit B-cell proliferation and reduce tumor growth?

MS. PATEL: Objection. Vague. Lacks foundation.

A. So in the case of Imbruvica and zanubrutinib, that's the case. I can't say that all molecules that inhibit BTK will be effective therapeutics.

Q. And one way that zanubrutinib and ibrutinib are shown to inhibit BTK is by measuring the occupancy of BTK in patients; is that right?

MS. PATEL: Objection. Lacks foundation. Vague.

A. The way you state the question, it's not correct. But if you restate it, I may have a better understanding.

Q. What's not correct about my question?

A. It's much too vague and not specific enough.

Q. What's vague?

A. Can you restate the question and we can dissect it?

Q. Well, let me state my question, and you can tell me what's vague about it. Okay?

One way that zanubrutinib and ibrutinib are

shown to inhibit BTK is by measuring the occupancy of BTK in patient samples who have received the drugs; is that right?

MS. PATEL: Same objections.

A. By measuring occupancy, you're measuring occupancy. In this instance, the occupancy doesn't necessarily mean you're inhibiting. We know it does but the occupancy doesn't necessarily demonstrate that.

Q. So in your opinion, when the -- when an irreversible BTK inhibitor is bound to BTK, when it occupies BTK, it doesn't necessarily inhibit BTK?

A. Say that again.

Q. Is it your opinion that when an irreversible BTK inhibitor occupies BTK, it doesn't necessarily inhibit BTK?

A. Forgetting about zanubrutinib or ibrutinib, if some BTK inhibitor occupies BTK and inhibits it doesn't necessarily mean it will lead to clinical effect, cell killing, as an example.

Q. Okay. So my question was different. My question was different.

It's whether it inhibits BTK, not whether it has a clinical effect. So is it your opinion that when an inhibitor occupies BTK, it doesn't necessarily inhibit BTK?

A. I would say that when you have a molecule if you're saying that has been shown to inhibit BTK and it is occupying BTK, then presumably, it would lead to killing.

Q. And in leading to killing, that means it would be killing the CLL or SLL cells?

A. In the case of zanubrutinib and ibrutinib, it becomes more complicated if you're just doing a generalized inhibition of BTK. Because a -- theoretically, a molecule can affect other targets, and we know that in the case of toxicity as Imbruvica with, say, atrial fibrillation. But in terms of efficacy, that could also be affected.

Q. I just -- I want to focus a little. You said that if a compound inhibits BTK occupies BTK, then presumably, it would lead to killing. And I just want to clarify that when you say "lead to killing," you mean lead to killing CLL and SLL

cells; is that right?

A. In the case of Imbruvica and zanubrutinib, that's the case. But there would be theoretical considerations where you could have a molecule that inhibits BTK but at the same time, because of effects on other proteins, does not lead to killing.

Q. And you have not identified any examples of compounds that inhibit BTK. But at the same time, because of effects on other proteins, does not lead to killing; is that right?

A. That's right.

Q. Okay. And occupancy, the occupancy of BTK was measured in the clinical trials for Imbruvica and Brukinsa; is that right?

A. That was in the publication from Dr. Byrd in the New England Journal of Medicine.

Q. And that related to occupancy measurements that were done for ibrutinib; right?

A. Right.

Q. And were occupancy performed for zanubrutinib in clinical studies?

MS. PATEL: Objection. Lacks foundation.

A. Not --

(Indiscernible crosstalk.)

Q. I think you spoke over. Could you repeat your response?

A. Not in Dr. Byrd's study. That was focused on Imbruvica.

Q. My question is not related to Dr. Byrd's.

Just the occupancy of zanubrutinib in BTK was also measured when zanubrutinib was studied clinically; is that right?

A. I would have to --

MS. PATEL: (Inaudible.)

THE WITNESS: Apologize.

MS. PATEL: Same objection.

A. I would have to review the individual articles to feel comfortable answering that question.

Q. So you're not familiar with whether or not the occupancy was part of the clinical assessment of zanubrutinib?

A. It would be an assumption on my part that it was. But I would want to review the articles.

Q. And why would you assume that it was in -- that occupancy was included in the clinical assessment of zanubrutinib?

MS. PATEL: Objection. Form.

A. It's often part of the clinical development of compounds.

Q. Occupancy is often part of the clinical development of compounds?

A. Not always. But it can be and is.

Q. And in particular, for irreversible inhibitors, occupancy has become part of the clinical development and understanding of the compound in clinical studies?

MS. PATEL: Objection. Vague. Lacks foundation.

A. Occupancy is a component of the assessment. It's not done in every instance.

Q. Let's take a look at Exhibit 1053, and I'm not sure if that's one of the ones that was included in your binder.

(Exhibit 1053, previously marked, is attached to the transcript.)

MS. PATEL: Dr. Rosen, that should be Tab 32 of your binder.

Brenda, is that the Guo 29 article?

MS. DANEK: Yes.

BY MS. DANEK:

Q. Dr. Rosen, do you have 1052 -- or sorry -- Exhibit 1053 in front of you?

A. I do.

Q. And this is one of the references you reviewed in forming your opinions in this case?

A. This would have been reviewed last fall when we were putting together the declaration.

Q. And have you had -- have you reviewed it more recently than that?

A. I have not.

Q. I want to -- you know, please feel free to take a look through it, but I want to ask you some questions about occupancy. And I'll just direct you to the second page of the document in the left-hand column.

A. I have that.

Q. Okay. And in the middle of the page,

there's a paragraph that starts "For traditional reversible inhibitors."

Do you see that?

A. I do.

Q. Okay. And it says that, [As read] For traditional reversible inhibitors, a drug candidate target profile in terms of pharmacokinetics would have high oral bioavailability, low clearance, and reasonable half-life, while a covalent inhibitor can persist in vitro PD even after it has disappeared.

And in that sentence, does PD refer to pharmacodynamics?

MS. PATEL: Objection. Outside the scope of his declaration.

A. Though most likely it refers to pharmacodynamics, that would make sense, I don't see the abbreviation -- maybe you can point me to it -- on the previous page or the page above that.

Q. If you look on the right-hand column?

A. On the previous page?

Q. No, I'm sorry, on the same page. Apologies. The last full paragraph, the last sentence

indicates -- that starts with "Possibly due to the rigidity."

Do you see that?

And in there it says --

A. I do.

Q. -- "Led to poor pharmacodynamic (PD) effects."

Do you see that?

A. I do. It's a little bit unusual to have the abbreviation before you actually have it abbreviated, but that was my only reason for reviewing the previous component.

Q. Uh-huh.

A. I wanted to be accurate.

Q. I can appreciate that. Okay.

So here it -- the paper here indicates that a covalent inhibitor can persist in vivo PD even after it has disappeared.

And we agree that PD stands for pharmacodynamic?

A. Okay.

Q. Okay. And then, two sentences later, it

says, [As read] For ibrutinib, a high dose (560 mgs daily) is required to achieve effective target BTK occupancy.

Do you see that?

A. I do.

Q. And so for -- so occupancy is used to assess what an effective dose would be?

MS. PATEL: Objection. Vague. Mischaracterizes the document. Outside the scope.

A. The effective dose is based on what we see in clinical trials where we do a Phase 1 study with a dose escalation to see what dose is effective and, at the same time, look for safety. This may give some indication, but the proof of the pudding is what's seen in human testing.

Q. My question was a little bit different.

My question was that occupancy was used to understand what an effective dose may be; is that correct?

MS. PATEL: Objection. Vague. Mischaracterizes the document. Outside the scope.

A. It is somewhat vague to me, and it's more of

a theoretical construct.

Q. Do you agree that effective BTK target occupancy is related to what -- strike that.

Do you agree that occupancy is used to assess what could be effectively inhibiting the BTK?

MS. PATEL: Objection. Vague. Form. Lacks foundation.

A. I agree that occupancy is one of the considerations. It may not, however, give true accuracy in terms of clinical benefits.

Q. And in your opinion, without full clinical trials, you would not be able to conclude that a drug is therapeutically effective?

MS. PATEL: Objection. Vague. Lacks foundation.

Dr. Rosen, feel free to look at your declaration to answer these questions.

MS. DANEK: Counsel, you have been making a series of speaking objections, and I would appreciate if you could be a little bit reserved in the coaching.

MS. PATEL: Counsel, I am not -- I have not

been making speaking objections. You've been asking questions and I have stating objections. We disagree with that, but let's move forward and see if it --

A. So maybe if you can point me to the appropriate part of my declaration so that there's no confusion.

Q. So I'm referring to your testimony. You said the effective dose is based on what we see in clinical trials where we do a Phase 1 study with a dose escalation to see what dose is effective and, at the same time, look for safety.

Did you -- is that your testimony?

A. Yes, that's correct.

Q. Okay. And so your opinion is that, in the absence of a Phase 1 study, you would not have information about whether or not a dose a therapeutically effective?

MS. PATEL: Objection. Vague. Calls for speculation. Lacks foundation.

A. Well, it's my opinion that the reason we do a Phase 1 trial is to know what an effective dose is

and what the potential toxicity would be.

Q. And then one of the targets for assessing an effective dose is achieving an acceptable BTK target occupancy?

MS. PATEL: Objection. Vague. Lacks foundation.

A. That would be presumptive.

Q. What is presumptive?

A. That the occupancy percentage is essential.

Q. So the occupancy percentage is essential to understanding if a dose is effective?

MS. PATEL: Objection. Mischaracterizes prior testimony.

A. No.

Q. What do you mean -- sorry.

A. It's presumptive that a certain level of occupancy is essential for a clinical effect or for toxicity.

Q. Okay. So I just want to make sure I understand your opinion there.

In your opinion, occupancy of BTK is essential to see a clinical effect from inhibiting

BTK?

MS. PATEL: Same objection.

A. The sentence was incomplete. That occupancy is essential but the degree of occupancy may not impact the therapeutic effect or the toxicity.

Q. What do you mean that the degree of occupancy may not impact the therapeutic effect?

A. That you could have an amount of occupancy that leads to an effect, and it could be different, potentially, for different BTKI inhibitors, and as well as the toxicity that's seen, which are off-target effects, as, for example, the atrial fibrillation with Imbruvica.

Q. So you said that you could have an amount of occupancy that leads to an effect; is that right?

MS. PATEL: Objection. Mischaracterizes prior testimony.

A. That there may be a level of occupancy for a BTKI inhibitor that's -- and this requires experimentation and human testing -- that leads to a clinical benefit without undue toxicity. But the clinical benefit for BTKI inhibitors may be

different at different occupancy levels. Some may be more potent than others, and the toxicity may not require the same level of occupancy.

THE WITNESS: I wonder, if you don't mind, we've been going for about an hour. Can we take a ten-minute break just so I can catch up on some patient-related issues?

MS. DANEK: Of course. That's not a problem.

THE WITNESS: Would ten minutes be okay?

MS. DANEK: Ten minutes works fine.

REMOTE TECHNICIAN: Off the record. The time is 10:59.

(A short break was had.)

REMOTE TECHNICIAN: Back on the record. The time is 11:09.

BY MS. DANEK:

Q. Dr. Rosen, during the break, did you confer with counsel at all?

A. No.

Q. I want to pull up Exhibit 1014, which is the Imbruvica package insert. Is that one of the

documents you have in front of you?

(Exhibit 1014, previously marked, is attached to the transcript.)

MS. PATEL: That should be --

THE WITNESS: I believe it's in the first binder.

MS. PATEL: Uh-huh. I think it's Tab 13 of your binder.

BY MS. DANEK:

Q. Do you have Exhibit 1014 in front of you, Dr. Rosen?

A. I'm sorry. These binders are quite large. It takes me a moment to --

Q. Lawyers generate a lot of paper.

A. I apologize.

THE WITNESS: What tab did you say it was under?

MS. PATEL: I think it's 13 of the first binder.

THE WITNESS: Okay.

MS. PATEL: And just to confirm, Counsel, this is, you said, Exhibit 1014 Imbruvica label,

dated May 2023.

Is that -- just to make sure I'm directing Dr. Rosen to the correct tab. Is that what you're --

MS. DANEK: Exhibit 1014, yes.

MS. PATEL: Okay.

A. I have it.

BY MS. DANEK:

Q. Okay. And, Dr. Rosen, are you familiar with this exhibit?

A. I have not reviewed it for purposes of today's deposition, but I'm familiar with it.

Q. And it's one of the exhibits that you've cited in your declaration?

A. Correct.

Q. And you're familiar with FDA package inserts, generally?

A. I am.

Q. You understand that's where the maker of the drug writes out information about the drug and how to use the drug and other data available about the drug?

A. Correct.

Q. So I want to turn your attention to page 47 of the document. Let me know when you're there.

A. I'm there.

Q. Okay. And at the top, there's an underlined heading called "Lymphocytosis."

Do you see that?

A. I do.

Q. And it indicates that [As read] Upon initiation of single-agent Imbruvica, an increase in lymphocyte counts (i.e., greater than or equal to 50 percent increase from baseline and above absolute lymphocyte count of 5,000 per mcL) occurred in 66 percent of patients in the CLL studies.

Do you see that?

A. I do.

Q. And so CLL patients who were treated with ibrutinib exhibit lymphocytosis?

A. They do.

Q. And you understand that not every patient exhibited lymphocytosis as reported here?

A. As reported here, yes.

Q. But in these trials, 66 percent of CLL patients did?
A. Correct.
Q. Okay. And let's take a look at Brukinsa's package insert, so that is Exhibit 1012.
(Exhibit 1012, previously marked, is attached to the transcript.)
MS. PATEL: Dr. Rosen, that should be Tab 11 of your first binder.
A. I have it.
BY MS. DANEK:
Q. And CLL patients who are administered zanubrutinib also experience lymphocytosis?
A. They do.
Q. And I want to turn your attention to page 29 of this document.
A. I have page 29.
Q. And you see at the top, there's a table of -- that has columns for parameter and then CLL and SLL patients with particular characteristics?
A. You're referring to the response parameters?
Q. Yes. Yes.

A. Okay. Because I would think that the characteristics are without deletion(17p).

Q. The parameters, yes, and then the CLL and SLL patients with that particular characteristic. Yep.

A. I do see that.

Q. Okay. And in the parameters, the response parameters that are identified, one is called nPR.

Do you see that?

A. I do.

Q. Do you know what nPR refers to?

A. They refer to it as a nodular partial response.

Q. Do you know what nodular partial response refers to?

A. That the lymph nodes in the spleen diminish but a lymphocytosis is seen.

Q. So the nodular partial response is a reference to lymphocytosis observed in CLL patients being administered zanubrutinib?

A. That would be my understanding, though not stated here.

Q. Okay. And then if we take a look at -- flip back to page 8. Let me know when you're there.

A. I'm here.

Q. There's another chart here, and it has laboratory parameters and then percent of patients who experience these parameters?

A. I see that.

Q. Okay. And the top -- the top row is lymphocytosis.

Do you see that?

A. I do.

Q. And so this is reporting patients who received zanubrutinib. There was observed lymphocytosis; is that right?

A. That would be my understanding, though I'm not looking earlier in the document.

Q. Yep. And there's a footnote there.

Do you see that?

A. I do.

Q. And in the Brukinsa package insert, BeiGene told the FDA that [As read] Asymptomatic lymphocytosis is a known effect of BTK inhibition.

Do you see that?

A. I do.

Q. Okay. And that's true, right, that inhibiting BTK results in asymptomatic lymphocytosis?

MS. PATEL: Objection. Vague.

A. It can.

MS. PATEL: Lacks foundation.

Q. I'm sorry. I think I missed your response.

A. It can.

Q. And the observed lymphocytosis in ibrutinib and zanubrutinib is the result of BTK inhibition; right?

MS. PATEL: Objection. Vague.

A. That is my understanding.

MS. DANEK: And so let's mark as Rosen Exhibit 1 a 2011 paper authored by you and Dr. Ma.

(Exhibit 1 was marked for identification and is attached to the transcript.)

MS. PATEL: Counsel, as we discussed earlier, could you -- it sounds as if that document is not currently of record in this PGR; is that

right?

MS. DANEK: That's right.

MS. PATEL: Could we -- could you send that to us so that Dr. Rosen may print it and have a hard copy to review.

MS. DANEK: Well, I believe it's downloadable from the exhibit -- I can email if it's easier for you.

REMOTE TECHNICIAN: Counsel, would you like for me to put it in the chat?

MS. PATEL: Oh, sure. You'll have to excuse me. I'm ...

BY MS. DANEK:

Q. So, Dr. Rosen, let's proceed with the document on the screen. And to the extent there are questions that require you to have the hard copy, you know, we can come back to it. But let's see if we can't navigate the remote deposition as it exists.

MS. PATEL: I would just note for the record, as we discussed earlier, we said Dr. Rosen prefers to review documents in hard copy rather than

on the screen. It would facilitate this deposition if you were to send him -- if I could send him the PDF and then he could print it out and review the hard copy.

BY MS. DANEK:

Q. So, Dr. Rosen, do you see the exhibit on the screen? You should be able to control the document.

A. I do see it.

Q. And this Rosen Exhibit 1 is a publication entitled, "Signal transduction inhibitors in chronic lymphocytic leukemia," authored by Shuo Ma and Steven T. Rosen; is that right?

A. That's right.

Q. And you're the Steven T. Rosen that is the author of this paper?

A. I am.

Q. Okay. And do you remember or recall this paper?

A. No.

Q. Do you recall writing papers about treatment of signal transduction inhibitors in CLL generally?

A. No.

Q. Do you have any reason to doubt that this is a paper that you authored and published?

A. I'm sure I did write it in conjunction with my colleague, Dr. Ma, almost 15 years ago. I don't question that.

Q. Okay. And in publishing articles, you would have reviewed the contents of the article to make sure they were accurate and complete?

A. In that time frame, yes.

Q. And today, you also would do the same?

A. Yes, though knowledge changes over the course of 15 years.

Q. Certainly.

And in this --

A. Excuse me. As do opinions.

Q. And in this paper from November of 2011, you have a section -- if you turn to the third page -- on "Bruton's tyrosine kinase inhibitors."

Do you see that?

A. I see the third page.

Q. And do you see the section on BTK inhibitors?

A. I do.

Q. And in the -- in this section, you report on clinical study results from Pharmacyclics ibrutinib?

A. I see in the last sentence, it says that [As read] PCI-32765 -- which I understand to be ibrutinib, that's -- (Audio disruption) -- at that time by Pharmacyclics -- is an orally available, irreversible, small-molecule inhibitor of BTK.

Q. And going into the second column on that page, you lay out additional details about the clinical study results from ibrutinib?

A. I can't see the other page. You'd have to show me.

Q. It's the second column. You should have control and be able to scroll on the document.

A. Oh, I apologize. I -- that's not one of my skill sets, so you'll have to help me.

Q. All right.

A. But I'm patient. So you can show me.

Q. Okay. So starting at the top of the second column --

MS. DANEK: If we can scroll up there.

Okay.

Q. -- you report on clinical study, the clinical studies of ibrutinib.

Do you see the summary there in that discussion?

A. I do.

Q. Okay.

MS. DANEK: And if we scroll down to the sentence starting, "Of the 45 patients evaluable," which is at the bottom of the screen now.

A. I see that.

Q. Okay.

MS. DANEK: If we can scroll down so we can see that section.

Q. And here, it reports that "Of the 45 patients" -- or you report, rather, [As read] Of the 45 patients evaluable for response, complete remission was achieved in one patient, partial response (PR) in 16, and nodal response with lymphocytosis in 19 patients.

Do you see that?

A. I do.

Q. Okay. And so here, you're reporting on the lymphocytosis that was observed in CLL patients being administered Imbruvica or, at that time, ibrutinib?

