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UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

- - - - - x
BEIGENE USA, INC., AND :
BEIGENE, LTD., :
Petitioner, : Case No. PGR2024-00009
v. : U.S. Patent No.
PHARMACYCLICS LLC, : 11,672,803
Patent Owner. :
- - - - - X

Deposition of HOLLIS SHOWALTER, Ph.D.
Conducted Virtually
Friday, November 8, 2024
9:04 a.m. EST

Job No.: 558921
Pages 1 - 71
Reported by: Debra A. Whitehead

1 Deposition of HOLLIS SHOWALTER, Ph.D., conducted
2 virtually.

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4
5 Pursuant to notice, before Debra Ann Whitehead,
6 E-Notary Public in and for the Commonwealth of
7 Virginia.

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C O N T E N T S

EXAMINATION OF HOLLIS SHOWALTER, Ph.D.	PAGE
By Mr. Frazier	7

EXHIBITS MARKED IN TODAY'S SESSION
(None Marked)

EXHIBITS MARKED IN PRIOR SESSIONS
(Not attached)

BEIGENE EXHIBIT	PAGE
Exhibit 1001 U.S. Patent No. 11,672,803	43
Exhibit 1003 Declaration of Hollis Showalter, Ph.D.	31
Exhibit 1105 Reply Declaration of Dr. Hollis Showalter, Ph.D.	9
Exhibit 1133 Article, Rule of Five Violations Among the FDA-Approved Small Molecule Protein Kinase Inhibitors, by Roskoski	50

EXHIBITS MARKED IN PRIOR SESSIONS - CONTINUED

(Not Attached)

PHARMACYCLICS EXHIBIT	PAGE
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Exhibit 2063	Article, Discovery and	22
	Evaluation of	
	Pyrazolo[3,4-d]pyridazinone as a	
	Potent and Orally Active	
	Irreversible BTK Inhibitor, by	
	Zhang, et al.	

1 P R O C E E D I N G S
2 HOLLIS SHOWALTER, Ph.D.,
3 having been duly sworn, testified as follows:
4 EXAMINATION BY COUNSEL FOR PATENT OWNER
5 BY MR. FRAZIER:
6 Q Good morning, Dr. Showalter.
7 A Good morning, Dr. Frazier.
8 Q You can hear me all right?
9 A I can hear you fine.
10 Q Excellent. Excellent. I know you've
11 been deposed before, including in this case. I'll
12 just go back over a few ground rules to help
13 things move smoothly.
14 First, I'd ask that you try not to speak
15 at the same time I do. I'll try to ask a clear
16 question and stop and give you a chance to answer,
17 and I'd ask that then you not speak over me.
18 Can you do that?
19 A Yes, sir.
20 Q Excellent. And I assume this morning
21 you're not on any medication or have any condition
22 that would keep you from providing full and

1 truthful testimony.

2 Is that correct?

3 A That's correct.

4 Q And again, breaks, I'm always happy to
5 accommodate. I would ask that we complete any
6 pending question before taking a break. But just
7 let me know if you need a break. All right?

8 A Okay.

9 Q Great. To prepare for your deposition
10 today, did you look at anything that was not cited
11 in your reply declaration?

12 A I have not.

13 Q And do you have a copy of your reply
14 declaration in front of you?

15 A I can pull it up real quickly here. It's
16 in front of me.

17 Q And this is Exhibit 1105?

18 A Exhibit 1105, that's correct.

19 Q All right. And maybe if we could go
20 ahead and put that on the screen and we'll make
21 sure we're all looking at the same thing.

22 MR. FRAZIER: So Exhibit 1105, please.

1 (BeiGene Exhibit 1105, previously marked,
2 not attached.)

3 Q So, Dr. Showalter, we have now Exhibit
4 1105 on the screen, which is titled Reply
5 Declaration of Dr. Hollis Showalter, Ph.D. And
6 this is your reply declaration in this case.

7 Correct?

8 A That's correct.

9 Q All right. And since this declaration
10 was signed and submitted, have you identified any
11 errors in it?

12 A I have not. I don't -- I haven't
13 discerned any obvious errors. I think it's a
14 clean document.

15 Q And if you could turn then to Paragraph 2
16 in the declaration. It's on -- I don't seem to
17 have numbered pages, so I guess it's just
18 Paragraph 2 in the declaration.

19 A Okay, I'm there.

20 Q All right. And you provide there a
21 summary of your opinions.

22 Is that correct?

1 A I see a summary of my opinions relative
2 to some of the opinions of Dr. Scott and Eck, Dr.
3 Scott and Eck.

4 Q And in particular I want to focus you on
5 the third line where it says, "I disagree with
6 Dr. Scott and Dr. Eck to the extent that their
7 definition of the POSA team requires a modeler."

8 Do you see that?

9 A I see that.

10 Q All right. And so is it your
11 understanding then or your view that a POSA would
12 not take into account the modeling of binding
13 interactions?

14 A So a POSA would take into account the use
15 of modeling. But the issue is at what stage of a
16 project you would engage a modeler.

17 Q We're talking specifically you said that
18 you disagree with Dr. Scott and Dr. Eck to the
19 extent of their definition of the POSA team
20 requires a modeler.

21 So you would agree that the POSA team
22 would include someone with experience in modeling

1 structure -- chemical structure relationships.

2 Correct?

3 A Not at the outset --

4 MS. PATEL: Objection. Form.

5 Dr. Showalter, if you could just pause
6 before starting to answer the question a second so
7 I can put an objection, please.

8 Objection. Form.

9 A So not at the outset. I disagree that a
10 modeler would be required at the outset of a
11 project.

12 Q But is it your understanding that we're
13 using a single definition of a person of ordinary
14 skill in the art in this case?

15 A That's my understanding.

16 Q Right. And so that person of ordinary
17 skill in the art definition does require a
18 modeler. Right?

19 MS. PATEL: Objection. Form.

20 A That person would not, per se, require a
21 modeler at the outset of the project.

22 Q All right. If you're making a

1 distinction, are you then agreeing that it would
2 require the input of a modeler later in the
3 project?

4 A I agree that could -- it could engage a
5 modeler at a later stage of the project, but not
6 at the outset of a project.

7 Q All right. And the distinction that
8 you're making at the outset of the project versus
9 later in the project is because you feel that at
10 the outset of the project it's a screening
11 process?

12 Is that what you're saying?

13 MS. PATEL: Objection. Foundation.

14 A So I'm not making the assumption that it
15 is a screening process that we're talking about.

16 Normally one would not be screening using
17 modeling. One would be screening using wet
18 experimental techniques. You take a library of
19 compounds and -- that a company would have in
20 their possession, and you would want to be
21 screening that library of compounds. It wouldn't
22 make any sense to engage a modeler at that point.