A. Yes.

Q. Okay. And you report that [As read] The latter response describes a unique clinical response of this agent with reciprocal change of lymphocyte count and lymph node sizes -- many patients experienced rapidly reduced lymphadenopathy with concurrently increased peripheral blood lymphocytosis during the initial few weeks of treatment.

Is that right?

A. That's correct.

Q. And that aligns with your experience using ibrutinib regarding the appearance of lymphocytosis after being administered ibrutinib in CLL patients?

A. Correct.

Q. And then, a couple sentences down, you say, [As read] This phenomenon is likely due to the unique impact of BTK inhibition on promoting

lymphocyte trafficking out of the protective lymph node and bone marrow microenvironment.

Is that right?

A. Correct.

Q. So the mechanism for lymphocytosis is the -- the unique impact of BTK inhibition on promoting lymphocyte trafficking?

MS. PATEL: Objection. Mischaracterizes the document. Vague.

A. I'm sorry. Repeat the question. Apologize.

Q. Sure. So the unique impact of BTK inhibition on -- sorry.

A. Are you reading a sentence of mine right now?

Q. Yeah. In your sentence there, it says, [As read] The unique impact of --

A. Oh, I see, yes.

Q. [As read] -- BTK inhibition on promoting lymphocyte trafficking --

A. I see that.

Q. [As read] -- is what causes lymphocytosis?

A. Correct.

MS. PATEL: Same objections.

Q. Okay. Okay.

MS. DANEK: We can take this document down.

Q. Okay. So also we've been talking about your expertise in treating CLL and SLL patients but you also have conducted a number of clinical trials; is that right?

A. I have.

Q. And you've been involved in Phase 1 studies?

A. I have.

Q. And those studies frequently involve dose escalation?

A. They do.

Q. And that's where patient cohorts are given increasing doses of drug?

A. Correct.

Q. That's a common approach for these initial trials and designing those initial trials?

A. Yes.

Q. And in the -- these Phase 1 studies, it's common to see patient responses at different doses that are assessed in those studies?

A. Yes.

Q. And another aspect of clinical trials is assessing the safety of the drug candidate?

A. Correct.

Q. And safety considerations include identifying adverse events?

A. They do.

Q. And a drug can be therapeutically effective and still result in significant adverse events; is that right?

A. Yes.

MS. PATEL: Objection. Vague. Lacks foundation.

A. You want me to respond?

Q. I think you already did.

A. Yeah. I would just say that it is correct that a drug can be effective but also carry significant toxicity, and that actually is the case with Imbruvica.

Q. And ibrutinib is an effective treatment for CLL and SLL; right?

MS. PATEL: Objection. Calls for

speculation.

A. It's an effective drug with significant toxicity, correct.

Q. And ibrutinib remains approved by the FDA for the treatment of CLL and SLL today?

A. Correct.

Q. And ibrutinib has been the -- in the past, it has been the standard of care for CLL and SLL patients?

MS. PATEL: Objection. Vague.

A. Again, timeline is critical. Ibrutinib had first emerged as a therapeutic, was the only BTKI inhibitor available, and it is effective. With subsequent second-generation BTKIs, the majority of us are no longer using ibrutinib because of its toxicity profile.

Q. But not because it's not effective; right?

A. Correct, though zanubrutinib happens to be more effective than ibrutinib, as shown in the Alpine trial.

Q. Okay. So I want to talk about the analysis that you conducted for this matter.

You conducted your analysis from the perspective of a person of ordinary skill in the art; is that right?

A. I'm an expert, but I understand what a POSA would have to know in order to render an opinion.

Q. It might be helpful -- sorry. Didn't mean to interrupt.

A. Yeah. When I was doing my initial review, we discussed that in depth.

Q. And when you say "we discussed that in depth," do you mean you discussed that in depth with your counsel when you were preparing your declaration?

A. Correct, that they explained to me --

MS. PATEL: Objection. Privilege. Objection.

Counsel, are you asking for the substance of our discussions with --

MS. DANEK: I am not. I was asking to clarify what his testimony was, that it wasn't that he was referring to discussions we had had during today's deposition.

MS. PATEL: Okay. Could you rephrase your question and --

MS. DANEK: I think we're all clear. I'm not asking for the substance of any --

MS. PATEL: Okay.

BY MS. DANEK:

Q. So it might help if we turn to a paragraph in your declaration. If we turn to paragraph 175 of Exhibit 1005 -- I said 175. I meant 174.

A. This would be paragraph 174?

Q. Yeah. It's on page 77 of the document.

A. I have it.

Q. And it lays out here your opinion about what the level of ordinary skill in the art would be; is that right?

A. It does.

Q. And it includes at least two members; is that right?

A. Correct.

Q. And one of the members would be a member that had at least a medical degree with training in hematology and oncology, including several years of

clinical experience in treating hematologic malignancies. That would be a clinical member; is that right?

A. Correct.

Q. The second member would be a member that had least a Ph.D. in chemistry, organic chemistry, or a related field with training as a medicinal chemist, and that would be the chemist member?

A. Correct.

Q. And your -- you are analyzing the claims from the perspective of the clinical member; right?

A. Correct.

Q. And you don't have the training to analyze the claims from the perspective of the chemist member?

A. Correct.

Q. And the chemist member is part of the team because it's important to have the perspective of someone who understands the structure and function of protein kinase inhibitors?

A. Correct.

MS. PATEL: Objection. Vague.

Q. And the clinical member wouldn't have that understanding; right?

MS. PATEL: Objection. Vague.

A. The clinical -- the clinical member would not necessarily have the skills about the structure of the molecule. The functional aspects the clinical member could have knowledge of and obviously the clinical impact.

Q. But not how the structure impacts those functional aspects; right?

MS. PATEL: Objection. Vague. Lacks foundation.

A. Not the actual structure itself.

Q. And they would need to rely on the understanding of the chemist member as to how the structure affects the activity?

A. In general, yes.

Q. Now, you indicate in here that you have analyzed the views of the -- of a POSA as of both 2010/2011, and July 2020; is that right?

A. I said accurately represent the views of a POSA as of both the 2010/'11, and July 2020 time

periods, at least as to those limitations of the challenged claims.

Q. And so you analyzed the claims at both time points, 2010/2011 and July of 2020?

A. I looked at the claims in both time periods but, for purposes of today's discussion, I reviewed only the 2020.

Q. So your opinions in your declaration -- your opinions in your declaration are limited to the perspective of a person of ordinary skill in the art as of July of 2020?

A. No, as --

MS. PATEL: Objection. Mischaracterizes prior testimony.

A. No. As I said, as of both 2010 and '11 and July 2020 time periods.

Q. What did you mean when you said "I looked at the claims in both time periods but, for purposes of today's discussion, I reviewed only the 2020"?

A. In terms of materials that I reviewed for the deposition, I mentioned earlier to you that I reviewed my declaration, Dr. Showalter's

declaration, the appeal board's review, and the '803 patent. I didn't go back and review the previous patent.

Q. Okay. I understand.

A. So if -- yeah.

Q. And if you turn -- maybe it's easier if we turn to paragraph 32.

A. 32?

Q. Yeah, page 15 of the document.

A. And this is --

Q. I'm sorry. I said 32. I meant -- that's where you lay out your understanding of the priority date, how to assess priority date of a patent?

A. I'm sorry. It's not page 15. It's -- what page is it?

Q. It's 15 of the document, page 9 of the declaration.

A. Oh, okay.

I'm on the same page.

Q. Do you see paragraph 32?

A. I do.

Q. And paragraph 32 lays out your -- 31 and 32

lays out your understanding of how to assess the effective filing date and, therefore, the time from which to analyze patent claims?

A. Yes, I believe I understand that in terms of the ruling that happened in 2013 and the subsequent claims that may occur.

Q. And you applied that in, if we look at paragraph -- sorry, I keep flipping back and forth -- 171 -- no, 172 of your declaration. So that's going back to page 77 of the document, 71 of the declaration.

A. I have that.

Q. Okay. And so here you've applied the perspective of a POSA both time frames, 2010/2011 and 2020?

A. Correct.

Q. Okay. And so certain parts of your declaration are from a perspective of a person of ordinary skill in 2020?

A. Correct.

Q. And other parts are from the perspective of a person of ordinary skill in 2010/2011?

A. Correct.

Q. Okay. And if your -- in your analysis, if you cited authority or if you used 2020 as your perspective, then you cited authority after 2010/2011?

A. I don't understand that language.

Q. Sure.

So in your analysis, you cited references from a variety of years; is that right?

A. Correct.

Q. Okay. And so if you cited references dated after 2010/2011, that analysis -- your analysis was from the perspective of a person of ordinary skill in the art in 2020?

MS. PATEL: Objection.

A. Correct.

MS. PATEL: Vague.

Q. And at certain points, you refer to the date 2010/2011, say, you know, for example, in paragraph 270, you say "as of June 2010/2011."

Do you see that in the previous page from where we were?

A. I'm sorry. If you could point me to that, I'll pull it up.

Q. All right. I'm just, sort of, trying to find an example. So paragraph 270.

A. Paragraph 270, I'll turn to that.

Q. Yeah. 268. Many of the paragraphs in this section here.

Do you see references to --

(Indiscernible crosstalk.)

A. Is this where I say, "The state of the art in BTK space as of June 2010/2011 was limited"?

Q. Yes.

And there's a number of places where you say similar things as of note as of June 2010/2011.

In including a reference to June 2010/2011, where you intend to signify that those -- that analysis of those paragraphs was from the perspective of a person of ordinary skill in the art in 2010 and 2011?

A. Yes.

Q. And if you didn't include a reference to June of 2010/2011, then the analysis was from a

perspective of a person of ordinary skill in the art in July of 2020?

MS. PATEL: Objection. Form. Vague. Lacks foundation.

A. You'd have to give me specific examples because some may span the entire period.

Q. But if you cited references dated after July of 2010 -- or I'm sorry -- dated after 2010/2011, then that was analysis from the perspective of a person of ordinary skill in the art in July of 2020?

MS. PATEL: Objection. Form. Vague. Lacks foundation.

A. If you could give me exact examples, it would be beneficial for me. I don't want to misspeak.

Q. All right. You understand -- you understand that this dispute is about certain claims in the '803 patent?

A. I do.

Q. And you analyzed those claims as part of conducting your analysis of -- the perspective of a person of ordinary skill in the art?

A. I did.

Q. And part of analyzing the claims, you analyzed the meaning of certain terms within the claims?

A. I did.

Q. Okay. So I want to direct you to a paragraph starting at 164 on page 74 of the document.

A. I'm sorry. Which page?

Q. 74 of the document but 68 of the declaration. Paragraph 164.

A. I have it.

Q. Okay. And in the -- in this section, you analyze the meaning of "method of treating" and "therapeutically effective amount" as used in the claims of the '803 patent?

A. Correct.

Q. And you identify that the specification defines a method of treating in paragraph 164; is that right?

A. Correct.

Q. And in the definition of "method of

treating," there's not a reference to safety or adverse events, is there?

A. There is not.

Q. And you -- in paragraph 166, you identify that specification defines "therapeutically effective amount."

Do you see that?

A. I do.

Q. And in the definition of "therapeutically effective amount," there's no reference to safety or adverse events?

A. Correct. Well, let me say -- that is correct in paragraph 166.

Q. And in -- you can look at the patent itself, but you've reproduced the claims in your declaration.

A. What confused me before is as I go on in paragraph 67 that [As read] I understand that the specification further defines 'effective amount' as used 'therapeutically effective amount' as 'an amount effective to achieve a desired pharmacologic effect or therapeutic improvement without undue

adverse effects.

Q. All right.

A. [As read] ('Considering the age of the individuals typically diagnosed with CLL and SLL, there is a need in the art for a simple and effective treatment of the disease with minimum side effects that do not impede on the patient's quality of life. The instant invention fulfills this long-standing need in the art.')

That was what was noted in that paragraph.

Q. Right.

And in your declaration, you include the text of the claims that you analyzed. And if it's helpful to turn to that, it's starting at paragraph 105 on page 50 of the exhibit and 44 of the declaration.

A. This is page 68? I'm sorry?

Q. No. Page 50 of the document and 44 of the declaration. Paragraph 105.

A. Well, what I'm seeing on the screen is different. I'm sorry. I apologize.

Q. I don't -- there. They've moved it.

A. Okay. I'm sorry. I was looking at the screen. I got confused.

I have page 44, "Challenged Claims"?

Q. Yes.

A. Yes.

Q. And in these paragraphs starting here, you lay out the text of the claims that you analyzed from the '803 patent?

A. Correct.

Q. Okay. And for example, in paragraph 105, you lay out the text of Claim 1?

A. Correct.

Q. Okay. And in the text of Claim 1, there's no reference to a method of treating CLL or SLL that is FDA approved?

A. Correct.

Q. And that's the same for Claim 8, which you summarize in paragraph 111?

There's no reference to FDA approved in the claim?

A. Correct.

Q. And there's no reference to FDA approval in

any of the other claims that you analyzed, 2 through 7, 12, or 20?

A. Correct.

Q. Okay. So now I want to talk about your analysis of the background of the technology.

Well, actually, let me ask you this.

So in analyzing the claims, you didn't apply a need for FDA approvability in assessing whether or not a compound would meet the therapeutically effective amount; right?

A. Correct.

Q. And you would -- you would agree with me that a compound can be therapeutically effective and have adverse events; right?

A. Correct.

MS. PATEL: Objection. Asked and answered.

Q. And a compound can be therapeutically effective and have even serious adverse events; right?

MS. PATEL: Objection. Asked and answered. Lacks foundation.

A. I believe I have answered it, but yes, there

are compounds that are approved that have serious side effects. And Imbruvica is an example.

Q. Okay. So now let's talk about your discussion of the background of the technology. So this is a section that starts at paragraph 46, which is at page 20 of your declaration -- or I'm sorry -- page 20 of the document, page 14 of the declaration.

A. I'm seeing something, different, again on the screen. I apologize.

Q. I don't --

MS. DANEK: Yeah. If we could move to the portions of the declaration that I call out so that Dr. Rosen can confirm, that would be helpful, Erin.

A. I just want to make sure we're looking at the same thing.

REMOTE TECHNICIAN: Yes. It's just taking me a moment to get there.

MS. DANEK: Oh, okay.

A. Yes. We're on the same page.

BY MS. DANEK:

Q. Okay. And this is where you outline your analysis of the background of technology relevant to

the subject matter of the claims of the '803 patent that you analyzed?

A. Yes.

Q. Okay. And this discussion of the background of the technology was not limited to the perspective of a person of ordinary skill in the art in 2010 or 2011?

MS. PATEL: Objection. Vague.

A. So I do find the question somewhat vague, but if the question is about lymphocytosis, that wasn't appreciated, as far as I know, in 2010-11. That was --

(Indiscernible crosstalk.)

Q. The court -- apologize. Let me be a little bit more precise.

You cite references throughout your discussion of the background technology that are dated after 2010/2011; is that right?

A. I do.

Q. Okay. And so the analysis of the background of the technology in this section is not limited to what a person of ordinary skill in the art would

have understood in 2010/2011; is that right?

MS. PATEL: Objection. Mischaracterizes the declaration. Lacks foundation. Vague.

A. Again, I want to make sure that I'm accurate and don't misspeak. So some of the observations occurred after 2010/2011, and so an expert could know what was happening 2010 and '11 and would have to then follow the literature to know what's happening in the subsequent years.

Q. Well, you would agree with me that references published after 2010/2011 would not be available to a person of ordinary skill in the art in 2010/2011; right?

MS. PATEL: Objection. Asked and answered.

A. If published after, they wouldn't have seen that information in 2010 or '11.

Q. Okay. In paragraph 51, you discuss -- this is in the section called "Bruton's Tyrosine Kinase and the B-Cell Receptor Pathway."

Do you see that?

A. I do. Now it's on your screen as well.

Q. And here in this paragraph, you say towards

the middle-bottom of the paragraph, [As read] BTK 'is required for normal B-cell development' and 'plays a crucial role in proliferation and survival of malignant B-cells,' including in CLL and SLL.

Do you see that?

A. I do.

Q. So one of the causes of CLL and SLL is abnormal BTK activity?

MS. PATEL: Objection. Vague. Mischaracterizes the declaration.

A. That's not what's stated there. It plays a crucial role. I don't know if it's causative. In fact, I'm not sure of any evidence that it's causative.

Q. Abnormal BTK activity appears in patients who have been diagnosed with CLL and SLL; is that right?

A. That's right.

Q. Okay. And that is one of the reasons that BTK inhibitors were developed was to inhibit the activity of BTK that was observed associated with CLL and SLL; is that right?

MS. PATEL: Objection. Calls for speculation. Outside the scope.

A. I don't know the original reason, but that is the case that inhibiting BTK with these specific molecules, Imbruvica, zanubrutinib, acalabrutinib, does effectively treat CLL.

Q. And BTK is significantly overexpressed in CLL and SLL patients compared to normal B-cells; right?

MS. PATEL: Objection. Vague.

A. It is.

Q. And that's one of -- that's one of the reasons that BTK was a therapeutic target for treating CLL and SLL?

MS. PATEL: Objection. Calls for speculation. Vague. Outside the scope.

A. It does play a crucial role in proliferation and survival of malignant B-cells, as stated in the declaration.

THE WITNESS: Could we take another ten-minute break? I'm okay if you want to ask more questions first but then --

MS. DANEK: No, we can take a break.
THE WITNESS: Okay. If you don't mind, just on the hour so I can catch up on everything.
MS. DANEK: Uh-huh.
THE WITNESS: Thank you.
(A short break was had.)
REMOTE TECHNICIAN: Back on the record. The time is 12:10.
BY MS. DANEK:
Q. Dr. Rosen, we were talking about BTK and its properties in CLL and SLL. Your paragraphs here, starting at paragraph 51, there's a number of paragraphs that you refer to Dr. Showalter's declaration, starting actually in paragraph 52.
A. I see that.
Q. Okay. And in paragraph 52, you report on the primary amino acid structure and the three-dimensional structure of BTK as you understand from Dr. Showalter; is that right?
A. That's right.
Q. And you don't have any independent knowledge or understanding of the structure of BTK?

A. I wouldn't consider myself an expert. I know the terminology and the different domains, but I would defer to Dr. Showalter as a true expert in that domain.

Q. Okay. And so the information that's included in paragraph 52, 53, and 54 on the structure of BTK and that cites to Dr. Showalter's declaration, you would defer to him on all of the analysis of the BTK structure?

A. I would.

Q. Okay. And you're not offering any opinions in this proceeding related to the BTK structure?

MS. PATEL: Objection. Lacks foundation. Asked and answered.

A. You'd have to be a little bit more definitive.

Q. So --

A. I'm sorry. Go ahead. I apologize. Go ahead.

Q. So all of the information, for example, in 52, 53, and 54 related to the BTK structure is information you got from Dr. Showalter and you're

not offering an independent opinion or analysis of the BTK structure that's described in paragraphs 52, 53, and 54?

A. So that is correct, but if you're saying does structure have an impact on what a small molecule may do, I have knowledge in that regard, but I'm not the expert on the domains that I said Dr. Showalter would be relied upon.

Q. And in paragraph 55, you describe a number of activities of the BTK in the B-cell antigen receptor signalling pathway; is that right?

A. Let me just read through it.

Q. Yeah.

A. If you could just repeat the question?

Q. Sure. In paragraph 55, you describe a number of activities of BTK in the B-cell antigen receptor signalling pathway; is that right?

A. Yes. It's more extensive than that, but that's a component, yes.

Q. And in your discussion in paragraph 55, you cite a number of exhibits that were published after 2010/2011. This paragraph was not limited to the

perspective of what a person of ordinary skill in the art would have understood in 2010/2011; is that right?

MS. PATEL: Objection. Lacks foundation. Vague. Counsel is testifying.

A. If any of the references are after that date, then that information wasn't known prior to 2010 or '11.

Q. Okay. Now, in paragraph 56, you identify -- it's the first paragraph in the section entitled "Treatment of CLL and SLL Using BTKIs."

Do you see that?

A. I do.

Q. And in this paragraph, you state that, [As read] Because BTK is a critical component of the BCR signalling pathway and the BCR signalling pathway is key to the development of normal B-cells, as well as the survival and proliferation of malignant B-cells and CLL/SLL, inhibiting BTK and disrupting signalling and proliferation of malignant B-cells can impact progression of CLL and SLL.

Is that right?

A. So that statement is correct, though there may be other signalling pathways also affected.

Q. And so inhibiting BTK disrupts the signalling and proliferation of malignant B-cells?

MS. PATEL: Objection. Mischaracterizes the declaration.

A. So ibrutinib, zanubrutinib, and acalabrutinib do that. Not necessarily any molecule that inhibits BTK. You can inhibit BTK and not be an effective therapeutic because it can be affecting other proteins, et cetera. So it's necessary but not sufficient in order to have a therapeutic.

Q. And the reason it wouldn't be an effective therapeutic if a compound inhibits BTK is because it would affect other proteins? It could affect other proteins?

MS. PATEL: Objection. Mischaracterizes prior testimony.

A. Inhibiting BTK would be necessary if you're looking at BTK inhibition as the therapeutic approach, but -- so it's necessary but it's not sufficient. You could inhibit BTK and it may not

kill the cell for reasons that we don't know or that are to be, you know, further discovered or because it's excessively toxic.

Q. And you have not identified any examples of a compound that inhibits BTK but doesn't kill a CLL/SLL cell?

A. I'm sure they exist. I haven't particularly studied that. That's not my own work.

Q. Right. And you didn't identify any of those examples in preparing your declaration; right?

A. No, but it's unlikely, if they discovered something that bound or inhibited and it didn't work, that it would be published.

Q. And so your opinion that inhibiting BTK will not necessarily disrupt the signalling and proliferation of malignant B-cells is based on the assumption that there are examples of that existing?

A. No --

MS. PATEL: Objection. Mischaracterizes the prior testimony.

A. Just with the knowledge that inhibiting any target is -- that you feel would be a therapeutic is

necessary but not sufficient. You have to demonstrate that it actually mediates killing. That would be the first step, in vitro. And then, if you want to actually advance it as a clinical therapeutic, you'd have to do the pre-clinical testing in animals and subsequently human testing.

Q. But you have not identified any mechanism by which in a compound that inhibits BTK would not result in killing CLL and SLL cells?

MS. PATEL: Objection. Asked and answered. Mischaracterizes testimony. Mischaracterizes the declaration.

THE WITNESS: Sorry.

A. I can state again, I don't particularly study this issue, the BTK inhibition, in my lab. But in addition, if negative results are seen, they're rarely published, and so I wouldn't see that in the literature.

Q. Okay. So you're not aware of a mechanism by which a BTK inhibitor inhibits BTK but doesn't result in disrupting the signalling and proliferation of malignant B-cells?

A. I'm only aware of the handful of compounds that have been published.

Q. And none of them have a mechanism by which they inhibit BTK but don't result in the disruption of signalling and proliferation of malignant B-cells; right?

A. So for the handful of compounds that are in the clinic, that's why they're in the clinic because they're effective and they inhibit BTK. But as Dr. Showalter mentioned in his declaration, there's a billion possibilities of developing molecules that may inhibit BTK, and I'm confidence there are many that may bind, could inhibit, but either aren't effective in killing the cell or wouldn't be clinical candidates.

Q. But you're not aware of any specific examples that would meet either of those characteristics, that they're -- they inhibit but don't -- aren't effective in killing the cell or wouldn't be clinical examples -- or clinical candidates?

MS. PATEL: Objection. Asked and answered.

A. And so, in this instance, it's a presumption that would have to be proven by experimentation.

Q. Okay. And you, in the statement, you agree that inhibiting BTK can impact the progression of CLL and SLL; right? Turning back to paragraph 56.

A. So I read that the compounds that are in the clinic that inhibit BTK have been shown to impede the progression of CLL and SLL.

Q. And your statement here isn't limited to those compounds. Your statement is that inhibiting BTK and disrupting signalling and proliferation of malignant B-cells can impact progression of CLL and SLL; right?

A. So I did state that, [As read] A BTKI can inactivate BTK activity and disrupt the BCR signal pathway by binding to the ATP-binding site located in the kinase domain of BTK.

Q. Okay. All right. So turning a couple of pages to paragraph 61?

A. I have that.

Q. Okay. And this is a section, section -- I think we're in section 4-D; is that right?

A. "Structure-Activity Relationship."

Q. Yeah. So section 4-D is called, yeah, structure-activity relationship or SAR?

A. Yes.

Q. What is SAR?

A. Structure-activity relationship refers to how the structure and the function essentially relate.

Q. Okay. And as we've discussed a number of times, the specifics of the structure you would leave to the chemist or Dr. Showalter, and your focus is understanding what the function is; right?

A. I would defer to Dr. Showalter concerning the structure of the chemical entity and the potential bonding.

Q. And you -- you're not offering any -- any opinions of what a person of ordinary skill in the art would understand about the structure. Your analysis focuses on what a person of ordinary skill in the art would understand about the function of a BTKI; right?

MS. PATEL: Objection. Mischaracterizes the

declaration. Asked and answered.

A. So I would be confused by answering that. I mean, my feeling is that I, obviously, understand what a POSA would know in the biologics, but I could also understand what a POSA would need to have in order to opine about the chemical structure and the target. I'm not an expert in that domain. That's Dr. Showalter.

Q. And that's not the analysis you've offered here; right?

A. I defer to --

MS. PATEL: Objection.

A. -- Dr. Showalter.

MS. PATEL: Objection. Mischaracterizes the declaration.

A. So here I'm commenting that Dr. Showalter's declaration is -- speaks to the structure of the molecules.

Q. And the particular functions that you've analyzed -- or strike that.

So Dr. Showalter has analyzed the structural limitations of the '803 claims; right?

A. Correct.

Q. And he's analyzed the functional limitations as it relates to inhibiting BTK and covalently binding to the cysteine of BTK; right?

A. Correct.

Q. And you've analyzed -- separately, you've analyzed the functional limitations of the '803 claim as it relates to effectively treating CLL and SLL?

A. Correct.

Q. And the functional limitations that you saw of safely treating CLL and SLL; right?

A. Correct.

Q. And the functional limitation as it relates to the BTK inducing the lymphocytosis?

A. Can you clarify that? I'm not sure I understand what you're saying.

Q. Sure.

I'm just trying to understand the scope of your analysis as it relates to the functional limitations you assessed.

You assessed, essentially, three functional

limitations, the effectively --

A. Can you go to where in my declaration you want me to opine about? I just want to make sure -- again, I don't want to misspeak.

Q. Let me -- let's turn back to these discussions, and we can come back to that point later.

A. Okay.

Q. So in section 4-D-1, starting at paragraph 63, you have a section titled "Effective Treatment."

Do you see that?

A. I do.

Q. And this is the structure-activity relationship of effective treatment, as you understand it?

A. It is within section D.

Q. In paragraph 64 -- or paragraph 63, you state that it's your opinion [As read] that the Z-prime structure of a BTKI impacts in unpredictable ways whether and at what dose a BTKI will be an effective treatment for CLL and SLL.

Is that right?

A. Correct.

Q. Okay. But you're not offering any opinion as to what specific structural changes to Z1 may be understood by a POSA to have an effect on -- to have any particular effect; right?

A. Correct.

Q. Okay. And in paragraph 64, you outline your understanding of Dr. Showalter's analysis of Z prime and the structure and its impact on its ability to covalently bind BTK and inhibit BTK activity.

A. Yes.

Q. Okay. And then you at state the bottom of page 23, [As read] Because whether a compound covalently binds BTK unpredictably impacts whether that compound inhibits BTK activity and effectively treats CLL and SLL, it is my opinion that changes in the Z-prime structure of the BTKI likewise will unpredictably impact whether such a BTKI will be an effective treatment for CLL and SLL.

A. Correct.

Q. Okay. And you don't have any cites in that

paragraph; right?

A. Cites meaning references?

Q. References, right, for that sentence.

A. No. That would just be knowledge.

Q. Okay. And then in paragraph 65, you state that [As read] Even if a BTKI's Z-prime structure is known and that BTKI is known or assumed to covalently bind BTK, a POSA could not discern from those facts alone whether and at what dose it would be effective in treating CLL and SLL.

A. Correct.

Q. And "those facts alone" is referring to the start of the sentence, the BTKI Z-prime structure and the fact that the "BTKI is known or assumed to covalently bind to BTK"?

A. Can you clarify that for me? I want to make sure I better understand what you're asking me.

Q. Sure.

I'm just trying to understand what "those facts alone" refer to in your sentence here at the start of paragraph 65.

Do "those facts alone" refer to the specific

Z-prime structure and that that BTKI with that specific Z-prime structure "is known or assumed to covalently bind to BTK"?

A. So as stated, even if a BTKI structure is known and the "BTKI is known or assumed to covalently bind to the BTK," so say it does, "a POSA could not discern from those facts alone whether and at what dose it would be effective in treating CLL and SLL." It's pretty straightforward. I can't say it in a better way.

Q. Okay. So the basis for your opinion that a BTKI that is known to inhibit BTK may not effectively treat CLL and SLL is that the structure could affect the PK and PD properties?

MS. PATEL: Objection. Mischaracterizes the declaration.

A. It would be much broader than just PK and -- pharmacokinetics and pharmacodynamics. It's every aspect. We don't whether just inhibiting and binding is gonna kill the cell. We don't know whether it's gonna be effective in pre-clinical models. We don't know what the toxicity will be in

humans as well as the efficacy. And so there's a broad spectrum of experimentation that's necessary to know whether or not something would be a clinical candidate.

Q. You've not identified any example of a BTK inhibitor that inhibits BTK and doesn't result in disrupting the BCR signalling pathway in a CLL/SLL cell?

MS. PATEL: Objection. Asked and answered.

A. I think we've discussed this at length. I have no other opinions about it outside of what I've stated before.

Q. Okay. And so in putting together your declaration and supporting your opinions that you don't know what would happen, you've identified the best evidence that you can to support that opinion, and that best evidence doesn't include any examples to illustrate your opinion that inhibiting BTK would not result in inhibiting the BCR -- would not necessarily result inhibiting the BCR signalling pathway and disrupting the growth and proliferation of a CLL or SLL cell?

MS. PATEL: Objection. Mischaracterizes prior testimony. Mischaracterizes the declaration. Asked and answered. Form. Compound.

A. I'm not sure how to make additional comments concerning this question because you've asked it to me in several ways, and I've tried to answer it in several ways. There's nothing else I can say about it.

Q. Is it your opinion that a BTK inhibitor that -- or a compound that is known to inhibit BTK will not inhibit the BCR signalling pathway?

MS. PATEL: Objection. Mischaracterizes the testimony. Mischaracterizes the declaration.

A. It's my opinion you'd only know through experimentation.

Q. And the experimentation would have to show that the CLL and SLL cell died in order to show that it inhibited the BCR signalling pathway?

MS. PATEL: Objection. Mischaracterizes the testimony and declaration. Vague.

A. It would need to show, based on your initial question, that it's affecting the BCR signalling.

Q. And just inhibiting BTK, in your opinion, is not enough to demonstrate that it would disrupt the BCR signalling pathway.

A. In my opinion, you'd have to show it through experimentation. We've been surprised in many instances about therapeutics that affect a specific target that didn't have the ultimate impact you anticipated.

Q. But you've not identified any examples of a BTK inhibitor that, surprisingly, didn't inhibit the BCR signalling pathway; right?

MS. PATEL: Objection. Asked and answered.

A. So you had asked me this in a variety of ways, and, you know, as I stated before, this is not where I do my own personal research, and publications only tell you about the products that work.

Q. In your paragraph 65, you go on and state that, after the first sentence, [As read] whether and at what dose a BTKI is effective at treating CLL and SLL is a function of pharmacological properties ... that contribute to its physiological

effect.

Is that right?

A. So this is where I state [As read] Instead, whether and at what dose a BTKI is effective at treating CLL/SLL is a function of pharmacological properties of BTKI that contribute to its physiological effects, including ... pharmacokinetic properties (absorption, distribution, metabolism, and excretion).

But then I go on to say, [As read] as well as the pharmacodynamic properties, which include specificity, selectivity, affinity, potency, and occupancy. 'Pharmacological properties appear to translate into clinically meaningful safety and efficacy ...

And here, we're talking about advantages of zanubrutinib compared to ibrutinib.

Q. Okay. So let's break that down a little bit.

So one of the properties you point to that may affect whether or not -- a compound that does inhibit BTK would not be -- would not be an

effective treatment for CLL and SLL is the effects on its physiological properties; is that right?

A. Can you --

Q. I mean, I'm sorry. Its pharmacological properties.

A. Can you state that more succinctly for me? I apologize.

Q. Sure.

So one of the properties that you point to to explain why a compound that inhibits BTK may not be an effective therapy for CLL and SLL is that that compound may have pharmacological properties that contribute to its physiological effect; is that right?

A. Correct.

Q. Okay. And the pharmacological properties that you point to include PK properties and PD properties; is that right?

A. Correct.

Q. Okay. And so, for example, the PK properties that you list at the bottom of page 24 of paragraph 65, the pharmacokinetic properties include

polarity or C log P, permeability, pKa, aqueous solubility, and protein binding; right?

A. I'm sorry. Where are you --

Q. Yep. At the bottom of page 24, in the middle of paragraph 65, you identify physicochemical properties of a BTKI that impact its PK properties?

A. This is on page 24?

Q. Yes. Spanning to page 25.

A. Oh, I see. Starting the last sentence on page 24.

Q. Yes.

A. So I say, [As read] Additionally, physicochemical properties BTKI impact its pharmacokinetic properties, including, for example, polarity, passive permeability, pKa, aqueous solubility, and protein binding.

And then it goes on to say, [As read] Physiochemical properties, such as molecular weight, size, partition coefficient, acid dissociation constant and solubility have great impact on pharmacokinetics of traditional small molecule drugs and substantially used in the development of small

drugs.

Q. Right. So the properties that you point to include polarity (C log P), passive permeability, pKa, aqueous solubility, and protein binding; right?

A. Right.

Q. And the specific impact of a structural change on these PK properties is not something you're qualified to opine on; right?

MS. PATEL: Objection. Mischaracterizes the declaration. Vague. Lacks foundation.

A. So the specifics of that, an individual molecule, I would defer to Dr. Showalter.

Q. And the -- these PK properties, these pharmacokinetic properties, are properties that are routinely assessed when developing drugs for potential clinical assessment?

A. Yes.

Q. And one of the concerns of poor PK properties is that a compound may have poor bioavailability?

A. Yes.

Q. And so if a compound has poor solubility and

low bioavailability, the concern is that it might not be an effective treatment?

A. Correct.

Q. But compounds who -- that do have low solubility and low bioavailability have been shown to be effective treatments; right?

MS. PATEL: Objection. Vague. Outside the scope.

Q. You may answer.

A. They can be.

Q. And the references that you cite in paragraph 65, these references aren't specific to BTK inhibitors or BTK inhibitors having the structure included in the claims of the patent; right?

MS. PATEL: Objection. Lacks foundation. Vague.

A. I would need to see.

Q. Let's pull up --

MS. DANEK: Let's pull up Exhibit 1069.

THE WITNESS: Okay.

///

(Exhibit 1069, previously marked, is attached to the transcript.)

MS. DANEK: Or maybe more specifically, because you have them all, maybe 1046.

(Exhibit 1046, previously marked, is attached to the transcript.)

A. So this would be a general review? I don't know if BTKI is mentioned in this review without having the entire copy to review.

MS. PATEL: So, Dr. Rosen, it will be Tab 25 of the binders.

THE WITNESS: Oh, 25. Okay. Okay.

BY MS. DANEK:

Q. And just as you're looking at it, Exhibit 1046 is a publication from 2018. Is that right, Dr. Rosen?

A. I'm sorry. I apologize. I didn't hear what you said.

Q. Exhibit 1046 is a publication from 2018?

A. Well, I haven't gotten to it yet. This is Tab 25? This says "Pharmacology, Part 1: Introduction to Pharmacology and Pharmacodynamics"

by Geoff Currie. And the date is 2018, yes.

Q. And you have citation in this paragraph to page 3 of this paper. And that discussion -- I'll let you get to it, but that discussion, if you'll just confirm for me, isn't related to BTKIs or BTKIs with the structure of -- the structures falling within the claims?

A. This looks like a general review, and I don't see BTKI or BTK mentioned.

Q. And you've not -- you've not offered an opinion on how a person of ordinary skill in the art would understand ibrutinib structure in clinical activity in assessing the structure and function of another BTK inhibitor?

MS. PATEL: Objection. Vague. Mischaracterizes the declaration.

A. I'm not sure -- I apologize. I'm not sure I understand the question.

Q. Sure. You've not included in your analysis here of the effect of different structures -- or that different BTKIs with different structures may not effectively treat CLL and SLL. You haven't

analyzed the specific structure of ibrutinib and any particular structural changes from ibrutinib to what a person of ordinary skill in the art would understand those structural changes would impact the function of that new BTKI. You have not done that analysis?

MS. PATEL: Objection. Form. Compound.

A. What I believe I stated is that a POSA may be able to predict. But without experimentation, there's no way to know whether something will be effective. And someone who has skills like myself are somewhat distinct from skills that Dr. Showalter would have.

Q. Okay. And you've not -- you've not conducted an analysis of how the ability of ibrutinib to effectively treat CLL and SLL would have impacted an analysis of a structure that falls within the claims and whether or not it would have the ability to effectively treat CLL and SLL?

MS. PATEL: Objection. Form. Vague. Asked and answered.

A. I would say, at the highest level,

Dr. Showalter said that there were a billion perturbations that could be made, and you'd have to test all of them to know which may be effective.

Q. And so your analysis goes right to testing. There's no part of your analysis that assesses a structural comparison and understanding of the potential functional impact of structural differences between ibrutinib and any of the potential BTKIs within the claims?

MS. PATEL: Objection. Mischaracterizes the declaration. Asked and answered. Vague.

A. Is there a specific comment in my declaration that I should read relevant to this?

Q. I'm just confirming that's not an analysis that you've done.

MS. PATEL: Same objections.

A. My comment aligns with Dr. Showalter based on his declaration that there could be a billion perturbations of this molecule and it's impossible to know what may work unless you do experimentation.

Q. So just to confirm, you did not do any analysis that a person of ordinary skill in the art

or -- strike that.

Does your opinion that you have to do experimentation rely on an assumption that a person of ordinary skill in the art would not have any understanding of the function of a BTKI based on a structural comparison to ibrutinib and an understanding of ibrutinib's function?

MS. PATEL: Objection. Mischaracterizes the declaration. Asked and answered.

A. That's a -- was a very long question. I honestly couldn't follow all of it. If you could chop it into pieces --

Q. Sure.

A. -- maybe I'd understand it better. But I don't want to say something that's not correct so I just want to make sure that we're accurate when you ask me questions of that sort.

Q. Okay. You understand from Dr. Showalter that there could be potentially billions of compounds that fall within the structural limitations of the claims; is that right?

A. That's right.

Q. Okay. And you understand that the -- that these compounds that fall within the structure of the claims have -- will have particular structures that differ at what is called the Z-prime position; is that right?

A. Correct.

Q. Okay. And the other elements of the claims of -- of the compounds of the claims are structures that appear in ibrutinib; is that right?

MS. PATEL: Objection. Outside the scope. Calls for speculation.