1 Q All right. With respect to the exercise
2 here, you understand that the question concerns
3 the description and enablement under the patent
4 law of Claim 1 of the '803 patent. Correct?

5 A I agree with that.

6 Q Right. And so you agree that the
7 starting point for that analysis would include the
8 entire disclosure of the '803 patent?

9 A Would you -- would you repeat your
10 question?

11 Q Right. In analyzing that question of
12 whether there's sufficient written description
13 and/or enablement of Claim 1 under the patent law,
14 do you agree that the starting point would take
15 into account the entire disclosure of the '803
16 patent?

17 MS. PATEL: Objection. Foundation.

18 A So I'm not sure I understand your
19 question. Maybe you could paraphrase it, state it
20 in a different way?

21 Q You agree that the starting point for the
22 analysis that you're conducting is the disclosure

1 of the '803 patent?

2 A Yes, I think -- I think I agree with
3 that.

4 Q And it would also include the
5 understanding of a person of ordinary skill in the
6 art, the relevant knowledge of the field. Right?

7 A That would be one of the aspects that
8 would be relevant to this, yes.

9 Q Right. And the person of skill in the
10 art, for purposes of the written description and
11 enablement analysis of Claim 1, would take into
12 account the fixed structural parameters of Claim
13 1.

14 Is that correct?

15 A Did you say the fixed parameters?

16 Q Yes.

17 A So the -- a POSA would be aware that
18 Claim 1 includes two fixed parameters, the back
19 pocket substituent and the linker-warhead
20 substituent. So a POSA would be aware of those
21 two fixed parameters.

22 Q Right. Okay. And so then the only

1 question would be one of what is the -- what is
2 the ring system in the middle of the structure of
3 Claim 1. Correct?

4 MS. PATEL: Objection. Form.
5 Foundation.

6 A So Z prime would be a variable of that
7 claim.

8 Q Right. And Z prime is a substituted
9 fused heterocyclic ring system comprising from 2
10 to 4 nitrogen heteroatoms. Correct?

11 A That's what the claim says.

12 Q And so when you talk about the outset of
13 a project, a POSA at the outset of the project
14 would essentially be looking for compounds that
15 would fit the structure in Claim 1. Correct?

16 A A POSA would be looking to visualize
17 potential structures that would conform to the
18 definition of Z prime.

19 Q And it's your view, then, if I'm
20 understanding your opinion correctly, that such a
21 POSA, faced with that question of which cores to
22 put into the Z prime in Claim 1, would not invoke

1 available modeling information that was known in
2 the art.

3 Is that correct?

4 A That's correct, I think. First of all,
5 there's -- within the specification there is no
6 discussion of modeling, absolutely none. And even
7 if one wanted to invoke using modeling for
8 screening, modeling would be useful for screening
9 as sort of a first-pass evaluation to determine
10 which compounds might have potential to be
11 inhibitors of BTK, and then lead to the functional
12 limitation of also covalently binding to cysteine
13 481.

14 But even with modeling, even with
15 modeling, if you assume that one would carry it
16 out at an early stage, you're going to still be
17 left with a population of potentially millions,
18 billions of compounds.

19 And ultimately the compounds that would
20 meet your requirements for modeling, whatever the
21 modeling score or post might be that renders a
22 compound as one that would be a potential

1 inhibitor, eventually those compounds from a
2 virtual screen would have to be synthesized and
3 then tested within various in vitro assays,
4 including the kinase assay.

5 So modeling could have -- could have a
6 place here. But again, it doesn't -- it doesn't
7 substantially reduce the number of compounds that
8 meet the structural limitations.

9 Q All right. With respect to your analysis
10 of enablement and whether undue experimentation
11 would be required, you're not offering any
12 opinions with respect to what percent of the
13 compounds within the structural genus, the
14 structural features I believe you called them in
15 your report, would actually have the functional
16 characteristics of the claim.

17 Is that correct?

18 A I am not offering any --

19 MS. PATEL: Objection. Objection. Form.
20 Foundation.

21 A So I'm not offering any -- any numbers
22 regarding the number -- the percentages of

1 compounds that would meet both the structural and
2 functional limitations.

3 Q And so then the basis for your statement
4 that a person of skill would have to screen
5 millions of compounds is because in your view the
6 claim covers millions of compounds, and for
7 purposes of enablement you would need to add up
8 the time it takes to test all of those millions of
9 compounds.

10 Is that correct?

11 MS. PATEL: Objection. Foundation.

12 A So one would have to take into account
13 that testing compounds that have potential to be
14 active inhibitors of BTK, one would have to take
15 into account that that could involve extensive,
16 very extensive, experimentation.

17 Q Well, let's just go back to the starting
18 point.

19 You said that a person of ordinary skill
20 would need to test potentially millions of
21 compounds in connection with determining whether
22 Claim 1 is enabled.

1 Is that your view?

2 A That's my view.

3 Q All right. And that's not based on a
4 determination of the percentage of compounds
5 having the structural features that would also
6 have the functional features; that's because of
7 your view that the claim is broad enough to
8 encompass millions of compounds from a structural
9 standing. Right?

10 MS. PATEL: Objection. Form.

11 A Millions or billions. It could be more
12 than -- more than millions.

13 Q Right. So the reason that you're saying
14 that a person of skill would need to test millions
15 of compounds is because for your enablement
16 analysis, you are adding up the time it would take
17 to test all of the compounds in the genus.

18 Correct?

19 MS. PATEL: Objection. Form.
20 Foundation.

21 A So I just said earlier that you could use
22 modeling to -- to weed out compounds that you

1 think would not meet the functional limitations.

2 Q Okay.

3 A And that would still leave millions,
4 potentially billions, of compounds left to engage
5 in extensive experimentation.

6 Q If you turn to Paragraph 9 of your
7 declaration, please.

8 A Okay, I'm here.

9 Q All right. And in Paragraph 9 you say in
10 your experience as a medicinal chemist working in
11 drug discovery, I have never -- strike that.

12 Let me read it. I'll just read what you
13 have written here and go back.

14 So you've written at the bottom of
15 Paragraph 9, "Moreover, in my experience as a
16 medicinal chemist working in drug discovery, I
17 have never consulted with a modeler to screen a
18 library of compounds to assess which among them
19 binds the target kinase."

20 Do you see that?

21 A I see that.

22 Q And that's based on your personal

1 experience?

2 A That's based on my personal experience.

3 Q You agree that certainly by 2010, 2011
4 people were using in silico screening because of
5 lower costs and advancing computer power.