A. Are you referring now to the '803 patent and the structures that are in the '803 patent?

Q. Yes. Maybe it would be easier to take a look at that. So if we take a look at your recitation of the claims, which I believe appear --

A. Are we going back to my declaration?

Q. Yeah, we'll go back to your declaration.

A. Can I close the other?

Q. Yeah, you can.

A. Okay. Should we -- I think it's two or three minutes to 11. Did you want to start on this

or you want to take a break before and do the lunch?

Q. Let's continue here for a couple minutes.

A. Okay.

Q. So if we go --

MS. PATEL: Is that okay with you, Dr. Rosen?

THE WITNESS: That's fine with me. I want to be thoughtful because I know it's later for you guys. Give me one second to just close the other so that ...

A. Okay. We're going back to my declaration?

Q. Yes.

A. Which page?

Q. It's at page 53 of the document, 47 of the declaration, paragraph 114, as an example.

A. Okay.

Q. And in paragraph 114, you show a depiction of the chemical structure that appears in the claims of the '803 patent?

A. I see the structure.

Q. Okay. And you understand that the structures of the BTK inhibitors for use in the

claimed methods fall within this generic structure; right?

A. Say that one more time for me. I apologize.

Q. The structures of the BTK inhibitors to be used in the claimed methods fall within this generic structure; is that right?

A. This is the structure shown in '803?

Q. Yes.

A. So it's my understanding from Dr. Showalter that the Z, obviously, could have many, many different perturbations, he says a billion perturbations possibly, but also the linker is a distinct issue.

Q. Okay.

A. Without a medicinal chemist to opine on that, I'm only repeating what he says and the importance.

Q. Okay. Dr. Rosen, it's really important for you to listen to the question that I'm asking and respond to the question that I'm asking. I appreciate you have a lot of other opinions or analysis that you may have conducted, but I'm here

asking you about your opinions, and it would be really helpful if we listen to one another and if you respond to the question that I'm asking. Okay?

A. Okay. I'm sorry. I thought I did, and I thought I gave an appropriate answer, but I'm happy to rephrase it.

Q. So my question is that the structure that you have included in your declaration is -- represents the structures, the generic structure of the BTK inhibitors to be used in the claim methods; is that your understanding?

A. That was the structure that appeared within the '803 patent.

Q. Right.

And you understand from Dr. Showalter that there could be billions of different structures that fall within this generic structure; is that right?

A. That was his declaration.

Q. Okay. And the place where they differ is Z prime; is that right?

Is that your understanding?

A. My understanding is, as I said just before,

they differ in the Z prime, but he also makes a comment about the linker. And that would be a relevant question for Dr. Showalter, not for me.

Q. Okay. And I'm not asking the linker.

A. Yeah.

Q. Okay. What I'm asking is your understanding of what the structure is. Okay?

A. I see the structure.

Q. Okay. Now, do you have any understanding of what the other components of the structure of the BTK inhibitors for use in the claim methods --

MS. PATEL: Objection.

Q. -- besides Z prime.

MS. PATEL: Objection. Outside the scope. Asked and answered.

A. You need to be more specific. Are you asking about the components of the molecule and what they do?

Q. I'm asking about the component in the molecule and what they relate to.

Do you have any understanding of that?

A. I don't know what the word "relate to" means

in this context.

Q. Okay. So if we look at this structure, you can see the Z prime, sort of, in the middle; right?

A. Right.

Q. Okay. And then there's a component that's at the top of the structure. Can we just call that the top structure? Is that -- if I do that, will you understand what I mean?

A. The actual terminology is laid out in one of the documents I have. We can go through that.

Q. Dr. Rosen, if I refer to that structure as the top structure, will you understand what I mean?

A. Not entirely.

MS. PATEL: Objection.

A. You'd have to spell out what you mean by "top structure." I see a molecule at the top, but I don't know how far down you're referring.

Q. Do you see Z prime in the middle?

A. I see Z prime in the middle, but there is a better diagram that I, believe, is in the -- my declaration or Dr. Showalter's declaration that actually outlines the individual components of the

molecule.

MS. PATEL: Counsel, it's past 2:00 p.m. now. Is it time to take a break for lunch? I think you said that we'd go on for a couple more minutes. It's been --

MS. DANEK: We have not -- I think we need to finish this. So this has been somewhat -- we need to come to an understanding here. Okay? And then we can break.

MS. PATEL: Is that okay with you, Dr. Rosen, or would you like to take a break?

THE WITNESS: No, it's fine with me. I want to just make sure there's no confusion. I just want to make sure I'm accurate and consistent and don't misstate anything.

A. So when you make a statement about the top part of a molecule, I don't know whether you're talking about just the specific bond or all the way down to the second group. So there is a phenomenal representation of --

BY MS. DANEK:

Q. Yeah, sure.

MS. DANEK: Let's turn to Dr. Showalter's Exhibit 1003.

A. So let me get that. Yeah.

(Exhibit 1003, previously marked, is attached to the transcript.)

Q. And it's at paragraph 37 on page 19 of his declaration.

A. Page -- the structure ...

Q. So it's up on your screen. It's page 16 of the declaration, page 19 of the document.

A. So that really wouldn't satisfy what I was asking. You'll see on page 100, if you turn to it, that's what I would refer to, where you have the hydrophobic moiety back pocket, the heterocyclic --

Q. Can you look at your screen, Dr. Rosen? Is this what you --

A. Perfect, that's it. Yeah.

Q. Okay. Let's --

A. That way we can be consistent.

Q. Okay.

A. I don't mean to be difficult, but I just want to make sure I'm not saying anything that's

inaccurate.

Q. Yep. Okay.

So let's orient ourselves in the molecule. We have Z prime, which is the heterocyclic core in the middle; right?

A. Yes.

Q. Okay. And the top part is called the hydrophobic moiety; right?

A. Correct.

Q. And then there is a bottom part in this orientation. That is the linker and the warhead; is that right?

A. Yes.

Q. Okay. Do you have any understanding where the hydrophobic moiety and the linker and warhead come from in the structures of the BTKIs for use in the claimed methods?

MS. PATEL: Objection. Vague. Outside the scope. Asked and answered.

A. I honestly don't know what you're asking me.

Q. Do you --

(Indiscernible crosstalk.)

A. What do you mean, where do they come from? I don't know what that means.

Q. Let me -- I understand you don't understand. Let me ask my question, then.

A. Okay.

Q. Do you understand that --

MS. PATEL: Counsel, can you --

MS. DANEK: Excuse me, Counsel. Let me ask my question.

BY MS. DANEK:

Q. Do you understand that the hydrophobic moiety and the linker and warhead that are included in the structure of the claims are the structural components from ibrutinib?

MS. PATEL: Objection. Argumentative. Outside the scope. Asked and answered.

Counsel, please watch your tone.

A. So they look to me to resemble what you see in the Imbruvica molecule. I believe, based on what Dr. Showalter said, that the linker may be different. I don't want to make a comment. He should be the expert in that domain. And he

emphasizes, one, the billions of perturbations of Z, but he also --

Q. Dr. Rosen, I asked you whether or not these structures came -- come from ibrutinib and you answered that. So let's just keep on track with listening to my question and answering to my question. I'm happy for you to provide complete answers, but let's -- we have a limited amount of time here today, and I'd like to keep on track with the questions that I'm asking. Okay?

MS. PATEL: Counsel, please refrain from interrupting him so that he can actually provide those complete answers. You just interrupted him halfway through an answer.

BY MS. DANEK:

Q. Dr. Rosen, so just listen, please, very carefully to my questions. All right?

A. I am but sometimes a simple yes, no isn't adequate to communicate my thoughts. And so I'm trying to be complete. And I don't see any harm in being complete. You can always say you've told me more than I want to know, but I'm trying to be

complete.

Q. How about I ask for more information if I need it. Okay?

A. Okay. But I do know that if I'm not complete, it could be misconstrued because it's taken out of context. So it's very important for me to be able to tell you what I think relevant to your question.

Q. Let's stay on track.

A. Okay.

Q. In looking at the claims and the structures within the claims, you did not perform any analysis of different structures of BTKIs that fall within this genus of compounds to compare how those structures relate to ibrutinib; is that correct?

MS. PATEL: Objection. Vague. Outside the scope. Asked and answered.

A. I mean, I do find it too vague for me to really respond. It would have to be much more specific in nature.

Q. Did you perform any analysis comparing the structures of any BTK inhibitor to the structure of

ibrutinib?

MS. PATEL: Objection. Asked and answered. Outside the scope.

A. Well, I looked at the structure of ibrutinib versus zanubrutinib.

Q. So the only BTKI that you compared structurally to ibrutinib was zanubrutinib; is that right?

MS. PATEL: Objection. Mischaracterizes testimony. Asked and answered. Outside the scope.

A. So within the patent, there are other structures that were included.

Q. I'm asking about your analysis. You didn't do --

A. I'm not --

(Indiscernible crosstalk.)

Q. That's what I want.

You did not do any structural analysis comparing -- other than zanubrutinib, did not compare any BTKI structure to the structure of ibrutinib; right?

MS. PATEL: Objection. Argumentative.

Asked and answered.

A. So it wouldn't be entirely accurate to say that.

Q. What structural analysis did you do?

A. When you use --

MS. PATEL: Same objection.

A. -- the word "structural analysis," that confuses me. But there were many structures that appeared in the documents that I looked at, and none of them led to be clinical products, so it wasn't something I studied in detail. But I am not a medicinal chemist, and Dr. Showalter would opine on the broad spectrum of molecules that be synthesized that could potentially impact Bruton tyrosine kinase.

Q. Okay.

MS. DANEK: We can take a break.

(A short break was had.)

REMOTE TECHNICIAN: Back on the record, 1340.

BY MS. DANEK:

Q. Welcome back, Dr. Rosen.

We were looking at your declaration. I'd like to turn back to that if you have that in front of you.

A. I do.

Q. Okay. And in particular, let's turn to paragraph 70, which is on page 34 of the document and 28 of the declaration.

A. Okay. I have it.

Q. Okay. And in this section, you have been comparing particular properties between zanubrutinib and ibrutinib. And one of the properties you report here that differs is that zanubrutinib [As read] has been shown to have 'higher selectivity for Cys-481 in the active site of BTK compared with other structurally related kinases and better oral bioavailability.'

Do you see that?

A. I do.

MS. PATEL: Objection. Form.

Dr. Rosen, remember to pause after each question. Thank you.

Q. And so these properties, selectivity and

oral bioavailability are two that differ between ibrutinib and zanubrutinib; right?

MS. PATEL: Objection. Mischaracterizes the declaration. Vague.

MS. DANEK: Counsel, you've been giving a number of improper objections throughout the day. I'd just sort of point your direction to the PTAB's trial practice guide about the appropriate scope of objections, and if you could please limit your objections to those, I believe that would be more conducive to the deposition.

MS. PATEL: Counsel, I'm familiar with the PTAB's trial practice guide. We disagree that any of our objections have been inappropriate.

MS. DANEK: I mean, not to get on this right now, but, for example, you continuously say objection vague, mischaracterizing document. Those are actually explicitly called out as improper in the trial practice guide, so please limit your objections to those that are allowed in the trial practice guide so that we can have a productive deposition.

MS. PATEL: Counsel, you can continue asking your questions and I'll continue stating objections where necessary.

BY MS. DANEK:

Q. So, Dr. Rosen, let me get back to my question before your counsel's objections.

Two of the properties that differ between zanubrutinib and ibrutinib that you've identified are the selectivity of zanubrutinib for Cys-481 and the oral bioavailability; is that right?

A. Yeah. In paragraph 7, it actually says, [As read] Compared to Imbruvica, Brukinsa has been shown to have higher selectivity for Cys-481 in the active site of BTK compared with other structurally related kinases and better oral bioavailability.

Q. So, Dr. Rosen, again, if you would just listen to my question and answer my question, I understand that you have written things in your declaration. I'm trying to understand what your declaration says and -- or what it means. So, you know, please listen to my questions. If the only way that you can respond to a question is by

repeating the text in your declaration, let me know. But otherwise, you know, I'm looking for understanding what the text in your declaration means. So this was a simple question.

Two of the properties that you identified that differ between zanubrutinib and ibrutinib are oral bioavailability and selectivity for Cys-481; is that right?

A. That's the statement I just read.

Q. Okay. And you go on to say that this higher selectivity and bioavailability suggests that a lower dose of Brukinsa would be required in order to effectivity treat CLL or SLL; is that right?

A. That's correct. And that's what's stated in paragraph 70.

Q. Okay. And so one way that selectivity and bioavailability affect the ability of a compound to effectively treat CLL and SLL is that it affects the dose you will have to use; is that right?

MS. PATEL: Objection. Form. Mischaracterizes the document.

A. Sorry. Say it again, please.

Q. So one way that selectivity and bioavailability, differing properties of selectivity and bioavailability, impact the use of a BTK inhibitor for treating CLL and SLL is by impacting the dose you would have to use to treat CLL and SLL; is that right?

MS. PATEL: Same objections.

A. It can.

Q. Okay. And so for a less selective and less bioavailable drug, you would need a higher dose; is that right?

MS. PATEL: Same objections.

A. Possibly.

Q. And another -- in paragraph 71, another of the very different properties that you've identified between zanubrutinib and ibrutinib is that zanubrutinib has twice the unbound fraction in plasma and a greater AUC at its approved dose than ibrutinib; is that right?

A. Correct.

Q. And because of that, those properties, zanubrutinib is effective at a lower dose?

A. So as the last sentence says, [As read] Thus, these test results suggest that a lower dose of Brukinsa, compared to Imbruvica, would effectively treat CLL and SLL.

Q. Right. So a lower -- excuse me.

A higher unbound fraction in plasma and a greater AUC indicates that a lower dose would be effective to treat CLL or SLL; is that right?

A. It can.

Q. In paragraph 74, which is a couple of pages beyond here, you have a table comparing the various pharmacological properties of ibrutinib as compared to zanubrutinib?

A. Yes.

Q. Okay. And here you -- it's reported -- and you also, in here, include acalabrutinib?

MS. PATEL: Objection to form.

A. Yes.

Q. And acalabrutinib is another BTK inhibitor that's been approved for the treatment of CLL and SLL?

A. Yes.

Q. And it reports here various, as we noted, various pharmacological properties about the different compounds. One of them is the IC50 values against BTK?

A. Yes.

Q. And zanubrutinib has an IC50 value of -- it's reported as .5 nanomolar.

Do you see that?

A. Can you make it a little larger?

Q. Do you have your declaration in front of you?

A. Yes. It's also small.

Q. Oh, okay. Fair enough.

A. Yes.

Q. And ibrutinib's PK -- I'm sorry -- ibrutinib's IC50 value is reported as 1.5 nanomolar?

A. Yes.

Q. Acalabrutinib's IC50 value is reported at 5.1 nanomolar?

A. Correct.

Q. And all of these IC50 values are associated with compounds that have been shown to be effective

in the treatment of CLL and SLL?

MS. PATEL: Objection. Form. Calls for speculation.

A. All three compounds are FDA approved for the treatment of CLL/SLL.

Q. Okay. And in paragraph -- starting at paragraph 75, there's a couple of paragraphs describing the Alpine study?

A. Yes.

Q. Okay. And do you understand that the Alpine study was powered to detect the superiority of zanubrutinib over ibrutinib?

MS. PATEL: Objection. Form.

A. I would have to look at the publication. I thought it was the noninferiority, but I'm happy to look at the publication to make sure that I don't make any misstatements.

Q. Sure. If we look at paragraph 76, so the last sentence of paragraph 76, it states, [As read] The trial was powered to detect the superiority of zanubrutinib over ibrutinib.

Do you see that?

A. Yes. Can we look at the actual article? I know that the conclusion was that zanubrutinib was superior to ibrutinib.

Q. Are you disagreeing with your characterization that the trial --

A. No. I just want to verify.

Q. Oh, okay. It's Exhibit 1043. Do you have that in front of you?

(Exhibit 1043, previously marked, is attached to the transcript.)

MS. PATEL: Dr. Rosen, that would be Tab 22 of your binder.

THE WITNESS: 22. Okay.

MS. PATEL: Correct.

BY MS. DANEK:

Q. And, Dr. Rosen, I just would like to focus your attention on the question I asked so that we can continue to make progress, which is that the Alpine studies was powered to detect the superiority of zanubrutinib over ibrutinib?

A. So here's the statistical analysis. It starts on 321, and says, [As read] We estimated that

a sample of 600 patients would provide the trial with greater than 90 percent power to detect the noninferiority of zanubrutinib to ibrutinib with regard to overall response. The noninferiority of overall response between zanubrutinib and ibrutinib was tested in a pre-specified interim analysis of overall response involving the first 415 patients who had undergone randomization as well as at the final analysis of overall response involving all patients who had undergone randomization, approximately 12 months after 600 patients had been -- had undergone randomization. When the noninferiority and superiority --

Did you want me to continue?

Q. I didn't ask you to read any of that. So my question was --

A. Well, I want to go through it so there's no confusion what they said that they actually did.

Q. I'm asking for your understanding.

A. Well, that's -- my understanding is what they state. So I want to make sure I'm not misrepresenting what they say. I mean, I know it's

not a memory test so I'm trying to just respond to you.

So it says, [As read] When the noninferiority and superiority with respect to overall response was established, a hierarchical testing strategy was used to determine whether zanubrutinib was noninferior to ibrutinib with respect to progression-free survival when there were 205 occurrences of disease progression or death. The noninferiority was tested with a noninferiority margin -- and they give the hazard ratio -- with the use of a stratified Wald test based on the four randomization stratification factors, followed by superiority testing with the use of a stratified log-rank test. Hypothesis testing of progression-free survival involved two-sided significance level after the minimal alpha level was allocated to the interim analysis of overall response and the final analysis of overall response, it says (see the statistical analysis plan, available with the protocol). The statistical analysis plan was developed before the pre-specified

first analysis, which was the interim analysis of overall response; this pre-specified plan has not been amended.

Efficacy analysis involved --

Q. Dr. Rosen, I appreciate --

A. We're almost done.

Q. I mean, this is a lot -- this is not responsive to my question. I really would appreciate if you would just listen to my question and respond to my question. Reading paragraphs and paragraphs and paragraphs from a reference is not productive for the exercise that we're engaged in here.

A. So I disagree. In this instance, it is productive because it starts out as a noninferiority statistical analysis and, at the end, they were able to say there was actually superiority.

Q. Okay.

A. So the statement in my declaration holds --

Q. Great. That's all -- I just wanted to confirm --

(Indiscernible crosstalk.)

A. -- initial intent of that trial was noninferiority. So I can't give you a sound byte. I have to give you the explanation and what is meaningful.

Q. I'm not asking for sound bytes. I'm asking for answers to my questions. So let's --

A. But in this instance, I was trying -- this was a complicated one, as you saw. They started out at noninferiority, and it ended up as superiority.

Q. Okay.

A. So it's not a simple yes, no.

Q. And a BTK inhibitor that has less than superior efficacy is still -- can still be an effective treatment for CLL and SLL; right?

A. Correct.

Q. And the differences between ibrutinib and zanubrutinib that are identified in the Alpine study, they don't mean that ibrutinib is not effective to treat CLL and SLL; right?

A. Correct.

Q. And the differences that are observed in Alpine, that forms the basis for your opinion that

there will be at least some compounds that are BTK inhibitors but that won't be effective treatments for CLL and SLL?

A. That question, I don't understand.

Q. Okay. So you've relied on the Alpine study as an example for how different BTKIs could have different properties; is that right?

A. Not entirely. Again, if you can put it into piecemeal, I would have a better understanding. What the Alpine study showed was that the compound zanubrutinib was more effective and less toxic than ibrutinib. That's the take-home message.

Q. And one of the other differences is that zanubrutinib has a lower dose than ibrutinib; is that right?

A. That happens to be the case, but that's not the critical issue related to the Alpine study.

Q. And you agree with me that the claims don't require any specific dose; right?

A. That's my understanding.

Q. Okay. And now, in your next section, which is section 4-D-2, which starts at paragraph 81, do

you see that on page 33?

A. I do.

Q. Okay. And that is entitled, "Safe Treatment"?

A. Yes.

Q. Okay. And this, again, is under section 4-D. And if we remind ourselves that 4-D, the heading there is "Structure-Activity Relationship." That's back on page 22?

A. Yes.

Q. Okay. And the -- so in this section, you're laying out your understanding of the structure-activity relationship for safe treatment; is that accurate?

A. Can you state that again, please?

Q. Sure.

I'm just trying to understand. So you have this section 4-D that's entitled, "Structure-Activity Relationship"; right?

A. Correct.

Q. And within 4-D, you have a subsection 4-D-1 that is entitled, "Effective Treatment."

A. Correct.

Q. And in 4-D-1, that includes your assessment of structure-activity relationship as it relates to the function of effective treatment; is that right?

A. 4-D-1?

Q. Uh-huh.

A. Yes.

Q. Okay. And 4-D-2 is a separate section entitled, "Safe Treatment"; right?

A. Yes.

Q. Okay. And in this section, you lay out your analysis of structure-activity relationship as it relates to safe treatment.

A. Yes.

Q. Okay. And specifically, you discuss in this section side effects that have been observed in ibrutinib as compared to zanubrutinib, is that right, among other things?

A. Yes.

Q. And in addition to side-effect differences between zanubrutinib and ibrutinib, in paragraph 86, you report on clinical trials involving

tolebrutinib; right?

A. Yes.

Q. And tolebrutinib is another BTK inhibitor; right?

A. Yes.

Q. And you understand from Dr. Showalter that tolebrutinib falls within the genus of the claims here in the '803 patent; right?

A. That's my understanding.

Q. And you point out that that [As read] tolebrutinib passed Phase 2 clinical trials that demonstrated its efficacy for the treatment of multiple sclerosis.

But last year, given when this was written, so in 2022, [As read] the FDA placed a partial hold on Phase 3 clinical trials in multiple sclerosis due to reported cases of drug-induced liver injury in patients receiving tolebrutinib treatment.

Is that right?

A. Correct.

Q. Okay. And you were -- you have a statement here about the structural differences between

tolebrutinib and ibrutinib that you got from Dr. Showalter; right?

A. Correct.

Q. Okay. And so you're not offering an opinion about what the structural differences are and how a person of ordinary skill in the art would understand the structural differences; right?

A. Correct.

Q. Okay. You agree that tolebrutinib has demonstrated efficacy in the treatment of multiple sclerosis?

A. That's my understanding, but I haven't reviewed that literature in detail.

Q. But that's what you report here in your paragraph where you say, [As read] While tolebrutinib passed Phase 2 clinical trials that demonstrated its efficacy for the treatment of multiple sclerosis ...

Right?

A. Correct.

Q. Okay. And it showed activity in a Phase 2 trial; is that right?

A. Correct.

Q. And it's an example of a compound that safely and effectively inhibits BTK in patients?

A. It's representative of a compound that has efficacy. The safety issues are in question. That's why it was put on hold.

Q. It was a partial hold; right?

A. Partial hold. It's the same thing.

Q. And multiple sclerosis is a different indication than CLL or SLL; right?

A. Correct.

Q. And tolebrutinib had been determined to be safe enough to advance to Phase 2 clinical studies; right?

A. Presumably a Phase 1 trial showed a reasonable dose. But in Phase 2, these toxicities were witnessed and so there was a partial hold.

Q. And you don't offer any -- you don't offer any data about tolebrutinib's activity in CLL or SLL; right?

A. No. It's just illustrative of the fact that you do the clinical investigation, you don't know

what side effects may be seen and what humans can tolerate.

Q. And is it your opinion that the safety -- in order to be a safe treatment, a compound has to meet FDA safety requirements?

MS. PATEL: Objection. Form.

A. It's my opinion. And I know when the review board assessed the claims and specification and indications, they were focused on efficacy, and safety was not a consideration. As a clinician, I would think safety would be a consideration. But safety doesn't necessarily mean that you have to have FDA approval.

Q. Is it your opinion that tolebrutinib is not a safe treatment?

A. No. It's my opinion that some toxicity was witnessed, and so they wanted to pause and reevaluate.

Q. The -- in paragraph 87, you report on differences in safety and toxicity between ibrutinib and zanubrutinib; is that right?

A. Yes.

Q. And in particular, that there are "reduced side effects and improved tolerance" for zanubrutinib "as demonstrated in the Alpine study," as stated in the middle of the paragraph?

A. Yes.

Q. The reduced side effects and improved tolerance do not inform whether or not a BTKI can be an effective treatment. This relates only to whether or not it's a safe treatment?

MS. PATEL: Objection. Form. Lacks foundation.

A. Sorry. Can you please state that again? I got confused by the ending. It almost sounds like you had both side effects and toxicity the same. But if you could just repeat it, please.

Q. So the properties of having reduced side effects and improved tolerance, those relate only to whether or not, in your opinion, a therapy could be a safe therapy, not whether or not it could be an effective therapy; right?

A. So a therapy can be effective and safety would be a consideration once it's FDA approved for

the individual practitioner. So ibrutinib, as an example, has a significant incidence of atrial fibrillation. As a clinician, I feel uncomfortable with using ibrutinib because of that toxicity. I have colleagues that will use ibrutinib. So there's -- that's the distinction.

Q. So the side effect and tolerance that you cite here in paragraph 87 relates to -- relates only to safety, right, not to efficacy?

A. Yes. The tolerance I'm referring to as safety, not efficacy.

Q. And so a BTK inhibitor can reduce a sign or symptom of CLL and SLL and still have adverse events and poor tolerance.

A. Correct.

Q. When ibrutinib was first approved, the other available treatments for CLL and SLL included, effectively, cytotoxic chemotherapy and some immunotherapy?

A. Correct.

Q. And would you agree that ibrutinib is safer than the cytotoxic chemotherapy that was used

before?

A. Has a different side-effect profile. So the chemotherapy was destructive to the bone marrow. And ibrutinib carries the significant risk of atrial arrhythmias, in particular, but there is sudden death that's been witnessed.

Q. Is it your understanding that zanubrutinib does not have a risk of atrial fibrillation?

A. It's much lower and not dramatically above the background.

Q. So both ibrutinib and zanubrutinib have reported increased incidences of A-fib over background.

A. Both are above background, Imbruvica dramatically higher.

Q. And you report in paragraph 89, which spans over to two pages, a table comparing adverse events amongst the three approved BTKIs.

Do you see that?

A. I do.

Q. Okay. And so these are adverse events that have been reported and collected for ibrutinib,

acalabrutinib, and zanubrutinib; right?

A. Yes.

Q. And you agree, for example, that infection adverse events have been reported in all three -- for all three BTK inhibitors.

A. Yes.

Q. And bleeding adverse events have been reported for all three BTK inhibitors.

A. Yes.

Q. And we just discussed that atrial fibrillation adverse events have been reported for all three BTK inhibitors.

A. To different degrees, yes.

Q. Right. And rash, diarrhea adverse events have been reported at least for ibrutinib and zanubrutinib; right?

A. Yes.

Q. And other -- endothelial cell and lymphoid tissue adverse events have been reported for both ibrutinib and zanubrutinib?

A. Yes.

Q. Okay. So let's turn to paragraph 99, which

is at page 42 of your declaration and 48 of the document.

A. I have it.

Q. Okay. And this is subheading 3, "Lymphocytosis"?

A. Yes.

Q. And so just to orient us, we're still in section 4-D, which is "Structure-Activity Relationship" and now this is the third subsection of that section. So it is 4-D-3, the structure-activity relationship of lymphocytosis?

A. Yes.

Q. And there's just two paragraphs in this section; right?

A. Yes.

Q. And the only cites that you have in this section are to Exhibit 1002, which is the prosecution history of the patent, and 1001, the patent?

A. I would have to look to see whether those exhibits correspond to what you're referencing, but I assume that's the case.

Q. So we can just -- Exhibit 1001 and 1002 are the only citations you have in these paragraphs?

A. Yes.

Q. Okay. And in paragraph 99, you state that it would be unpredictable to know whether and at what dose BTK inhibitor structure -- strike that.

It would be unpredictable whether and at what dose a BTKI will result in lymphocytosis?

A. Yes.

Q. Okay. And you don't have a cite for that; right?

A. No, but even within the trial, some patients develop lymphocytosis and some don't.

Q. And that's an understood, not all patients respond the same; right?

A. Correct.

Q. Okay. But in the trials, for example, for ibrutinib, two-thirds of the patients have lymphocytosis; right?

A. Correct.

Q. And BeiGene, you know, informed the FDA, at least in its label, that lymphocytosis is a result,

a known result of inhibiting BTK; right?

A. Yes.

Q. In paragraph 100, I think it follows that you sort of lay out the reasoning behind your opinion that it's unpredictable whether and at what dose a BTK inhibitor will result in lymphocytosis.

And in it, you cite the patent. This is at the bottom of page 42. You say, [As read] The specification also discloses that, at sufficient doses, patients will exhibit lymphocytosis when administered a BTKI.

Right?

MS. PATEL: Objection. Form.

A. That is what the sentence says.

Q. Okay. And you don't include in here any example of a BTK inhibitor that inhibits BTK but doesn't induce lymphocytosis; right?

MS. PATEL: Objection. Asked and answered.

A. This has been asked by you in the past, and it's just the compounds that are available and have been studied, they inhibit BTK and they've had a lymphocytosis.

Q. So that means you're not aware of any example of a BTK inhibitor that inhibits BTK but doesn't induce lymphocytosis; is that right?

A. I would say that with the caveat of the medication that was used for multiple sclerosis, tolebrutinib, I have not in detail whether or not that causes a lymphocytosis in individuals who don't have CLL or SLL.

Q. Okay. And so whether or not -- oh, I'm sorry?

A. But in patients with CLL and SLL treated with BTK inhibitors, lymphocytosis is a known manifestation within a subpopulation.

Q. And so whether or not tolebrutinib induces lymphocytosis is not a basis on which you formed your opinion here; right?

A. Correct.

Q. Okay. Okay. In paragraphs 102 -- so the next section is a new section on statements that you read from litigation concerning Imbruvica.

Do you recall reviewing and commenting on those statements?

A. I recall reviewing and commenting and drafting it with the legal counsel from Weil.

Q. Okay. And I'm not asking for conversations that you had with the attorneys while preparing your declaration. I just wanted to anchor you in the analysis that you present here in these paragraphs.

So in particular, you note in paragraph 102 and 103 -- or in 102, certain statements from the Imbruvica -- prior Imbruvica litigation.

Do you see those recited?

A. The quotations?

Q. Yes.

A. Yes.

Q. And do you have an understanding that those statements were made about the state of the art absent the teaching in the specification regarding ibrutinib's clinical effects in CLL and SLL?

MS. PATEL: Objection. Form. Calls for a legal conclusion.

A. It would be outside of my understanding to comment on the legal perturbations of this.

Q. And do you understand that, for purposes of

written description and enablement that you've analyzed, you'd take into account the teaching of the patent specification?

A. Yes. I mean, actually, one of the considerations was the specifications versus claims, and when I went through the material, it seemed like the specifications were narrow and the claims were very, very broad. And so I got an understanding of the nuances of each in discussion with attorneys from Weil.

Q. Okay. And so for enablement written description, you take into account the teaching of the specification, and that's what you've done in this case; right?

A. Yes.

Q. And the statements that you quote here, do you have any understanding of whether or not those were made in the context of excluding the teaching of the patent from the understanding of a person of ordinary skill?

A. I would have to go back and look at the documents, and also this would be a question I would

want to dialogue with attorneys in terms of --

Q. So you don't have -- I'm sorry.

A. -- in terms of what it means --

Q. You don't have any --

A. Sorry.

Q. So you don't have any particular recollection of the context of these statements and how that would have informed your interpretation of them?

A. Well, the statements are all true. And they're meaningful. But outside of the fact that they're valid, I don't.

Q. Okay. Okay. So I want to turn to paragraph 115. And this comes at the end of a section where you're identifying and discussing the '803 patent and, in particular, the claims of the '803 patent. Let me know when you're there.

A. I'm there.

Q. Okay. And in 115 -- well, so, first, you understand or you've characterized the claims of the '803 patent as including structural limitations and functional limitations; right?

A. Yes.

Q. Okay. And we've discussed this before, but just to confirm, you're not opining in any way on the structural limitations of the claims; right?

A. I'm relying on Dr. Showalter's declaration as it relates to structure.

Q. Right. And so the functional limitations of the claims you lay out here in paragraph 14, your understanding of them is that the functional limitations of Claims 1 and 8 require that the BTKI that satisfies the structural limitation also perform the functions of, one, being irreversible and more specifically forming a covalent bond with Cys-481 of BTK; two, treating chronic -- well, treating CLL or SLL by administering a therapeutically effective amount; and, three, resulting in lymphocytosis; is that right?

A. Correct.

Q. So those are the three functions of the claims that you've identified and understand; is that right?

A. Yes.

Q. Okay. And the first function, whether or not a structure would irreversibly inhibit BTK by forming a covalent bond with Cys-481, that's a function that you don't opine on, you rely on Dr. Showalter to analyze that function; right?

A. Correct.

Q. Okay. But you've analyzed the other two functions that you've laid out here, the treating CLL and SLL with a therapeutically effective amount and resulting in lymphocytosis. Those are the two functions that you've analyzed?

A. Yes.

Q. And for the treating function, you've also identified that the -- that the claims require that, in order to treat with a therapeutically effective amount, you have to have an effective treatment and you also have to have a safe treatment that doesn't cause undue side effects. That's been the analysis that you used; right?

A. I would say my analysis first with efficacy, and the appeals board also agreed with the efficacy issue. I also personally think, as a clinician,

that safety is important. That was not the opinion of the appeals board. My opinions don't change either way.

Q. So your analysis of whether or not a particular BTK inhibitor is safe is one that you think a clinician would think is important, but is it now your opinion that those safe -- that that analysis as to the safety is not a requirement of the claim?

A. I'm not sure I understand that. What --

Q. That's --

A. -- I'm hoping to say is efficacy is what is critical, and that was what was critical to the appeal board. And Imbruvica is efficacious, and that's why I used it when it first became available. We all used it. I'm not questioning that. But as a clinician, safety becomes an issue and you decide is there a better drug to replace the drug that's efficacious but not as safe. My understanding is the appeal board felt that efficacy was the critical issue. None of my opinions change based on the appeal board, and I understand their decision.

Q. Okay. And we -- we looked at that structure that appears in the claim I think before lunch. And a representation of it is in paragraph 114, the prior paragraph to what we were just looking at. Just take a look at it.

A. Yes.

Q. Do you see that?

A. I do see it.

Q. And you've not analyzed which parts of the compounds are most important for binding or which relate to the binding function of the BTK inhibitor; right?

A. I recognize what Dr. Showalter said, but I am not the expert to have noted that in advance.

Q. And you also haven't analyzed what parts of the compound are important for efficacy; right?

A. Only based on what Dr. Showalter commented in terms of what binds to the target and what can affect the three-dimensional structure.

Q. Right.

And so you have not done any three-dimensional modeling or visualization of the

BTK inhibitors interacting with BTK; right?

A. That would be outside my expertise.

Q. And you've not analyzed the role of any particular part of the BTK inhibitor structure and how it imparts any particular function to the overall molecule; right?

A. Correct.

MS. PATEL: Counsel, we're almost to an hour since we started. I don't know if this is a good time to take a break.

MS. DANEK: Sure. This works if you want to take a break, Dr. Rosen.

THE WITNESS: It's completely up to you. I can go a bit longer if you'd like, and then we can take a break. It's really up to you.

MS. PATEL: Well, why don't we take a quick break.

REMOTE TECHNICIAN: Off the record 1433.

(A short break was had.)

REMOTE TECHNICIAN: Back on the record 1444.

BY MS. DANEK:

Q. Dr. Rosen, I want to turn in your

declaration to the paragraph -- the section starting at paragraph 184. This is on page 78 of the declaration and 84 of the document.

A. Can you put it on the screen as well? I just want to make sure we're talking about the same issue.

MS. DANEK: So page 84 of the document.

Great. Thanks.

BY MS. DANEK:

Q. So, Dr. Rosen, this section --

A. Just one second. I just want to get to it. So it's page 78. Okay. And 184 paragraph. Okay.

Q. Yep. Are you there?

A. I am.

Q. Okay. And this is a section of your report that's called, "The Priority Nonprovisionals Do Not Provide Written Description Support for the Challenged Claims"; right?

A. Correct.

Q. Okay. And you list -- you have a number of paragraphs, and all of these relate to your written description analysis of the specification of the

'803 patent; right?

A. Yes.

Q. And in paragraph 184, you identify that it's your opinion that the nonprovisional applications do not "provide written description support for independent Claims 1 and 8 as of 2010/2011"; right?

A. Yes.

Q. And you outline, in paragraph 185, a number of your understandings from Dr. Showalter's declaration; correct?

A. Correct.

Q. But nothing in paragraph 185 represents your independent opinions. They are just a report of your understandings of Dr. Showalter's analysis; right?

A. So I would say based on his opinions with my understanding that they're correct and if there are potentially a billion compounds to be studied, then I, obviously, concur with Dr. Showalter.

Q. Okay. But you have no independent opinion -- opinions related to the statements that are included in 185.

A. Yeah, I wouldn't be able to opine about the varied structures that could be created.

Q. In paragraph 186, you state that Claims 1 and 8 require the BTKIs of the claims that satisfy the structural limitations to also have the functional limitations of irreversible BTK -- strike that.

Let me start over. I got sloppy.

The first sentence indicates your understanding that the claims require BTKIs that irreversibly inhibit BTK and covalently bind Cys-481; is that right?

A. Correct.

Q. And that they also need to satisfy the additional functional limitations of being effective to treat CLL and SLL; right?

A. Correct.

Q. And you state that it's your opinion that [As read] not only does the specification not show that patent owner invented any BTKIs that meet the structural limitations beyond those disclosed in the specification ...

Do you see that?

A. Yes.

Q. And that -- that opinion that the specification doesn't show that the patent owner invented any BTKIs that meet the structural limitations beyond those disclosed in the specification, that opinion, is that based on your understanding of Dr. Showalter's analysis?

A. It's based on my understanding of what Dr. Showalter put in his disclosure.

Q. Okay. So you are not offering an opinion that the specification doesn't show that the patent owner invented BTKIs that meet the structural limitations beyond those disclosed in the specification. That's not your independent opinion.

A. It's Dr. Showalter's disclosure, and I concur with it, based on my review of what Dr. Showalter said.

Q. Okay. And you have a similar statement in paragraph 188 in the middle of the paragraph. It states that [As read] It is my opinion that, not only does the specification not show that patent

owner invented any BTKIs that meet the structural limitations beyond those recited in the specification ...

And, again, that's the same language, and so that is not an opinion that you've independently formed. It is your understanding of -- based on Dr. Showalter's analysis?

A. Yes.

Q. Okay. And then you've laid out your opinion that "the specification fails to provide blaze marks, common structural features, or representative species for the full scope of BTKIs" that satisfy the functions of effectively and safely treating CLL in this subsection A that begins at paragraph 190?

A. Yes.

Q. Okay. And the first section lays out your analysis of blaze marks and common structural features. That's (a)(1), subsection (a)(1)?

A. Yes.

Q. And so your analysis of blaze marks and common structural features, as they relate to the function of effectively and safely treating CLL and

SLL, spans paragraphs 190 to 203?

A. Correct.

Q. And your analysis of why you've concluded that there's no blaze marks or common structural features for BTKIs that would effectively and safely treat CLL and SLL is all included in these paragraphs?