6 Correct?

7 MS. PATEL: Objection. Form.

8 A I don't know that for a fact, so I don't
9 want to opine on that. That would be a question
10 you could ask Dr. Veal in his deposition, which is
11 upcoming.

12 Q Okay. You agree that the use of modeling
13 in determining structure function relationships
14 for kinases and BTK kinase in particular was
15 reflected in the scientific literature in the
16 2010, 2011 time frame. Right?

17 MS. PATEL: Objection. Form.

18 A I agree that there were disclosures,
19 papers, in which modeling was -- was utilized,
20 particularly I'm thinking of the Marcotte paper.

21 But later, speaking post 2010, 2011, of
22 course there were disclosures in both the patent

1 literature and in the journal literature of
2 compounds that were modeled and deemed to be
3 predicted to be active inhibitors of BTK that once
4 they were tested they were totally inactive.

5 Q And can you point me specifically to what
6 you're referring to there?

7 A So I can point you to the -- to the Zhang
8 article of 2020, in ACS Med Chem letters, which is
9 what we discussed during my earlier deposition.
10 Zhang discusses seven compounds that were
11 synthesized, and all of them met the structural
12 limitations of the '803 patent. Two of those were
13 deemed active, the other three were not deemed
14 active.

15 Q I think maybe we can pull that up.

16 MR. FRAZIER: So we have Exhibit 2063 I
17 believe is the Zhang article. If we could pull
18 that up.

19 (Pharmacyclics Exhibit 2063, previously
20 marked, not attached.)

21 A Okay. In just a little bit here. 2063?

22 Q Yes.

1 A Okay. It's up.

2 Q And so is this Exhibit 2063 the Zhang
3 article you're referring to?

4 A This is the article.

5 Q And this was not something you cited in
6 your initial declaration. But after you completed
7 that declaration you became aware of this article.

8 Correct?

9 A That's correct.

10 Q And your point with this article is that
11 there are some compounds that are -- that meet the
12 structural limitations of Claim 1, but in your
13 view do not meet the functional limitations of
14 Claim 1.

15 Is that correct?

16 A That's my view.

17 Q All right. And you identified three such
18 compounds?

19 A Three compounds.

20 Q All right. And which three are you
21 referring to?

22 A I'm referring to Compounds 7, 10, and 11.

1 Q All right. And you're focused on the
2 data in Figure 3 and Table 1.

3 Is that correct?

4 A I'm focused on the Figure 3 would have
5 compound -- structures of Compound 7 and 8. And
6 Table 1 would have those same -- would have
7 structures of 8 through 11.

8 Q Right. And so you agree that Compound 8
9 and 9 do correspond to the functional
10 characteristics of Claim 1 of the '803 patent.

11 Right?

12 A Those compounds are showing excellent to
13 I would say very good potency.

14 Q And you, yourself, are not opining on the
15 modeling aspects of these compounds in terms of
16 interpreting whether the modeling data would lead
17 one to conclude that Compounds 10 and 11, for
18 example, would or would not be active with respect
19 to the functional characteristics of the claim.

20 Is that right?

21 A So any issues regarding modeling I would
22 defer to Dr. Veal.

1 Q Okay. All right. And just to sort of
2 set the groundwork. At the beginning of Exhibit
3 2063 there is a reference to saying, in the
4 left-hand column about halfway down, it says, "The
5 irreversible BTK inhibitors can achieve a strong
6 binding to the relatively unique Cys481 residue of
7 BTK enzyme and exhibit a powerful advantage."

8 Do you see that?

9 A I do see that.

10 Q And among them, ibrutinib is the most
11 successful example and has been approved by the US
12 FDA as the first-in-class irreversible BTK
13 inhibitor for the treatment of, and then it lists
14 various conditions.

15 Do you see that?

16 A I see that.

17 Q So you agree then that ibrutinib was the
18 structural starting point for the Zhang authors,
19 as discussed in this Exhibit 2063?

20 A Yeah, I think the authors were inspired
21 by ibrutinib structure.

22 Q All right. Let's turn back to your

1 declaration, if we could.

2 A Okay.

3 Q Can we turn to Paragraph 12 in your
4 declaration?

5 Do you see Paragraph 12 says, Typically,
6 however, medicinal chemists will not make not
7 only -- strike that. Let me start again.
8 Paragraph 12, "Typically, however, medicinal
9 chemists will make not only additional compounds
10 suggested by modelers, but also compounds that
11 medicinal chemists believe, based on their
12 knowledge and experience, to be worth making and
13 helpful in understanding the SAR of the target
14 kinase."

15 Do you see that?

16 A I see that.

17 Q All right. So not every compound that's
18 made in a drug development program is necessarily
19 intended for development into a final drug
20 product. It may also make some that are just
21 interesting in understanding the SAR of the target
22 kinase?

1 A My experience has always been that
2 modeling was utilized to try to optimize your --
3 the series of compounds that you were making
4 toward getting maximum potency, selectivity, some
5 of those considerations for moving a compound on.

6 Q Okay.

7 A Not very often that -- I don't recall
8 situations of making -- doing modeling to make
9 compounds that wouldn't be active.

10 Q But if I'm understanding what you've
11 written in Paragraph 12, you're saying that aside
12 from modeling, a medicinal chemist might choose to
13 make compounds that are not necessarily likely to
14 become drugs themselves, but that would be helpful
15 in understanding the SAR of the target kinase.

16 Correct?

17 A So every compound -- from my experience,
18 every compound that was synthesized within a
19 series was not first modeled. That would have
20 been a lot of work. Medicinal chemists have
21 intuition outside of modeling as to what will make
22 a compound more potent, more drug-like, et cetera.

1 So I think that's what this statement here is
2 saying. That based on knowledge and experience,
3 medicinal chemists often make suggestions that
4 are -- that lead to much more potent, much more
5 selective inhibitors of whatever target compound
6 they were -- target they were looking at, BTK or
7 EGF or others.

8 Q You do agree, however, that a modeler
9 might have been able to provide some insight into
10 which molecules are less likely to work?

11 A That -- that is one useful aspect of
12 modeling, yes.

13 Q And you agree that a POSA, based on x-ray
14 crystal structures, would be able to make some
15 guesses based on the binding patterns to the hinge
16 region, that they would be able to make some
17 guesses as to which compounds yet to be discovered
18 would bind in the same fashion in the hinge
19 region?

20 A So x-ray crystallography is sort of the
21 gold standard of structure-based design. It's a
22 picture. It's a picture of an inhibitor bound to

1 its target. The target -- the inhibitor target
2 complex is -- you know, it's not static; it's
3 breathing. Okay?