MS. PATEL: Objection. Form.

A. I can't tell you with certainty. I assume yes.

Q. Okay.

A. Without agreeing, but I assume yes.

Q. And you've cited all of the materials that you relied on in forming your opinion that there are no blaze marks or common structural features for BTKIs that would effectively and safely treat CLL and SLL in these paragraphs.

A. I believe I have, yes.

Q. And so all of the material that you found that would support your opinion, your intention, at least, would have been to include them in these paragraphs?

A. That definitely would have been my intention.

Q. Okay. And you didn't exclude materials that you found or reviewed or considered that related to your opinion on blaze marks and common structural features for the ability to safely and effectively treat CLL and SLL from these paragraphs?

A. You're saying did I exclude any information?

Q. Uh-huh.

A. Not that I'm aware of.

Q. Okay. In paragraph 191, you quote the specification of the patent.

Do you see that?

A. Yes. [As read] The specification of the '803 patent describes --

Q. Yep.

A. -- that in some embodiment ...

And then it goes on to talk about the structure of any formula, yes.

Q. Right.

And you're not providing any opinion as we've noted a number of times, about what those

structures are; right?

A. Correct.

Q. Okay. And in paragraph 192, you state that "Of the species encompassed by" those formulas, structural formulas, "the specification describes only Imbruvica as treating CLL and SLL."

Do you see that?

A. Yes.

Q. Okay. And so you're -- again, you're not a chemist, and so you're not opining on any understanding of how the structural limitations relate to what a POSA would understand about the functional activity.

A. If you can repeat that.

Q. Sure.

A. Initially, I thought that I was in agreement, that you were focused on the structure of molecules that I would defer to Dr. Showalter. Once the testing is done, then functional considerations I would feel comfortable opining on.

Q. But you are not offering opinions on what structural features could distinguish a species that

safely and effectively treats CLL and SLL from a species that doesn't effectively treat CLL and SLL; right?

A. Correct.

Q. And you would need a chemist member of the POSA team to opine on how the structural features may result in -- be able to distinguish a species that effectively treats versus a species that doesn't effectively treat; right?

A. Can you say that one again? I apologize. I want to make sure --

Q. Sure.

A. -- I truly understand it.

Q. Actually, I think -- we don't need to complicate it more. I think we're in agreement on the structural features.

Now, you're also not opining on what blaze marks would distinguish a species that safely and effectively treats CLL and SLL from ones that would not safely and effectively treat CLL and SLL; right?

MS. PATEL: Objection. Form. Mischaracterizes the declaration.

A. If the question is am I opining on how a structure would be developed with the intention, I'm not the right one. But we also recognize that experimentation ultimately is the critical issue, even if a medicinal chemist thinks that this may be the ideal compound that's been produced.

Q. And you note in your sentence that starts on the bottom of page 81 in paragraph 192 that goes over to the top of page 8 --

A. Yes.

Q. -- 2, you state that the statement from the specification [As read] does not provide blaze marks or common structural features to distinguish the species that safely and effectivity treat CLL/SLL from ones that do not.

Right?

A. Yes.

Q. Okay. What structural features would -- do you have an understanding of what structural features would distinguish a species that safely and effectively treats CLL and SLL from ones that would not?

A. I would defer to Dr. Showalter.

Q. And do you have an understanding of what blaze marks would distinguish a species that safely and effectively treats CLL and SLL from ones that would not?

A. In terms of generating compound, I would defer to Dr. Showalter.

Q. And then you state, the last part of paragraph 192, [As read] The specification does not provide any guidance as to whether BTKIs having different chemical structures, other than Imbruvica, such as Brukinsa, could treat CLL/SLL effectively and safety; right?

Do you see that?

A. Right.

Q. Okay. And what guidance were you looking for as to what different chemical structures -- as to whether or not different chemical structures could treat CLL or SLL?

MS. PATEL: Objection. Form.

A. From Dr. Showalter's declaration, he stated clearly and on multiple occasions that there was a

billion permutations that could be developed based on the original structure that was provided in the documents, in particular the Z component. And so, based on that, I would say that the experimentation would be overwhelming. And a medicinal chemist may have a sense of what may be effective, but it all requires extensive testing, from in vitro to pre-clinical in animal models to clinical studies in humans.

Q. And you're not offering any opinions as to what that sense of medicinal chemist may have as to the effect of different structural changes might be on the ultimate activity of a compound; right?

A. Correct. I'm not a medicinal chemist.

Q. In paragraph 193, you state that the specification discloses a single BTKI that meets the claim limitations as an effective and safe treatment for CLL and SLL; right?

A. Yes.

Q. Is it your opinion that the specification and its examples fail to provide a POSA with any guidance or teaching regarding other species than

Imbruvica?

A. It's my understanding, from Dr. Showalter and my review of the information, that the specifications relate to Imbruvica or isomers of Imbruvica but not broader and would not relate to even molecules in the family of zanubrutinib.

Q. Okay. And is it your opinion that the specification in the examples fail to provide any guidance about other species of BTKIs based on the fact that the specification and examples do not present clinical trial results for these other species?

MS. PATEL: Objection. Form. Mischaracterizes the document.

A. No, it's based on Dr. Showalter's analysis and his disclosure and my review of his disclosure.

Q. Okay. And so you're not opining on any of the structural differences that may exist between different BTKIs and how those affect safety and efficacy?

MS. PATEL: Objection. Asked and answered.

A. I have answered this before, but correct. I

am not opining about the varied structures that could be created, just what would -- needed to be done once the structure existed to test to see is this a meaningful therapeutic compound.

Q. Got it. In your opinion, then, the specification and examples do not provide any guidance as to the efficacy and safety of any other species of BTKI regardless of what -- how different the structures are between that BTKI species and ibrutinib?

MS. PATEL: Objection. Form.

A. If I understood your question correctly, that would be definitely a question for Dr. Showalter. If something clearly resembled Imbruvica and was subtly different, I can't tell you. And it's also a legal issue how it relates to the patent. But Dr. Showalter obviously commented that there could be a billion permutation. So I am comfortable stating it is impossible to test all the permutations.

Q. Okay. So just to be clear, your opinion is that the specification doesn't describe any other

BTKI that could safely or effectively treat CLL or SLL, other than Imbruvica?

A. It's my understanding that the specifications relate to Imbruvica. Potential isomers from a medicinal chemist's perspective and from a legal perspective, I can't say that there are other molecules that may not be acceptable if they look just like Imbruvica. But the billions that could be produced related to the Z structure is a very different consideration.

Q. Okay. And so you haven't undertaken that analysis to understand structures that might look just like Imbruvica and whether or not they are taught by the specification?

MS. PATEL: Objection. Mischaracterizes testimony.

A. I've only considered what Dr. Showalter said in regards to this issue.

Q. Okay. And so your opinion that the specification fails to provide a POSA with any guidance or teaching regard any other species falling within the structural limitations relates to

your understanding that there are billions of other species that fall within the structural limitations?

A. That is my understanding.

Q. Okay. And so, for example, you didn't consider whether or not the -- a POSA would have been guided or taught by the specification to other species that might closely look like the structure of ibrutinib?

MS. PATEL: Objection. Mischaracterizes declaration.

A. I would rely on Dr. Showalter for that discussion.

Q. Okay. That's not an analysis you considered in forming your opinion here?

A. I did review Dr. Showalter's disclosure, and it all made sense to me. I'm not a medicinal chemist. If something didn't make sense to me, I would question it.

Q. Okay. And so there -- you stated earlier that you can't say that there are other molecules that may not be acceptable if they look just like Imbruvica.

Do you recall saying that?

A. I recall saying that and paraphrasing that Dr. Showalter would have to render an opinion about that. It wouldn't be something that I feel I have the expertise.

Q. Okay. And so for other BTKIs that look just like Imbruvica, there may be guidance and teaching in the specification that would tell a POSA that those BTKIs may be safe and effective treatments for CLL and SLL?

A. So that would be a question for Dr. Showalter when you take his deposition.

Q. Okay. Okay. So in paragraph 195, are you there?

A. I am.

Q. Okay. You state that not all BTKIs that fall within the scope of the structural limitations and covalently bind Cys-481 or any other residue of BTK will be effective and safe treatments for CLL and SLL; right?

A. Correct.

Q. And you lay out that opinion in this

paragraph, and the only cites you have here are to section 4-D-1 and 4-D-2. And we talked about those earlier; right? Those are your structure-activity relationship for effective treatments in 4-D-1 and structure-activity relationship for safe treatments in 4-D-2; right?

A. Let me just confirm that those were the sections. I have no reason to disagree, but I don't have the memory that those are the actual sections.

Okay.

Q. And then you also reference your discussion in -- later in section 9-B-1-D-1. And there's a labyrinth to navigate there.

A. Where are we looking now.

Q. Yeah, so in the middle of your paragraph 195 you have a reference to section 9-B-1-D-1?

A. Yes, I see this. I'm sorry.

Q. No, that's okay. So that is a reference to the paragraph starting at paragraph 265 and spanning to 276?

A. You want me to go there to 265?

Q. Yeah, just confirm. I'm sorry. To 273.

265 to 273.

A. Okay.

Q. Those are the only citations you give in this paragraph 195?

A. It appears to be the case.

Q. Okay. In paragraph 196, you state that, [As read] Whether and at what dose a BTKI effectively treats CLL/SLL is a function of pharmacological properties.

Do you see that?

A. I do.

Q. Okay. And then, in the second sentence, you say, [As read] Likewise, a BTKI's overall chemical structure affects its selectivity which, in turn, affects whether administration of that BTKI would result in undo adverse side effects.

Right?

A. Right.

Q. But you're not offering an opinion about how changes to a chemical structure would be understood to affect the selectivity of a BTKI; right?

A. In advance of experimentation?

Q. Right.

A. No.

Q. Okay. And so you're not offering an opinion on how a person of ordinary skill in the art would understand how changes in a structure would affect pharmacological properties either in advance of experimentation?

A. I want to make sure I don't answer in a misleading way. My understanding is that a medicinal chemist would predict what may be beneficial, and then experimentation would be done to see if the individual is correct.

Q. And you're not opining on what types of structural changes might be understood to have particular impact on pharmacological activity; right?

A. Outside of what Dr. Showalter disclosed, no.

Q. Okay. In the back part of the last part of paragraph 196, you reference that a patent owner withdrew Imbruvica's MCL and MZL indications because of issues with efficacy.

Do you see that statement?

A. I do.

Q. Okay. Is it your opinion that ibrutinib does not have efficacy in treating MCL and MZL because there's no approved indications for these diseases currently?

A. I believe it does have efficacy.

Q. And so the activity of -- and MCL and MZL are different diseases than CLL and SLL; right?

A. Mantle cell lymphoma and marginal zone lymphoma are distinct from CLL and SLL.

Q. And the activity of a drug in one type of lymphoma does not tell you about its activity in another type; right?

A. Not without testing.

Q. Paragraph 198 discusses your opinion about the specification not providing guidance to a POSA regarding pharmacological properties.

Do you see that?

A. Yes.

Q. And paragraph 198 doesn't include a citation to any reference or other portion of your declaration?

A. Correct.

Q. And you state here, at the sentence at the bottom of page 84 in paragraph 198, [As read] The specification does not describe what structural features of Imbruvica allows for effective and safe treatment.

Do you see that?

A. Correct.

Q. What is your understanding of the structural features of Imbruvica and how they relate to effective and safe treatment?

A. The structure of Imbruvica, as we discussed earlier with the different components, it wasn't until Imbruvica actually was given to patients that we actually witnessed the efficacy and the safety concerns.

Q. Do you have any understanding of how the structural features of Imbruvica relate to the safety and efficacy it exhibited once given to patients?

A. I think it remains somewhat open why it binds to some other targets in addition to BTK and

why it affects other signalling pathways. This, again, would be under Dr. Showalter's disclosure. But it clearly affects other targets, not just BTK.

Q. And you're not providing any opinions about how the structural features of ibrutinib relate to its ability to bind BTK and be an effective treatment for CLL and SLL; is that right?

A. I feel Dr. Showalter and, obviously, the original patent put that information together, and I'm not disagreeing with any of it.

Q. Your next statement is -- in this paragraph is, [As read] Moreover, the specification does not describe what modifications could be made to the structural features of Imbruvica that would still allow for it to be a safe and effective treatment for CLL and SLL.

A. Can you point me to which paragraph are we on?

Q. Yep.

We're still in paragraph 198. It's now the sentence at the very top of page 85.

A. Correct.

Q. And there's no citation for this --
A. Correct.
Q. -- your opinion here?
What --
A. Well, it's my opinion based on Dr. Showalter's disclosures.
Q. So you don't have any opinions on how a POSA would understand what modifications could be made to the structural features of ibrutinib that would still allow for a safe and effective treatment?
A. Well, I would rely on Dr. Showalter in terms of the structural issues. In terms of the functional issues, the testing from pre-clinical to clinical investigations, there, I would feel comfortable opining. But in terms of the actual --
Q. You would feel -- I'm sorry.
A. I'm sorry.
But in terms of the actual modifications of the molecule, that would be Dr. Showalter.
Q. So you're not opining on how a POSA would -- would expect or predict changes in the activity of a compound based on particular structural

modifications; is that right?

A. So I would predict that any time you modify a molecule, it may change its properties. That's without question. I would rely on Dr. Showalter to say how those modifications may affect the structure. But no matter what modifications occur, you would have to go through all the experimentation to bring it to human beings and see whether it works, even the most modest modifications.

Q. Right.

And so your opinion here is based on your ability to analyze the testing results that would have been done to assess the function of a compound?

A. Correct.

Q. But you're not opining on what a person of ordinary skill in the art would have predicted those testing results might have been based on what structural changes were made.

A. That would be under the domain of Dr. Showalter.

Q. Okay. And then similarly, your last sentence, you say, [As read] Nowhere in the

specification tells a POSA the pharmacological properties of other BTKIs or whether or at what dose other BTKIs could be effective and safe in treating CLL and SLL.

Right?

A. Correct.

Q. And, again, you are -- your opinion is based on an analysis of what -- strike that.

You're not offering an opinion about what a POSA would have predicted or expected specific structural changes would have to the pharmacological properties; right?

A. Correct. I would rely on Dr. Showalter for those disclosures.

Q. Right.

Your analysis would just be in the ability to analyze the results of the testing of the ultimate pharmacological properties that would have been conducted on any modified structure of a BTKI; right?

A. Yes, knowing from previous experience any modification can affect the function of a molecule.

Q. Okay. In paragraph 199, you note that "the specification directs a POSA to conduct testing ... to measure the pharmacological properties" and you have a couple of citations to the patent specification; right?

A. Correct.

Q. And you state that [As read] a POSA would not be able to predict a BTKI's IC50 value (and thus potency) based on the BTKI's Z-prime structure and/or the fact that the BTKI is known to covalently bind BTK.

Do you see that?

A. Yes.

Q. Okay. And then similar to what we were just discussing, you're not offering an opinion about what a POSA would predict about the effect on IC50 values based on what particular structural change was made. You're just opining that the testing would have to be done to measure those properties.

A. Correct.

Q. And in paragraph 203 -- let me know when you're there.

A. I'm there.

Q. You state that it is your opinion that [As read] the specification does not provide any blaze marks or common structural features to any BTKI other than Imbruvica that is an effective and safe treatment for CLL or SLL.

Correct?

A. Correct.

Q. So in your opinion, the specification provides blaze marks and common structural features for ibrutinib.

A. It shows the structure of ibrutinib. I'm relying on Dr. Showalter in terms of the blaze marks. I'm not a medicinal chemist.

Q. Okay. And so then what blaze marks are missing in your -- in coming to your opinion that the specification doesn't include the blaze marks to any BTKI other than ibrutinib?

A. It's based on Dr. Showalter's declaration.

Q. Okay. So you don't have an independent opinion on blaze marks as it relates to the structures of the BTKIs.

A. I would rely on Dr. Showalter.

Q. Okay. So the next section -- or not the next, but let's turn to one of -- the next major section that -- at -- starting at paragraph 205. It's got a heading B, "The specification does not describe any species other than Imbruvica would that satisfy the lymphocytosis limitation."

Are you there?

A. Yes, I saw that.

Q. Okay. And so this is a section -- you have a subsection (1) that is, "No Blaze Marks or Common Structural Features."

Do you see that?

A. Yes.

Q. Okay. And that is a section spanning paragraph 205 to 218. Nope, I'm sorry, 216.

A. Okay.

Q. Is that the section? You agree with those paragraphs?

A. Yes.

Q. Okay. And these paragraphs lay out your analysis and the basis for your opinion that the

specification doesn't describe any species other than ibrutinib that would cause lymphocytosis; right?

A. Correct.

Q. Okay. And you lay out and cited all of the materials that you relied on in coming to that opinion in these paragraphs; right?

A. Correct.

Q. And you included all of the materials that you found that supported your analysis that there were no blaze marks or common structural features for any other BTKI that satisfies the lymphocytosis limitation other than ibrutinib.

A. Correct.

Q. You didn't exclude any materials that you considered in -- in forming your opinion from these paragraphs.

A. No.

Q. Okay. In paragraph 206, you cite just the patent specification; right?

A. Correct.

Q. And do you consider the patent specification

authoritative in teaching the use of ibrutinib as a treatment for CLL and SLL?

MS. PATEL: Objection. Calls for speculation.

A. You used the term "authoritative"?

Q. Uh-huh.

A. That's more a legal term than a medical term, so I'm not sure. Legally, it may be considered authoritative. Medically, the patent just says this is a compound worth exploring that may have clinical benefit to humanity.

Q. And you relied on the patent specification as support for certain pieces of your analysis in forming your opinions here; right?

A. Yes.

Q. In paragraph 207, you cite only the patent specification and a reference to the previous section we were just walking through on blaze marks and common structural features for the safe and effective treatment of CLL and SLL.

Do you see that?

A. I do.

Q. So those are the only -- that's the only support for the analysis included in paragraph 207.

A. Correct.

Q. Okay. In the last or second to last sentence of that paragraph, it says, [As read] That statement does not provide blaze marks or common structural features to distinguish the BTKIs that satisfy the lymphocytosis limitation from ones that do not or at what doses.

And the "that" statement refers to a quote you have from the specification.

A. Correct.

Q. And in your analysis of what blaze marks or common structural features distinguish a BTKI that satisfies the lymphocytosis limitation from one that does not, you're not opining on what any particular structural modification would be predicted to have an effect on the lymphocytosis activity; right?

A. Correct. I would rely on experimentation.

Q. Okay. So you're not providing any opinion as to what structural features could distinguish a species that meets the lymphocytosis limitation from

ones that do not; right?

MS. PATEL: Objection. Mischaracterizes the testimony. Asked and answered.

Q. Go ahead and answer.

A. State your question again, please.

Q. Sure.

You're not providing any opinion as to what structural features could distinguish a species that meets the lymphocytosis limitation from ones that do not meet the lymphocytosis limitation.

MS. PATEL: Same objections.

A. It's my opinion you need to do experimentation in order to see whether or not the lymphocytosis occurs regardless of the alteration of the molecule.

Q. So in your opinion, any structural change to ibrutinib could not be understood by a POSA to result in a -- or could meet the lymphocytosis limitation.

MS. PATEL: Objection. Form.

A. I believe it could be predictive, but it has to be proven through experimentation.

Q. Okay. And you're not offering an opinion about how a POSA may be able to predict the effect of a structural change on the ability of a compound to meet the lymphocytosis limitation.

MS. PATEL: Objection. Asked and answered.

A. Correct.

Q. So you state here -- we read that the statement in the specification does not provide blaze marks to distinguish BTKIs.

What blaze marks were you looking for?