4 But the information you get from an x-ray
5 crystal structure is very useful in terms of
6 actually visualizing where certain functional --
7 certain substituents and certain functional
8 aspects of your inhibitor are engaging, engaging
9 the target.

10 Q You mention at the end of Paragraph 14 in
11 your declaration that Dr. Veal confirms that
12 modeling software in 2011 or even now cannot
13 accurately predict covalent bonding.

14 Do you see that?

15 A I see that.

16 Q Covalent binding I guess is what it says.

17 A Yes, it says covalent binding.

18 Q And again, consistent with Dr. Veal being
19 the one to defend the details of his opinions on
20 modeling, you're not providing a specific opinion
21 as to whether or not the modeling can predict
22 covalent binding?

1 Is that correct?

2 A I'm not --

3 MS. PATEL: Object to form.

4 A I'm going to again defer to Dr. Veal.
5 He's the expert in modeling.

6 Q All right. Let's turn to the next
7 section of your declaration, it's under Roman
8 Number 4, Response to Dr. Scott's Criticisms. And
9 if we could turn to Paragraph 17.

10 A Okay, I'm there.

11 Q And now in Paragraph 17 we're talking
12 about -- or you're talking about your Appendix A
13 structures. Correct?

14 A That's correct.

15 Q All right. And Appendix A is -- was
16 appended to your original report, which is Exhibit
17 1003 in this case.

18 Is that correct?

19 A That's correct.

20 Q And do you have a copy of Exhibit 1003
21 available to you?

22 A Give me a minute or two here.

1 Q Okay.

2 A Or less.

3 (BeiGene Exhibit 1003, previously marked,
4 not attached.)

5 A And you want me to go to Appendix A?

6 Q Well, I was going to ask you about
7 Paragraph 17 of your reply declaration, which is
8 Exhibit 1105, but it refers to the opening
9 declaration, so I just wanted you to have
10 available both of them.

11 So my question is specifically that you
12 indicate that the species identified in Appendix A
13 can be found in Exhibit 1097, which you say you
14 cite in your opening declaration, Exhibit 1003, at
15 Paragraph 257.

16 Do you see that in Paragraph 17 of --

17 A I see that.

18 Q And so then let's just turn, if we could,
19 to Exhibit 1003 of Paragraph 257.

20 A I made a mistake. I brought up one
21 thousand -- just a minute. I have it. I have it.
22 I have it. And where are we going with 1003?

1 Q So in 1003 let's go to Paragraph 257.

2 A 257. Okay, I'm at 257.

3 Q And so 257 you say, "As of June 2010,
4 2011, many of the irreversible kinase inhibitors
5 under development included a heterocyclic ring
6 system, but Imbruvica was the only inhibitor with
7 a heterobicyclic core that satisfied the
8 structural limitations," and you cite several
9 references there. Correct?

10 A That's correct.

11 Q All right. And then going on in
12 Paragraph 257 you say, "And while other
13 heterobicyclic structures were generally known in
14 the art, none of those structures were reported to
15 be used for scaffolds for reversible or
16 irreversible kinase inhibitors. See Exhibit
17 1097."

18 Do you see that?

19 A I see that.

20 Q So there's no reference connecting
21 Exhibit 1097 to Appendix A. Correct?

22 MS. PATEL: Objection. Form.

1 A Would you repeat that question?

2 Q Right. There's nothing that says that
3 Exhibit 1097 has anything to do with Appendix A.
4 Right?

5 MS. PATEL: Objection. Form.

6 A So it says, See Exhibit 1097. That's the
7 volume -- and let me just bring that up here real
8 quick. That's the comprehensive heterocyclic
9 chemistry. 1097. Let me bring that up.

10 Yeah, so that's the comprehensive
11 heterocyclic chemistry of volume. So there's like
12 12 volumes dealing with various heterocyclic ring
13 systems.

14 And from those volumes I drew the Z prime
15 structures which are enumerated in Exhibit A.

16 Q But you did not indicate in your Appendix
17 A that those structures have been drawn from
18 Exhibit 1097. Correct?

19 A Appendix --

20 MS. PATEL: Objection. Form.

21 A Appendix A is simply a compilation of
22 structures. There's no -- there's no discussion

1 of those structures. It's just simply shows all
2 the structures with their -- their CAS
3 nomenclature, each one with its CAS nomenclature.

4 Q So again, Appendix A does not refer in
5 any way to Exhibit 1097. Correct?

6 MS. PATEL: Objection. Form.

7 A So Exhibit 1097 is the source of the
8 structures that are enumerated in Exhibit A.

9 Q But that's not something that was
10 mentioned in your original declaration. Right?

11 MS. PATEL: Objection. Form.

12 A It's not -- it's not in Paragraph 257.

13 Q And if you want to review generally
14 Appendix A, there's no citation in Appendix A
15 indicating where all of these structures came from
16 either. Right?

17 MS. PATEL: Objection. Form.

18 A Do you want to repeat that question?

19 Q Right. Just, you said that there's no
20 citation to Appendix A in Paragraph 257.

21 And I was just also confirming that
22 there's no citation to Exhibit 1097 in Appendix A.

1 Right?

2 MS. PATEL: Objection. Form.

3 A If you go to Appendix A, there is not a
4 specific reference to Exhibit 1097.

5 Q Now, when you say in Paragraph 257 of
6 your original report that while other
7 heterobicyclic structures were generally known in
8 the art, none of those structures were reported to
9 be used for scaffolds for reversible or
10 irreversible kinase inhibitors, what was the basis
11 for your statement that they hadn't been reported
12 to be used for scaffolds for reversible or
13 irreversible kinase inhibitors?

14 A So the statement says, "And while other
15 heterobicyclic structures." So the implication
16 there is that each -- each of the cycles of the
17 bicycle would be heterocycles. None of those
18 structures were reported to be used for scaffolds
19 for reversible or irreversible inhibitors.

20 So if you take an example of an earlier
21 irreversible inhibitor for EGFR epidermal growth
22 factor receptor, these were bicyclic structures.

1 And quinacylin, the Z prime in that case would
2 have been quinacylin, which is a six six bicyclic
3 system. One of the rings is benzenoid, the other
4 one has two nitrogens.

5 Q And my question is, how did you scour the
6 literature to determine that none of the
7 heterobicyclic structures reported in Exhibit 1097
8 had been used as scaffolds for reversible or
9 irreversible kinase inhibitors?

10 MS. PATEL: Objection. Form.

11 A If you followed the literature during
12 this time period, there were relatively few papers
13 being published or patents being disclosed for
14 irreversible kinase inhibitors. So there weren't
15 that many examples of Z primes that were being
16 utilized for irreversible kinase inhibitor design.

17 Q And how about reversible kinase
18 inhibitors?

19 A So I would say for reversible kinase
20 inhibitors, I can't think off the top of my head.
21 Most of my experience was in the area of EGFR,
22 epidermal growth factor receptor inhibitors. And

1 so I guess I'm making the statement based on my
2 knowledge of inhibitors that came out of the EGFR
3 program.

4 Q So you didn't attempt to do any sort of
5 broad literature search beyond the structures that
6 you were aware of from the EGFR program?

7 MS. PATEL: Objection. Form.

8 A So, no, I did not do an exhaustive
9 search. That would have taken a lot of time, and
10 I was working on my declaration and other parts of
11 this project. So I did not invest the time to
12 actually determine all of the reversible
13 inhibitors that would have used heterobicyclic
14 structures.

15 Q All right. And if we go on to Paragraph
16 18. Now if we switch back to your reply
17 declaration, Exhibit 1105.

18 A Okay. Okay, I'm there.

19 Q All right. In Paragraph 18, toward the
20 bottom -- well, first you say that, "As I stated
21 very clearly in my opening declaration, Appendix A
22 and my related calculations considered only

1 whether the ring systems satisfied the structural
2 limitations. My analysis of breadth did not
3 consider whether those candidates also satisfied
4 the functional limitations."

5 Do you see that?

6 A I see that.

7 Q And we've already discussed that, that
8 you're not opining on what percentage of compounds
9 having the structural limitations in Claim 1 would
10 also meet the functional limitations.

11 Correct?

12 A That's correct.

13 Q And then you say, beginning then at the
14 bottom of Page 8, "Modeling capabilities would not
15 increase the predictability or replace the need
16 for experimental testing because the accuracy of
17 modeling in 2010, 2011, or even now would have
18 been limited."

19 Do you see that?

20 A I see that.

21 Q And then you cite a number of paragraphs,
22 but it's not clear what exhibit you're referring

1 to there.

2 Do you know what exhibit you're referring
3 to for the basis of that statement?

4 A So Paragraph 4. 33-34. So this may be
5 an error that I didn't catch. So I can't tell you
6 now exactly where -- what exhibit I'm looking at.
7 It could have been my original declaration.

8 Q You can go ahead and check that, if you
9 want. I think I looked, and I don't think that's
10 right. But maybe you could take a quick look and
11 determine if those citations seem to refer to your
12 original declaration.

13 A Yes, so looking certainly at Paragraph 4
14 of my original declaration. This is speaking of
15 my qualifications, so I don't think I'm referring
16 to my original declaration here.

17 For 33-34. So does this actually refer
18 to the -- to my reply declaration?

19 Q I pose the question to you. If you know
20 the answer to that, then go ahead and tell me.

21 Does -- do the paragraph citations at the
22 end of Paragraph 18 refer to paragraphs in your

1 reply declaration?

2 A So I'm scrolling through here. Which
3 paragraph were we initially talking about?

4 Q We're looking at Paragraph 18 of your
5 reply declaration.

6 A Yeah.

7 Q Has a string cite of a number of
8 paragraphs at the end of it. And my other
9 question is, is it possible that you're referring
10 to Dr. Veal's declaration there?

11 A The answer is I don't know.

12 Q But that would be consistent with your
13 deferring to Dr. Veal on questions of the
14 capabilities of modeling with respect to
15 predictability.

16 Is that correct?

17 A That's correct.

18 Q All right. Now, I guess going back to
19 the premise of this section of your reply
20 declaration, you're responding to some of
21 Dr. Scott's critiques. And if I can refer you to
22 Paragraph 20. You say, "Patent owner and

1 Dr. Scott contend that my calculations allow for
2 substitution at each and every available position
3 on Z prime," and then it goes on from there.

4 Do you see that?

5 A I see that.

6 Q And so is it your view that a POSA would
7 substitute or attempt to substitute each and every
8 available position on Z prime?

9 MS. PATEL: Objection. Form.

10 A So each and every available position on Z
11 prime? I think for any given Z prime a POSA would
12 consider substituting on any open position,
13 whether there were two, three, or as many as 13 I
14 think in cases of the nonaromatic, nonaromatic
15 bicyclic structures which I enumerate in Appendix
16 A.

17 So each and every available position on Z
18 prime, a POSA would consider substituting on, yes,
19 any one of those positions.

20 Q So your view is that a POSA would, in
21 fact, consider substituting at each and every
22 available position on Z prime?

1 MS. PATEL: Objection. Form.

2 A I think a POSA would -- would consider
3 based -- based on a Z prime, substitution at any
4 given open position.

5 Q You agree, then, though, that that
6 decision of whether to do further substitution
7 would be informed by modeling. Correct?

8 MS. PATEL: Objection. Form.

9 A Modeling would be one -- certainly one
10 tool that one could utilize to assess which open
11 sites are substitutable.

12 Q If we turn to Paragraph 21. I guess I'm
13 on to -- so Paragraph 21, the second sentence
14 says, "There are numerous other possible biaryl
15 ring systems that could have more than one or two
16 possible locations for substitution."

17 Do you see that?

18 A I see that.

19 Q All right. And then you drop a footnote
20 there to refer to aryl and biaryl.

21 Do you see that?

22 A I see that.

1 Q And you agree that the '803 patent does
2 not have an expressed definition of the word
3 "biaryl" in it?

4 A I don't recall a specific definition for
5 biaryl. But bi means two. So it simply makes
6 sense that biaryl is defined that biaryl would be
7 two aryls.

8 Q And the definition of aryl or aryl
9 encompasses heterocycles with more than one ring.
10 Right?

11 A It does not. In my view it does not.
12 The definition of aryl is that it's an aromatic
13 ring containing all carbons.

14 Q Okay. But it can be -- well, let's make
15 sure we're looking at the same part. If you could
16 turn -- do you have a copy of the '803 patent,
17 Exhibit 1001, handy?

18 (BeiGene Exhibit 1001, previously marked,
19 not attached.)

20 A Okay. Let me close out. Okay, I have
21 the copy.

22 Q And if you turn to Column 15?

1 A Let me blow this up a little bit.

2 Q Column 15, I'm there.

3 Then at the top of the page you see the
4 definition of aryl?

5 A "As used herein, the term 'aryl' refers
6 to aromatic ring wherein each of the atoms forming
7 the ring is a carbon atom."

8 Q Right. And you see that the aryl
9 definition encompasses collections of rings, not
10 just single ring molecules or substituents.