A. I think it's the opposite. There are no obvious blaze marks, so there's no way to predict without experimentation. And it goes back to what we talked about before about necessary but not sufficient, so everything that would bind to a BTK has to be tested.

Q. In paragraph 208, you describe that the specification includes examples of administering ibrutinib for the treatment of CLL and SLL. And you state that those examples [As read] do not provide a POSA with any guidance or teaching regarding any other species falling within the structural

limitations, including Brukinsa.

Right?

A. Correct.

Q. And again, in your opinion, there's no guidance about any other species regardless of how similar that species is in structure to ibrutinib.

A. It's my opinion you can make a prediction. But without experimentation, you can't be definitive.

Q. And, again, those predictions about what the activity would be -- outside your expertise, those predictions would be a medicinal chemist or someone with experience in protein kinase structure-function relationship?

A. Correct.

Q. In paragraph 210 -- let me know when you're there.

A. I'm there.

Q. You state that [As read] The specification does not describe what structural features of Imbruvica results in lymphocytosis.

A. Correct.

Q. What is your understanding of the structural features of Imbruvica that result in lymphocytosis?

A. I don't believe it's clear outside of inhibiting BTK.

Q. And you aren't -- you're not offering any opinion on how a POSA would understand what structural features impart the ability to inhibit BTK; right?

A. Please state that again.

Q. Sure.

You're not offering an opinion as to how a POSA would understand which portions of the compound impart the ability to bind and inhibit BTK.

A. Well, in Dr. Showalter's declaration, he discusses the portion that binds to the Cys-481 and he discusses the other components of the molecule. So as the medicinal chemist, he's the expert. That's not my domain.

Q. Okay. And this paragraph 210, there's no citations to any reference for your analysis that you've conducted here.

A. Correct. That would be based on my review

of the materials provided to me and Dr. Showalter's disclosure.

Q. Okay. But you've not cited any of the materials that you reviewed or Dr. Showalter's declaration in this paragraph; right?

A. Correct.

Q. All right. Paragraph 212, you state that not all -- actually, let me pause.

Are you there?

A. I am.

Q. Okay. Great.

You state that [As read] not all BTKIs that satisfy the structural limitations covalently bind Cys-481 or any other residue ... and are an effective and safe treatment for CLL and SLL will satisfy the lymphocytosis limitation.

Right?

A. Correct.

Q. And there's no citation for your opinion in this paragraph; right?

A. Correct.

Q. And you say -- you conclude the paragraph

with [As read] a POSA reading the specification would understand that not all BTKIs that satisfy these other limitations at a certain dose would also result in lymphocytosis at the same dose.

Right?

A. Correct.

Q. And there's no citation for that opinion.

A. Correct.

Q. And you've not identified any BTKI that satisfies the other limitations that also doesn't result in lymphocytosis; right?

A. We, I think, discussed this before. There are only a limited number of Bruton tyrosine kinases that are in the clinic, and so comments can only be made about those.

Q. And you're not aware of any BTKI in the clinic that doesn't induce lymphocytosis; right?

A. Only that lymphocytosis is not universally seen in all patients, and so we know that there's complexities to the binding and what happens in that regard.

MS. DANEK: Well, I think we've been going

for about an hour if you want to take a break.

THE WITNESS: Okay. Thank you.

So what time do you want to resume? At 5 to?

MS. DANEK: Sure.

REMOTE TECHNICIAN: Off the record. 1543.

(A short break was had.)

REMOTE TECHNICIAN: We are back on the record. The time is 1553.

BY MS. DANEK:

Q. Dr. Rosen, we are -- we were talking about your analysis of written description in your declaration. I want to turn your attention to a section that starts at paragraph 219. It's at page 93 of the declaration and 99 of the document.

A. It starts with (a) Claim 2?

Q. Yes.

And so we were going through your analysis of blaze marks and common structural features as it related to Claims 1 and 8 in the prior discussion we were just having; is that right?

A. Correct.

Q. Okay. And so you've separately set out a section describing the dependent claims in this subsection 2 that starts at paragraph 19 -- 219.

A. Yes.

Q. And in this section, you discuss your written description analysis for Claim 2, Claims 3 to 7, 12, and 20; right?

A. Yes.

Q. And turning to your discussion of Claim 2 in paragraph 219, you describe the limitation of Claim 2 and report that "it's identical to Claim 8 except that" it "requires BTKI to specifically covalently bind Cys-481"; right?

A. Yes.

Q. And then in paragraph 220, you state that you [As read] understand from Dr. Showalter's declaration that this limitation does not reduce the number of species that satisfy the claimed structural limitations.

Right?

A. Correct.

Q. And it is on that basis that you have the

opinion that Claim 2 lacks written description support; correct?

A. Correct.

Q. So other than the discussion relying on Dr. Showalter about the breadth of the number of species, your opinion related to Claim 2 is identical to your analysis for Claims 1 to 8.

A. Correct.

Q. Okay. And then Claims 3 to 7, you describe the content of those claims in paragraph 222. And then you have a similar statement as you had for Claim 2 in paragraph 223 that the limitation in Claims 3 to 7 do not reduce the number of species; is that right?

A. Correct.

Q. And so you conclude, then, that Claims 3 to 7 lack written description support for the same reasons as Claim 1; right?

A. Yes.

Q. So you don't have a separate opinion as to a written description for Claims 3 to 7. It is identical to your analysis for the written

description for Claim 1; right?

A. Correct.

Q. Okay. And then Claim 12, similarly, you identify that the limitation in Claim 12 does not reduce the number of species -- appreciably reduce the number of species and that Dr. Showalter states that it still allows for billions of BTKIs for the limitation in Claim 12; right?

A. Correct.

Q. And so you, therefore, conclude that Claim 12 lacks written description support for the same reasons as Claim 1; right?

A. Yes.

Q. And so you don't have an independent written description analysis for Claim 12. It is identical to your written description analysis for Claim 1.

A. That's what's stated here in the declaration.

Q. Okay. Claim 20, similarly to Claim 12, you state that you understand that Dr. Showalter has opined on the number of species that fall within Claim 20. And based on that understanding, your

opinion is that Claim 20 lacks written description support for the same reasons as Claim 1; right?

A. And that's written in paragraph 230, yes.

Q. So you don't have an independent written description opinion for Claim 20. Your opinion is identical to your analysis for Claim 1.

A. Correct.

Q. Okay. Okay. In the next section B, you lay out your analysis of the -- whether or not the specification provides enabling support for the challenged claims. And that is beginning at paragraph 231?

A. Correct.

Q. And in this paragraph, you, again, rely on Dr. Showalter's declaration that "a POSA would not know, without undue experimentation, which of the billions of species that meet the structural limitations would also satisfy the functional limitation" of irreversibly binding BTK to Cys-481; right?

A. Correct.

Q. But you've undertaken an analysis as to

whether or not there would be undue experimentation as to whether or not the BTKIs that meet the structural limitations and bind and inhibit BTK would also effectively and safely treat CLL and satisfy the lymphocytosis limitation; right?

A. Can you repeat that? I got confused.

Q. Sure.

So you're only analyzing an enablement with respect to the -- safely and effectively treating CLL and the lymphocytosis limitation; correct?

A. Correct. Once a compound was predicted, it would have to go through all the experimentation, as we talked about before, in vitro, pre-clinical, and then clinical investigations.

Q. Okay. In the next section, you describe your analysis for whether or not the specification enables a POSA to practice Claims 1 and 8; right?

A. Yes.

Q. And these are paragraphs 232 through 273 -- or 276.

A. So here, we're talking about the breadth of the independent claims.

Q. No, no, no. It's an even simpler question than that. Just wanting to outline that your enablement analysis for independent Claims 1 and 8 is included in the section 1 here that encompasses paragraphs 232 to 276.

A. Without reading this in detail, just skimming through it, I believe that that is accurate.

Q. And, again, you included all of the support for your enablement analysis as it relates to Claims 1 and 8 in paragraphs 232 to 276?

A. Yes.

Q. And --

A. There's nothing omitted.

Q. And you looked for materials that would support and corroborate your opinions and included them to the extent you found them in these paragraphs?

A. Yes.

Q. Let's look at paragraph 233.

A. 233.

Q. You start -- sorry.

A. I'm ready.

Q. You there? Okay.

You start the paragraph with an understanding of what Dr. Showalter's analysis is on the breadth of the claims; right?

A. Yes.

Q. Your second sentence states, [As read] However, a minor difference in structure could potentially impact whether a BTKI meeting the structural limitations would also meet the functional limitations.

Do you see that?

A. I do.

Q. And you don't have any citation for that sentence?

A. Correct.

Q. Are you offering any opinion as to what a POSA would consider to be a minor difference in structure for a BTKI?

A. No, only the comment that I made earlier that any modification needs to be tested.

Q. And whether or not that modification is

minor would need to be assessed by someone with medicinal chemistry or understanding of protein kinase structure-function relationship?

A. Well, subsequent functional testing. So the minor modification may be recommended by the medicinal chemist, but the verification that it has efficacy would need to be directed through functional analysis at all the levels we've talked about before. In vitro, pre-clinical, and then clinical investigation.

Q. And you're not offering an opinion as to whether or not any particular structural difference could be classified as minor?

A. Correct.

Q. And you're not offering an opinion as to how a person of ordinary skill in the art would understand any particular structural change, how it would impact the ability to treat CLL or SLL?

A. I'm of the opinion that whatever changes are made, they have to be experimentally verified.

Q. So in your opinion, any structural change to a BTKI cannot be understood to be a safe and

effective treatment for CLL or SLL without testing that compound?

A. Correct.

Q. And the testing that would need to establish whether something is an effective treatment for CLL and SLL would need to be a clinical study?

A. Well, first, it would start with in vitro testing. Then it would go to pre-clinical. And ultimately given to patients.

Q. And -- sorry.

A. No, I mean, it wouldn't be acceptable for any modification of a therapeutic to be given to human beings without the initial testing as well.

Q. And in order for a POSA to understand that any compound that inhibits BTK could be an effective treatment for CLL, there would need to be all of that testing, all of the pre-clinical testing, the animal testing, and the administration to human patients?

A. Correct.

Q. And that is true, all of that testing would be required to understand whether something could be

an effective treatment for CLL regardless of how similar the structures of the BTK is to ibrutinib?

A. Any modification of ibrutinib would require experimentation and clinical testing for it to be advanced.

Q. So by "advanced," you mean advanced in clinical development with the aim of getting regulatory approval and ultimately being able to commercially market it?

MS. PATEL: Objection. Mischaracterizes testimony.

A. To be advanced that it would be something that could -- would be evaluated in patients and seen to be efficacious and safe.

Q. So any modification -- any structural modification to ibrutinib would require all of the pre-clinical testing that you discussed, the animal model testing and the patient clinical studies, to understand -- for a POSA to understand that that BTKI could be an effective treatment for CLL and SLL?

A. Correct.

Q. And, again, you state here in paragraph 233 that a minor difference in structure could potentially impact whether a BTKI could meet the functional limitations, but you don't give any example of a BTKI that meets the structural limitations that doesn't meet the functional limitations; correct?

A. We discussed this before. I only know the ones that are in the clinic at this time. And if there's negative results, they're not put forth. So ...

Q. If we look at paragraph 236, this, again, is a reference to your understanding of Dr. Showalter's analysis of experimentation that would be required to identify compounds having the ability to inhibit BTK?

A. Correct.

Q. And you're not offering any independent analysis of the amount of experimentation necessary to identify a compound that can inhibit BTK?

A. Correct.

Q. And in your paragraph 237, you state that,

[As read] To determine whether the potentially billions of compounds meeting the structural limitations and binding to Cys-481 also effectively and safely treat CLL would have required extensive experimentation as of 2010/2011.

Right?

A. Yes.

Q. And so is it your opinion that inhibiting BTK would not be therapeutically effective in treating CLL and SLL?

A. It's my opinion, as we talked about earlier, that, for a BTKI inhibitor, it's necessary but not sufficient.

Q. And it's not sufficient because there could be -- there could be low bioavailability, for example?

A. As an example, it could bind to other proteins, as an example. It may not be as effective in killing the CLL cells for reasons we might not even understand. And it could have other toxicity that we didn't predict pre-clinically.

Q. And the fact that it could bind other

proteins, would that relate to the potential for a BTK to exhibit adverse events?

A. Yes.

Q. The fact that it binds to other proteins is not related to whether or not it would be effective in inhibiting BTK in the patient, though; right?

A. Potentially, not whether it would inhibit BTK, but whether the effect on another protein within a CLL cell even could affect the death of the CLL cell or the loss of adhesion. These are unknown until you do experimentation.

Q. And you've not -- sorry. You've not identified any BTK inhibitor that binds to another protein or induces another mechanism that prevents it from treating CLL or SLL?

A. Just as I said before, just the compounds that are available. And I don't know any negative results.

Q. And for certain of your concerns about a BTK inhibitor not effectively treating CLL and SLL, such as bioavailability and solubility, those would impact the dose that would be required to see

effective treatment; is that right?

A. It could affect the dose, but it also could be that you can't get adequate amounts that patients would tolerate.

Q. What do you mean by "that patients be would tolerate"?

A. That there would be an ability to deliver an adequate amount of compound at one time or whatever intervals are given.

Q. Compounds with low solubility and low bioavailability are still able to be effectively dosed; isn't that right?

A. Yes.

Q. And you've not identified any example of a BTKI that has -- that is not able to deliver an adequate amount at a particular time?

A. Well, all of the BTKs that have been reported and are in the clinic have enough bioavailability.

Q. In paragraph 238, you state that -- are you there?

A. I'm here.

Q. You state that a POSA would have to screen and test each of the potentially billions of BTKIs that satisfy the structural limitations and were found to covalently bind BTK in order to determine whether and at what dose they would be effective in treating CLL and SLL?

A. Yes, I see that.

Q. The examples of the tests that you identify are in vitro assays, pre-clinical studies in cell and animal models, and clinical studies in human populations; right?

A. Yes.

Q. And those in vitro assays, pre-clinical studies in cells and animal models, and clinical studies are standard tests that are conducted on drug candidates; right?

A. They're standard but, for each drug, they may be different.

Q. And this, the drug -- the specification identifies the pre-clinical assays and cell and animal models as well as clinical studies for ibrutinib; right?

MS. PATEL: Objection. Foundation.

A. They do mention examples. It's not extensive but examples are given.

Q. And, in fact, if we take a look at paragraph 245 --

A. I see.

Q. -- you identify a number of examples of testing that the specification reports to do to understand the -- or to evaluate the BTK function; right?

A. Yes.

Q. Okay. And so the -- you agree that the specification teaches the experiments that a POSA would need to conduct in identifying, for example, the appropriate dose of BTK to be used in the claimed methods?

MS. PATEL: Objection. Mischaracterizes the document.

A. I feel that the cellular functional assays that are listed here show activity related to BTKI inhibition. It's usually after you go into the animal and pre-clinical studies that you come up

with reasonable dosing that would be brought forward in the clinic.

Q. And part of understanding the reasonable dosing would be understanding in -- the target occupancy for BTK in this context; right?

A. Understanding the occupancy is relevant to knowing whether occupancy relates to efficacy.

Q. And at what dose you can achieve the occupancy of BTK that would be effective in inhibiting BTK activity; correct?

A. And that would be seen in the in vivo models or in humans.

Q. And those in vivo models are standard models that have been worked out for assessing these pre-clinical properties; right?

A. So for every therapeutic that's being advanced, with some mild exceptions, there are in vivo models that can be analyzed. At a minimum, toxicity can be looked at in pre-clinical in vivo models.

Q. In paragraph 245, at the end of the paragraph, you state -- or you -- yeah, you state

[As read] Although large numbers of candidates can be tested in available commercially high throughput assays ...

Do you see that?

A. I do.

Q. And so you agree that there were commercially available high throughput assays to conduct a number of these experiments?

A. There are.

Q. And your -- are you relying on Dr. Showalter's assessment that there are potentially billions of candidates in -- strike that.

Let me start over.

You conclude the sentence that there would be [As read] extensive experimentation that would be necessary to test the ... billions of candidates.

Right?

A. Right.

Q. And so the extensive experimentation relies on your understanding that there would be billions of compounds to test?

A. Correct.

Q. And that understanding that there would be billions of compounds to test comes from Dr. Showalter's analysis?

A. That's in his disclosure, yes.

Q. That's not a separate analysis that you've conducted?

A. I -- as I said earlier, I'm not a medicinal chemist. He is opining on the broad spectrum of therapeutic compounds that potentially can be developed based on the structure that we talked about earlier.

Q. And so your -- your opinion that there would be extensive experimentation required is -- relies on that numerical determination that there's billions of compounds to test?

MS. PATEL: Objection. Mischaracterizes the document.

A. There's a vast array of compounds that could be developed. He used the expression billions and I'll let him defend that and I'll accept that because he's the expert. But whether it was a

billion or a hundred million, the experimentation is substantial in order to find compounds.

Q. In paragraph -- so if we turn to the next paragraph 246.

A. I have it.

Q. You start the paragraph discussing that [As read] a POSA would need to perform selectivity screening in order to assess ... off-target binding.

Is that right?

A. Yes.

Q. And that selectivity is important for off-target effects or harmful side effects?

A. Correct.

Q. So selectivity testing relates to your analysis as to whether or not a BTK inhibitor could be a safe treatment for a CLL?

A. Yes.

Q. But selectivity does not -- strike that.

Selectivity does not relate to whether a BTK could be an effective treatment -- or, I'm sorry -- a BTKI could be an effective treatment for CLL and SLL.

A. I would say in general, that's the case. But theoretically, there's the possibility you're affecting a separate protein within the CLL cell that changes the dynamics of what happens when you inhibit BTKI or BTK, I should say.

Q. And that's a theoretical concern that you've not cited any examples of that actually happening?

A. Well, this goes back to the fact that only a few compounds that we can discuss because they're in the clinic, and we don't know the negative results that may be seen.

Q. So you haven't identified or cited any example of this theoretical concern of yours?

A. Correct.

Q. So the second half of 246, you state that [As read] in vitro testing would not be enough to establish whether any given BTKI satisfies -- that satisfies the structural limitations could effectively and safely treat CLL or SLL.

That a POSA would not have been able to predict the pharmacological properties in animals based on the pharmacological properties in cell

models; is that right?

A. Correct.

Q. Okay. And so you would have to conduct animal testing to determine the dose a BTKI could effectively treat CLL and SLL?

A. Yes.

Q. And those animal testing models are well known in the field?

A. The animal model testing for -- if we're specifically talking about BTK inhibitors, so there are models that are used by the different companies. And they've standardized those.

Q. And they're known -- those models are known in the field beyond just proprietary to individual companies; correct?

A. That is correct.

Q. And you conclude that the [As read] animal testing of potentially billions of candidates would be extensive.

A. Yes.

Q. And that's -- the number of candidates informs your opinion as to whether or not the animal

testing would be extensive?

A. Yes.

Q. And so that understanding that there are billions of candidates comes from Dr. Showalter's analysis.

A. The number comes from Dr. Showalter, yes.

Q. And then similarly in paragraph 247, you discuss testing in cell and animal models for PK and PD and toxicology of a drug candidate.

A. Yes.

Q. And you conclude that the amount of experimentation to perform the pre-clinical tests that you describe in this paragraph would be extensive; is that right?

A. Yes.

Q. And that that would be undue experimentation?

A. Yes.

Q. And your conclusion that the pre-clinical studies are undue experimentation relies on the -- your understanding that there would be billions of candidates that would need to be tested?

A. That would rely on the numbers provided by Dr. Showalter, correct.

Q. In paragraph 248, you outline the experimentation that you, in your opinion, would need to be conducted in clinical tests?

A. Yes.

Q. And you identify that these clinical tests take years to conduct?

A. Yes.

Q. And that the -- but the parameters and design of clinical studies are standard within -- to assess the efficacy of BTKI would be understood by the field?