11 Right?

12 A Let's see. Yeah, I see a list of ring
13 systems.

14 Q And so that's down where it says, The
15 examples of aryl groups include, but are not
16 limited to phenyl, naphthalenyl, phenanthrenyl,
17 anthracenyl, fluorenyl --

18 A Uh-huh.

19 Q -- and indenyl.

20 Do you see that?

21 A I see that.

22 Q Right. And you agree that with respect

1 to fluorenyl, that encompasses a multi-ring system
2 in which some of the rings are aromatic and one of
3 the rings is not aromatic. Right?

4 MS. PATEL: Objection. Foundation.

5 A So that fluorenyl is a tricyclic ring
6 system. The two -- the distal rings, if you will,
7 the two rings on -- the two rings that are
8 aromatic that are fused to a nonaromatic central
9 ring.

10 Q Right. So the definition of aryl in the
11 patent encompasses ring systems that are partially
12 aromatic and partially not aromatic. Correct?

13 MS. PATEL: Objection. Form.
14 Foundation.

15 A It has -- if you look at the definition
16 again of aryl, it refers to an aromatic ring, not
17 rings, wherein each of the atoms forming the ring
18 is a carbon atom.

19 So if you have a ring system with
20 three -- three fused rings, then that doesn't fit
21 the definition. Fluorenyl would not be aromatic.

22 Q So your view is that fluorenyl is not an

1 example of an aryl group in the '803 patent?

2 A That's my position. Furthermore, as
3 discussed later, for a ring to be aromatic or a
4 ring system to be aromatic, it must conform to
5 Huckel's rule, which specifies that an aromatic
6 ring or ring system has four N plus 2 electrons, N
7 being an integer.

8 So if you look at fluorenyl, using that
9 definition, you have two aromatic rings that are
10 connected by one bond. Okay? If you count up the
11 electrons here, it's going to be six with each
12 aromatic ring. So it's 12 total electrons. That
13 does not conform to the formula of Huckel for N
14 plus 2.

15 Q Okay. All right. Let's move on to
16 Paragraph 25.

17 A Okay.

18 Q One moment. All right. So Paragraph 25
19 refers to the Lipinski rules. Correct?

20 A Where do you see that?

21 Q Paragraph 25 of your declaration.

22 A Oh, just a second.

1 Q Yep.

2 A Yes. Okay. I see that.

3 Q And you quote from Dr. Scott. And you
4 say, "Dr. Scott states that a POSA would recognize
5 that too many substituents, especially large ones
6 such as aromatic rings, would increase the
7 molecular weight to significantly above 500
8 daltons, where achieving any level of oral
9 exposure would be unlikely."

10 Do you see that?

11 A I see that.

12 Q All right. Now, your next sentence you
13 say, "Rather than abide by Lipinski's rules, the
14 specification itself violates them by expressly
15 listing 75 potential optional substitutions for
16 use in the claimed invention, including bulky
17 substitutions such as heteroaryl groups that would
18 result in a high molecular weight species."

19 Do you see that?

20 A Yes, I see that.

21 Q All right. But you agree that a person
22 of ordinary skill would be guided by Lipinski's

1 rules in selecting from among the optional
2 substitutions set forth in the '803 patent?

3 MS. PATEL: Objection. Form.

4 A Do you want to restate that question?

5 Q Yeah. Just do you agree that a POSA,
6 looking at the optional substitutions in the '803
7 patent, would be guided by Lipinski's rules?

8 MS. PATEL: Objection. Form.

9 A A POSA would be looking to select those
10 substituents that would result in improved binding
11 to the target BTK.

12 So I think the fact that the
13 specification lists all these possibilities, that
14 means that they're in play for selection by a POSA
15 to append to a given ring system.

16 Q We can agree that the goal of
17 substituting would be to -- generally would be to
18 improve the binding, as opposed to the
19 unsubstituted version. Correct?

20 MS. PATEL: Objection. Form.

21 A I would agree with that. If you're
22 choosing substituents to adorn your Z prime, you

1 want to choose ones that will provide increased
2 potency, selectivity, whatever you're looking to
3 improve.

4 Q Right. And Lipinski's rules are there to
5 help guide those selections in the direction of
6 things that are more likely to improve the
7 characteristics of the compound rather than make
8 it worse. Right?

9 MS. PATEL: Objection. Form.

10 A So I agree -- I agree with that. But
11 over the years since Lipinski introduced his
12 rules, he has stated that one shouldn't
13 necessarily take the guidelines, the rules,
14 literally; that they really, he intended that
15 these should be guidelines.

16 And there are now numerous examples in
17 the literature where Lipinski's rules have been
18 violated and one still has therapeutically useful
19 either preclinical candidates or clinical
20 candidates or drugs.

21 Q All right. Now, in Paragraph 26, along
22 those lines you cite to azithromycin as an example

1 of a compound that would violate Lipinski's rules?

2 Is that correct?

3 A Azithromycin is an excellent antibiotic,
4 orally absorbed, that has a molecular weight I
5 think of 749, 750. So it would violate Lipinski's
6 guidelines by 250 daltons with respect to
7 molecular weight.

8 Q But you would agree that azithromycin is
9 a natural product or natural product derived
10 compound. Right?

11 A I would agree with that.

12 Q Right. And therefore, Lipinski's rules
13 are less relevant to natural products. Right?

14 A So I don't have in front of me or in my
15 list of various references for various programs
16 I've worked in. I don't recall that statement
17 being made, that natural products are given a pass
18 when it comes to complying with Lipinski rules.

19 Q Well, let's go to the Exhibit 1133 that
20 you cite here.

21 (BeiGene Exhibit 1133, previously marked,
22 not attached.)

1 Q If you can pull that one up.

2 A Okay. Let me close. Roskoski.

3 Q Yes.

4 A I have it up.

5 Q Sorry, I'm opening my copy of it.

6 All right. If you turn in the article,
7 the Roskoski article, Exhibit 1133, to Page
8 1133.006, according to the numbering the parties
9 put on.

10 A Okay, I'm there.

11 Q And if you go down to the bottom of the
12 left-hand column on Page 6 there you see it says,
13 Excluding the macrolides, the average molecular
14 weight of the orally effective FDA approved
15 protein kinase inhibitors is 477 with a range of
16 306 to 615.

17 A Oh, Dr. Frazier, sorry.

18 Q Yes.

19 A You say you're .006?

20 Q Yes.

21 A Left column?

22 Q Yep. Bottom of the left column and going

1 over to the top of the right column.

2 A Okay. I gotcha. I gotcha.

3 Q And I don't know if we can get Page 6 on
4 the screen. I'm still seeing Page 1.

5 There it is. Okay.

6 Yeah. So either your copy or the copy on
7 the screen, I'm just reading from the bottom of
8 the left column. It says, "Excluding the
9 macrolides (everolimus, sirolimus, and
10 temsirolimus), the average molecular weight of the
11 orally effective FDA-approved protein kinase
12 inhibitors is 477, with a range of 306 to 615."