A. Yes.

Q. And you state that the clinical studies of potentially billions of candidates constitute undue experimentation?

A. Well, ultimately, the candidates that make their way to the clinic because there's an enormous amount of experimentation first. Presumably, those would have all gone through the pre-clinical testing and appeared safe and efficacious in animal models.

Q. I'm not sure that answered my question. Let me ask it again.

So in your paragraph 248, you state at the sentence spanning pages 104 to 105 that [As read] These clinical studies of the potentially billions of candidates would constitute undue experimentation.

Do you see that?

A. Yes, I do.

Q. And so your conclusion that this would be undue experimentation is based on the -- your understanding that billions of candidates would need to be tested in the clinic?

A. That's not how I interpret the sentence, if it misleads you. I think of it as a funnel. It would be say a billion candidates that could be produced --

Q. Uh-huh.

A. -- it would be an enormous amount of work to screen them both in vitro and in the pre-clinical models and in toxicology. By the time you got to human beings, it wouldn't be putting a billion

different compounds into human beings. That's obviously not realistic or wouldn't be allowed. But the initial experimentation to get to the point of what would go into a human being involves billions of compounds.

Q. In the paragraph starting at page 2 -- I'm sorry. In the paragraphs starting at paragraph 250 and going to 254, you describe your opinion about the quantity of experimentation related to lymphocytosis?

A. Yes.

Q. Okay. And it's your opinion that the quantity of experimentation would have been extensive?

A. It's the same issues related to efficacy.

Q. In paragraph 251, you recite your understanding of Dr. Showalter's opinion regarding the number of compounds that fall within the structural limitations and meet certain of the functional limitations?

A. Yes.

Q. You don't have, again, a separate opinion

from Dr. Showalter? You rely on his analysis for the statements that you lay out in paragraph 251?

A. I do.

Q. In paragraph 253, you provide your opinion that [As read] a POSA would not have known which of the potentially billions of species would result in lymphocytosis ... without extensive experimentation.

A. Yes.

Q. And the only citation you give in paragraph 253 is to the patent specification?

A. Yes.

Q. So you agree that the patent specification instructs how to identify lymphocytosis from the administration of a BTKI?

A. A lymphocytosis, whether it's from a BTKI or another therapeutic, is understood clinically.

Q. So how to identify lymphocytosis is -- would have been a standard assessment that a person of ordinary skill in the art would have understood?

A. How to identify it?

Q. Uh-huh.

A. Yes.

Q. And you -- and the test to identify a lymphocytosis in a patient population is a standard test?

A. Yes, a simple blood test.

Q. It's a simple test.

You conclude that testing each of the potentially billions of species would require extensive experimentation?

A. It's the same issues as we discussed before. A large funnel that the initial analysis, in vitro testing, and pre-clinical testing ultimately leads to a narrower group of molecules that would be brought forward into the clinic. But that initial testing is theoretically overwhelming. And this is based on Dr. Showalter's declaration.

Q. So the conclusion that the testing is extensive is based on the -- your understanding that there would be a large number of species that would need to be tested?

A. That could be generated, yes.

Q. Okay. In the next section, you describe the direction and guidance presented in the working

examples from the specification?

A. Correct.

Q. Okay. And you agree that the -- in paragraph 256, you state that there's no indication in the specification that any BTKIs, other than Imbruvica, could be safe and effective to treat CLL and SLL?

A. Correct.

Q. Do you understand that the specification identifies that ibrutinib's occupancy of BTK correlates to its AUC?

A. Can you repeat that?

Q. Sure. Are you aware that the specification identifies and explains that ibrutinib's occupancy of BTK correlates to its AUC?

MS. PATEL: Objection. Foundation.

A. It would make sense.

Q. And that the dose that achieves that occupancy was, therefore, identified as being a therapeutically effective for treating CLL?

MS. PATEL: Same objection.

A. That's my understanding.

Q. And so BTK occupancy is a measure of what makes a particular dose of ibrutinib effective?

MS. PATEL: Objection. Mischaracterizes the testimony.

A. I stated earlier it can.

Q. In paragraph 261, this section starts your opinion that -- or analysis of the direction and guidance and working examples related to lymphocytosis?

A. Yes.

Q. And you agree that the specification discloses that, at a sufficient dose of the claimed BTKIs, there would be lymphocytosis?

A. Yes, lymphocytosis was seen with all of the BTKIs in the clinic.

Q. And, in fact, in paragraph 262, you state that the specification discloses that, at sufficient doses, patients will exhibit lymphocytosis when administered a BTKI; right?

A. Yes.

Q. In paragraph 263, you lay out your opinion that there's no guidance as to whether or not a

particular BTKI would cause lymphocytosis; is that right?

A. Yes. I think we've talked about this on a number of occasions, yes.

Q. And there's no citations to any references or other portions of your report or declaration in this paragraph; right?

A. Right.

Q. Your -- the last sentence of your paragraph here on 263 says, [As read] A POSA reading the specification would understand that not all BTKIs that satisfy these other limitations at a certain dose would also result in lymphocytosis at that same dose.

Right?

A. Right.

Q. And you have not identified any example of a BTKI that satisfies the other limitations at a particular dose that doesn't result in lymphocytosis at that dose; right?

A. It's the same issue we've talked about before with a limited number of compounds in the

clinic and negative results not being published.

Q. So this is a theoretical concern of yours that a BTKI could inhibit BTK and treat CLL but not induce lymphocytosis?

MS. PATEL: Objection. Mischaracterizes the testimony.

A. I think the BTKIs that have been in the clinic to date have all had lymphocytosis.

Q. So there's no evidence from clinical experience that indicates that a BTKI that inhibits BTK and treats CLL will not induce lymphocytosis?

A. We would only know if the compound was given to patients.

Q. And none of those examples have been reported; right?

A. Not to date. But we know that individuals have not had a lymphocytosis with treatment. So we know it's more complex than what's on the surface.

Q. The next section, you lay out your analysis of the unpredictability of the art, the nature of the invention, the state of the prior art, and the relative skill of those in the art; right?

A. Correct.

Q. And you agree that, in this instance, the state of the art -- I'm sorry -- the relative skill of a person of ordinary skill in the art is very high?

A. The POSA --

Q. Yes.

A. -- you're referring to? Yes.

Q. And you agree that, as of 2010, the state of the art -- and turning your attention to 268.

A. Yes, I see.

Q. -- that BTKI had been identified as a target for drugs for the treatment of BTKI expressing malignancies like CLL and SLL?

A. Yes.

Q. And paragraph 267, you state that, [As read] The chemical structure of a BTKI affects its pharmacological properties and thus whether and at what dose the BTKI would be effective and safe?

A. Yes.

Q. But you, as we've discussed, you are not a chemist to identify how a chemical structure could

be predicted to affect the pharmacological properties?

A. Correct.

Q. And in 268, you state that there was a general awareness of inhibiting BTK?

A. Yes.

Q. And that BTK was known to have apoptotic function? Was that known in the art?

A. The BTK was anti-apoptotic function.

Q. Right. So inhibiting BTK would have apoptotic function?

A. Yes.

Q. And that was known in 2010 and 2011?

A. Yes.

Q. And you agree that irreversible BTK inhibitors were known as of 2010 and 2011?

A. Yes.

THE WITNESS: Would we be able to take another break now?

MS. DANEK: Oh, sure.

THE WITNESS: I think we went another hour.

MS. DANEK: Sure.

THE WITNESS: I believe we went another hour.

REMOTE TECHNICIAN: Off the record 1646.

(A short break was had.)

REMOTE TECHNICIAN: Back on the record. The time is 1656.

BY MS. DANEK:

Q. So, Dr. Showalter, we were discussing your opinions on enablement and, in particular, your section between -- paragraph 265 -- starting at paragraph 265. And I want to continue talking about paragraph 268.

A. I believe you said Dr. Showalter.

Q. I did. I didn't mean to. We've been saying his name a lot.

A. Okay. Okay. I just wanted to make sure you realized that.

Q. So, Dr. Rosen.

A. Yeah. That's all right.

Q. So I want to continue discussing paragraph 268.

A. Yes.

Q. In the second to last sentence, you state that the relationship between a BTKI's structure, ability to inhibit BTK, efficacy, and safety have yet to be characterized as of June 2010/2011; right?

A. And that, again, would be a Dr. Showalter consideration.

Q. So you do not have an opinion or an analysis about what a person of ordinary skill in the art would have understood about a BTKI structure and its ability to inhibit BTK, efficacy, and safety?

A. Not independent of Dr. Showalter.

Q. Okay. In paragraph 269, you state that, [As read] Drug developers were concerned about the negative consequences of employing covalent inhibition, including increased toxicity resulting from off-target binding?

A. Yes.

Q. And so this analysis of the state of the art in paragraph 267, does this relate to your analysis concerning whether or not a particular BTK inhibitor would be a safe treatment?

A. So the -- in terms of the clinical

consequences, yes. In terms of off-target effects, even though that is something that I would also be involved in functionally testing, that would be something that a medicinal chemist would take into account in thinking of these compounds.

Q. But those still all relate to the -- ultimately the safety properties of the BTKI as opposed to the efficacy properties?

A. Can we go back to the sentences? I just want to make sure I don't misstate anything.

Q. So we're at the first sentence of paragraph 269.

A. So almost certainly it would be the toxicities, but I can't say definitively that an off-target effect within the CLL cell itself wouldn't affect the ability of the BTKI inhibitor to effectively kill the cell or to cause the lymphocytosis.

Q. Right. And you've not identified any mechanistic studies or examples of a pathway that would interact with and interfere with a BTKI's ability -- that inhibits BTK its ability to

effectively treat CLL; right?

A. Correct.

Q. In 269, you have two additional sentences after the first sentence we just read. And they both summarize your understanding of Dr. Showalter's analysis?

A. Yes.

Q. And these are not independent opinions or analyses that you've conducted. They are entirely Dr. Showalter's opinions?

A. Correct.

Q. If we turn to paragraph 274, let me know when you're there.

A. I'm here.

Q. And here you describe the unpredictability of the art, the state of the prior art, and the relative skill of those in the art as it relates to lymphocytosis?

A. Yes.

Q. Okay. And there are three paragraphs here?

A. Yes.

Q. Okay. And there's, the only citation in

these paragraphs 274 to 276, is to your earlier -- your earlier section 4-D-3?

A. Yes. Let me just see what was said in 4-D-3. Do you happen to have the --

Q. Yeah, 99, paragraph 99.

A. Yes.

Q. So the only support for your opinion that the -- that whether or not a BTKI would satisfy the lymphocytosis limitation is unpredictable is included in your paragraphs 99 and 100?

A. Yes.

Q. In your next section, starting at paragraph 277, you detail your assessment of enablement for the dependent claims?

A. Yes.

Q. And this spans paragraphs 277 to 292?

A. Yes.

Q. Okay. And for Claim 2, you include in paragraph 278 that your understanding from Dr. Showalter that the number of species that fall within Claim 2 are not reduced as compared to Claim 1; is that right?

A. Can you show me the sentence? I'll look at it.

Q. Sure.

In paragraph 278.

A. Oh, I see. [As read] This limitation therefore does not reduce the quantity of experimentation that would be required.

Yes.

Q. Right.

And your conclusion that the -- that Claim 2 does not reduce the quantity of experimentation required is based on Dr. Showalter's analysis about the number of species that fall within Claim 2 as compared to Claim 1?

A. Yes.

Q. Okay. And so it is in relying on that analysis of the number of species within Claim 2, you conclude that Claim 2 is not enabled for the same reason as Claim 1 is not enabled; right?

A. Yes.

Q. You don't offer an independent opinion as to whether or not Claim 2 is enabled separate from

whether Claims 1 or 8 are enabled; right?

A. Correct.

Q. And in the next paragraphs, you discuss Claims 3 to 7?

A. Yes.

Q. And similarly, you rely on Dr. Showalter's analysis that the limitations in Claims 3 to 7 "do not reduce the number of species that satisfy the ... structural limitations."

Do you see that in paragraph 282?

A. I do.

Q. And based on that understanding of the number of species that fall within Claims 3 to 7, you conclude that these limitations don't reduce the quantity of experimentation required; is that right?

A. Correct.

Q. And on that basis, you conclude that the claim -- Claims 3 to 7 are not enabled for the same reasons that Claim 1 are not enabled; right?

A. Correct.

Q. And you do not conduct a separate analysis that Claims 3 to 7 are not enabled different from

why you've concluded that Claim 1 is not enabled.

A. Correct.

Q. Claim 12, you discuss starting at paragraph 285?

A. Yes.

Q. And you recite your understanding from Dr. Showalter's declaration that the number of species failing within Claim 12 are not appreciably reduced?

A. That's what he said.

Q. And based on that understanding of the number of species that fall within Claim 12, you conclude that there would be undue experimentation required to practice the scope of Claim 12?

A. Yes.

Q. Okay. And you state that Claim 12 was not enabled then for the same reasons that Claim 1 is not enabled?

A. Correct.

Q. So you do not conduct an independent analysis for why Claim 12 was not enabled separate from why Claim 1 is not enabled, in your opinion.

A. There -- all of these claims related to Dr. Showalter's declaration about the volume of species that would need to be considered.

Q. And so your analysis for why Claims 12 was not enabled is identical to your analysis of why Claim 1 is not enabled.

A. Yes.

Q. And then finally for Claim 20, you identify from your understanding from Dr. Showalter's declaration that Claim 20's limitations do not appreciably reduce the number of species that satisfy the structural limitations?

A. Correct.

Q. And based on that understanding of the number of species that fall within Claim 20, you conclude that there would be undue experimentation to practice the scope of Claim 20?

A. Correct.

Q. And you state that it's your opinion that Claim 20 is not enabled for the same reason as Claim 8?

A. Correct.

Q. So you do not conduct a separate analysis whether Claim 20 is enabled different from Claim 8.

A. Correct.

MS. DANEK: If we can take a break, I actually think this went a lot faster than I thought it would. If we could take maybe, like, a 15 or 20-minute break, we probably would be able to wrap up and get you -- apologies if you moved your call and it's irrevocable, but I think we might be able to wrap up shortly.

THE WITNESS: Okay. Do you need a break? I don't need a break.

MS. DANEK: Yeah. Let's take a 20-minute break, and then I think I can identify any loose ends that I need to follow up on and be efficient with your time.

THE WITNESS: Okay. I'll just wait. Whenever you come back, I'll just be sitting here. I've gone to the bathroom. I don't need to eat so ...

REMOTE TECHNICIAN: Off the record 1709.

(A short break was had.)

REMOTE TECHNICIAN: Back on the record 1724.

BY MS. DANEK:

Q. Dr. Rosen, could you turn to paragraph 66 in your declaration? It's at page 25 of the declaration or 31 of the document.

A. Yes.

Q. And in this paragraph, you report -- it's at the bottom of the paragraph spanning to the next page. You report IC50 values for six compounds.

Do you see that?

A. Yes.

Q. And the six compounds that you report IC50 values, you understand are compounds that fall within the structural feature -- or the structural limitations of the claims?

A. That's my understanding.

Q. Okay. And that understanding came from Dr. Showalter; right?

A. Correct.

Q. And the six compounds that you report -- well, one of them is ibrutinib; right?

A. Yes.

Q. And the other five compounds are -- have a different structure than ibrutinib; right?

A. He referred to them as isomers.

Q. The compounds that are listed in your paragraph 66, is it your understanding that these are isomers of ibrutinib?

A. I don't see it in my statement so I don't recall these are the exact ones he used as isomer. I'll just refer to these as six that were in the document.

Q. Okay. And the -- these structures that you report in paragraph 66, you report IC50 values for them; right?

A. These were taken from Dr. Showalter.

Q. So all of your analysis on these compounds you got from Dr. Showalter? You don't have --

A. I wouldn't have an independent opinion of Dr. Showalter related to these compounds.

Q. Including their IC50 values, their measured IC50 values?

A. I would rely on Dr. Showalter for this commentary.

Q. Okay. And in addition, these -- you then don't have any opinion as to whether or not these compounds would be effective treatments for CLL --

MS. PATEL: Objection.

Q. -- and SLL?

MS. PATEL: Objection. Form. Mischaracterizes the document.

A. So as I said earlier, that even the most subtle modification would need to go through complete testing, including exposure to humans to know whether or not it's an effective therapy with adequate safety.

Q. And you're not -- so these aren't examples of compounds that have -- that do not have efficacy in the treatment of CLL and SLL; right? They're just unknown what their efficacy in treating CLL and SLL are?

A. If these compounds haven't been put into human beings, that's the case.

Q. And you're -- you're not aware of any evidence that any of these compounds have failed to treat CLL or SLL in patients; right?

A. I'm not aware that any of these compounds have been given to patients, outside of Imbruvica.

Q. And so you're -- these compounds aren't examples of how the structure of a BTK inhibitor can unpredictably impact whether or not it will safely and effectively treat CLL or SLL; right?

MS. PATEL: Objection. Form.

A. I can only say that I see the structures and the IC50, but there's no information to tell me whether or not they would be effective in individuals and whether they would cause a lymphocytosis or any other changes.

Q. And, in fact, the information we do have about these compounds is their IC50 values; right?

A. Correct.

Q. And the IC50 values that are reported for these compounds range from 1.5 nanomolar to nearly 30 nanomolar?

A. Yes.

Q. And you're not offering any opinion that those IC50 values would -- would not be expected to treat CLL or SLL in a patient; right?

A. Correct.

Q. And you're not offering any opinion that an IC50 value of -- between 1.5 nanomolar and 30 nanomolar is -- would be expected to not be effective to treat CLL or SLL in a patient; right?

A. Correct.

Q. From your perspective, a person of ordinary skill in the art would have no understanding of whether or not these compounds would be able to effectively treat CLL or SLL in the absence of a clinical study?

MS. PATEL: Objection. Form. Mischaracterizes statement.

A. It would require pre-clinical and then clinical studies.

Q. You would need all of those studies, the pre-clinical and clinical studies to understand whether or not a person of ordinary skill in the art would understand if these -- any of these compounds would effectively treat CLL or SLL?

A. Yes.

MS. DANEK: I don't have any further

questions. I really thank you for your time today. I know it was an early morning for you and a long day so I appreciate it.

THE WITNESS: Thank you. And thank you for your kind consideration of all the breaks. I appreciate that.

MS. PATEL: Why don't we take just -- just give me one or two minutes and I can see if we can wrap for the day or not.

MS. DANEK: Sounds good.

REMOTE TECHNICIAN: Off the record, 1731.

(A short break was had.)

REMOTE TECHNICIAN: Back on the record. The time is 1732.

MS. PATEL: So we have no redirect so we can wrap the deposition.

THE WITNESS: Okay.

Thank you both for being so considerate.

MS. DANEK: Great. Thank you very much.

(Off the record at 5:33 p.m.)

CERTIFICATE OF COURT REPORTER - NOTARY PUBLIC

I, TIFFANY M. PIETRZYK, Certified Shorthand Reporter No. 084-004371, CSR, RPR, CRR, and a Notary Public within and for the State of Illinois, do hereby certify:

That STEVEN ROSEN, M.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, BeiGene USA, Inc. and BeiGene, LTD., was represented by counsel at the deposition.

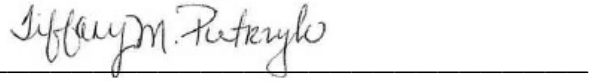
I further certify that the deposition of STEVEN ROSEN, M.D. occurred virtually, via Zoom videoconference, on Monday June 17, 2024, commencing at 10:02 a.m. CST to 5:33 a.m. CST.

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 to 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 and affixed my notarial seal this 19th day of June, 2024.

My commission expires: February 28th, 2024



NOTARY PUBLIC IN AND FOR THE
STATE OF ILLINOIS

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