13 Do you see that?

14 A I see that.

15 Q And so you agree then that broadly
16 speaking, the protein kinase inhibitors known in
17 the art as of even April 2023 are largely
18 following the Lipinski rule of 500 molecular
19 weight. Right?

20 MS. PATEL: Objection. Form.

21 A That is a -- that is what the data
22 showed, yes.

1 Q Okay.

2 (Discussion off the record; technical
3 difficulty.)

4 MR. FRAZIER: Could we take a short break
5 at this point.

6 (A recess was taken.)

7 BY MR. FRAZIER:

8 Q So, Dr. Showalter, if we could turn to
9 Paragraph 32 of your declaration.

10 A Yeah, I'm there.

11 Q And so you have done further calculations
12 of the numbers of compounds that are covered by
13 the structural limitations?

14 Is that correct?

15 A That is correct.

16 Q And that's what's in this section, I,
17 guess it's within the Roman 4, but it's Section A
18 titled Grossly Conservative Calculations.

19 A Yes.

20 Q Is that right?

21 A Yes.

22 Q And just so I understand. With respect

1 to the Appendix A Z prime structures, you did not
2 do any modeling of those to determine which would
3 be more or less likely to have -- to form
4 compounds that would meet the functional
5 limitations.

6 Is that correct?

7 A That's correct, no modeling was done.

8 Q And that includes that you did not
9 attempt to account for Dr. Veal's analysis that
10 certain of the E2, E3, or E4 scaffolds would not
11 lead to productive functional binding.

12 Is that right?

13 A That's correct.

14 Q And if we turn to Paragraph 37.

15 A Okay.

16 Q You see at the top of the page there --
17 I'm sorry, at the end of Paragraph 37 on the top
18 of Page 21 where it says, "Further, it is still my
19 opinion"?

20 A Top of page -- top of page which?

21 Q Twenty-one.

22 A Twenty-one. Okay. Let me back up a

1 little bit.

2 Q Yeah. It's crossing the two pages there,
3 as you can see on the screen. And you can pull up
4 on your own copy.

5 A Got it. Page 21, Paragraph 35?

6 Q Thirty-seven. It's right above the Roman
7 numeral 5.

8 I'm looking at the section that says,
9 "Further, it is still my opinion."

10 Do you see that?

11 A Which paragraph? Thirty-seven?

12 Q Yeah. Paragraph 37, at the top of Page
13 21, has the words, "Further, it is still my
14 opinion."

15 A Let me -- let me bring up 21, because --
16 top of 21.

17 So of 21 is, at least in my copy, starts
18 out with, Two of which can be any of the 12
19 optional substituent -- substitutions.

20 Q If you see on the screen where we are
21 there, Paragraph 37?

22 A Let me -- let me go to your copy. Okay.

1 MS. PATEL: Are you referring to the
2 document page number 21 or to the stamped .021?
3 That might help.

4 MR. FRAZIER: I see that.

5 Q So it's Page Number 21, and it looks like
6 it's stamped 23. So it's 1105.023. That's why
7 we're not connecting.

8 A Yeah. Okay. I'll just go with your
9 copy.

10 Q Okay. Yeah, so at the top of Page 21,
11 which is 1105.023, I believe, it says, "Further,
12 it is still my opinion that a POSA would not have
13 been able to practice the full scope of the
14 challenged claims without engaging in undue
15 experimentation because a POSA would have needed
16 to conduct multiple experiments of at least over 4
17 million potential species to figure out which of
18 those species would have satisfied the functional
19 limitations."

20 Do you see that?

21 A I see that.

22 Q All right. And that, again, goes to the

1 idea that, am I correct that your enablement
2 opinion is grounded in the amount of
3 experimentation that would be required to test all
4 of the 4 million or more species that you count as
5 within the structural limitations?

6 A Yes.

7 MS. PATEL: Objection. Form.
8 Foundation.

9 A So that -- that's my assumption.

10 Q All right. Let's go down then to
11 Paragraph 39.

12 A Okay. I want to bring -- just a second
13 here. I want to bring back --

14 Q Yeah. Go ahead.

15 A -- my copy.

16 Okay. Paragraph -- I have Paragraph 39
17 up.

18 Q In Paragraph 39 you're referring to
19 Exhibit 1109, which is a WO '185 patent.

20 Is that right?

21 A One-one -- Exhibit 11 -- this is the
22 '185? That's correct.

1 Q And your opinion there is focused on the
2 two different compounds, Compounds 2 and Compound
3 9.

4 Is that right?

5 A Yes.

6 Q And were there other compounds that were
7 within the structural limitations of the claims
8 that are discussed in the '185 patent?

9 A I would have to go back and review the
10 '185 patent --

11 Q Okay.

12 A -- to definitively give you an answer.

13 Q All right. I don't need you to do that
14 right now. But you're focused on Compounds 2 and
15 9. Correct?

16 A Yes.

17 Q And your point is that they both meet the
18 structural characteristics of Claim 1, but one is
19 reported in the '185 patent as having an IC50
20 value of less than 10 nanomolar and the other is
21 greater than 1,000 nanomolar.

22 Is that correct?

1 A As I recall, that's what -- yeah, that's
2 what we have listed here, what I have listed,
3 yeah.

4 Q And did you do any modeling or are you
5 aware of any modeling that considers why there
6 might be a structural -- or a functional
7 difference between those two compounds?

8 A So certainly I didn't do any modeling.
9 And I would defer to Dr. Veal's modeling studies,
10 whether he actually modeled these two compounds.
11 It's possible also that Dr. Eck modeled one of
12 these. I don't -- I can't recall specifically in
13 his declaration whether he had modeled this, these
14 two compounds.

15 Q And I assume you have not done any actual
16 testing of these compounds to confirm the reported
17 activities. Correct?

18 A Repeat that question?

19 Q You have not done any testing yourself to
20 confirm whether the reported IC50s are correct or
21 not?

22 A So I don't have a lab anymore. So no, I

1 wouldn't have done any testing.

2 Q Then further in Paragraph 39 you cite to
3 Compounds 20 and 30 from Exhibit 2024, which is
4 the '446 patent.

5 Is that correct?

6 A That's correct.

7 Q All right. And you understand that
8 Dr. Eck commented about those structures and the
9 relevance of modeling information to those
10 structures.

11 Is that right?

12 A That's right.

13 Q But you have not provided any
14 counter-analysis or commentary to Dr. Eck's
15 analysis of Compounds 20 and 30 in the '446
16 patent.

17 Is that correct?

18 A That's correct.

19 Q All right. Let's turn to Paragraph 47,
20 if we could.

21 A Okay. I'm there.

22 Q All right. And this again goes back to

1 the Zhang 2020 article that we had discussed
2 earlier.

3 And I think we covered this before, but
4 let me just confirm. You have not done any
5 modeling with respect to the Zhang 2020 compounds
6 either. Correct?

7 A I have not done any modeling.

8 Q All right. And you're not providing a
9 modeling analysis with respect to the Zhang 2020
10 compounds?

11 A That is correct.

12 Q And with respect to, if we jump to
13 Paragraph 50, you comment in Paragraph 50 on the
14 statement in Zhang 2020 that the authors said that
15 they were going to keep the acrylamide moiety as a
16 Michael acceptor unchanged initially and search
17 for a novel structural motif as the central core,
18 hoping to generate irreversible BTK inhibitor with
19 potent activity.

20 Do you see that?

21 A Yes.

22 Q And you put in bold the word "novel."

1 Is that right?

2 A Uh-huh. That's correct.

3 Q And in terms of the novelty of the
4 structural motif, you're not putting great weight
5 on just the characterization by the authors of the
6 article as to whether it truly is novel or not.

7 Right?

8 MS. PATEL: Objection. Form.

9 A So novelty isn't -- is in the eyes of the
10 beholder.

11 My evaluation of the Z prime bicyclic
12 core structure that they came up with has a
13 relatively high degree of novelty, the left hand
14 ring at the six position has been modified from
15 ibrutinib, either an oxygen or nitrogen was
16 substituted for carbon. And then to make the
17 bonding work, they added a carbonyl then at the 7
18 position. So that's a fair amount of change
19 structurally.

20 So in my view -- in my view these are
21 relatively novel compounds.

22 Q And as you sit here today, you don't know

1 whether or not the authors of the Zhang article,
2 Exhibit 2063, were aware of or considered the
3 specification of the '803 patent in conducting
4 their work. Right?

5 MS. PATEL: Objection. Form.

6 A So I'm not aware of that. I wouldn't
7 want to speculate.

8 Q And then let's jump then to Paragraph 53.

9 A Okay, I'm there.

10 Q All right. In Paragraph 53 you talk
11 about the '446 patent. Correct?

12 A Yes. Yes.

13 Q All right. And you indicate that
14 Compounds 30 and 122 are examples of compounds
15 that satisfy the structural limitations but would
16 not meet the functional limitations.

17 Is that correct?

18 A That's correct.

19 Q And again, you're not commenting on the
20 modeling aspects of the compounds in the '446
21 patent. Right?

22 A I am not.

1 Q All right. But then you say at the
2 bottom, you say, "Further, the fact that the
3 inventors of the '446 patent were investigating
4 and developing these compounds, some of which were
5 ultimately shown to be inactive, supports my
6 opinion that there was a lack of predictability in
7 2010/2011 (and even today) with respect to
8 irreversible BTKIs satisfying the challenged
9 claims."

10 Do you see that?

11 A I see that.

12 Q Now, first of all, you say investigating
13 and developing, but you don't have any information
14 as to which, if any, of these compounds were
15 actually being developed by the inventors of the
16 '446 patent. Right?

17 MS. PATEL: Objection to form.

18 A "Developing" maybe is too strong a word
19 here. I should have said investigating and
20 evaluating these compounds, some of which were
21 ultimately shown to be inactive.

22 Q Okay. And likewise, are you aware of

1 whether the '446 patent indicates that the authors
2 or the inventors did or did not have available to
3 them modeling information?

4 A So there's no indication in the patent
5 that they did have modeling capability. But they
6 certainly would have been aware of modeling
7 software that they could have used.

8 Q Right. But you don't know one way or the
9 other whether they actually attempted a modeling
10 analysis before embarking on their chemical
11 synthesis program?

12 A That's correct.

13 Q Then if we turn to Paragraph 54.

14 Here in Paragraph 54 now you're talking
15 about the WO '289, which is a Beijing patent
16 publication.

17 Do you see that?

18 A Yes.

19 Q And then the same point here, you mention
20 a Compound 81. And Dr. Veal has done a modeling
21 analysis, but you're not commenting one way or the
22 other on that analysis. Correct?

1 A I am not commenting on his work.

2 Q And then down further, though, you say
3 that the fact that the inventors of the WO '289
4 were investigating and developing this compound,
5 which was ultimately shown to be inactive,
6 supports my opinion that there was a lack of
7 predictability in 2010/2011, and even today, and
8 so forth.

9 Would you agree with the same point, that
10 you don't know, in the case of the WO '289 patent,
11 that the inventors were actually developing
12 Compound 81, as opposed to just investigating and
13 testing it?

14 A Yeah. So again, this may be a poor
15 descriptor here. I would just say investigating
16 and evaluating. I have no information regarding
17 whether this compound made it beyond initial
18 synthesis and testing. The fact that it's
19 inactive would suggest that it immediately got
20 dropped from any further testing.

21 Q All right. Then let's turn to Paragraph
22 56. And we talked a bit earlier about this. In

1 Paragraph 56 you're discussing the WO '185 patent,
2 which is Exhibit 1109.

3 Is that right?

4 A That's right.

5 Q All right. And again, I think we talked
6 about this before, but you're commenting on
7 Compounds 2 and 9.

8 Again, with respect to the WO '185
9 patent, Exhibit 1109, you're not aware of whether
10 those patent inventors actually had modeling
11 information available to them in connection with
12 their structure function testing. Right?

13 MS. PATEL: Objection. Form.

14 A That -- so that's correct.

15 Q Just looking through a couple of things
16 here, and then we may be able to wrap up.

17 MR. FRAZIER: All right. I think that's
18 it. No further questions from me. Thank you,
19 Dr. Showalter.

20 THE WITNESS: Thank you very much,
21 Dr. Frazier.

22 MS. PATEL: Let's just take a five-,

1 ten-minute break and then see if I have anything.

2 MR. FRAZIER: Okay. Very good.

3 (A recess was taken.)

4 MS. PATEL: We're all good. We can
5 close.

6 (Off the record at 11:04 a.m. EST.)

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foregoing testimony, and the same is a true,
correct and complete transcription of the
testimony given by me, and any corrections appear
on the attached Errata sheet signed by me.

(DATE)

(SIGNATURE)

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C E R T I F I C A T E

I, Debra Ann Whitehead, E-Notary Public in and for
the Commonwealth of Virginia, do hereby certify:

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

I further certify that the adverse
parties, BeiGene USA, INC., and BeiGene, LTD, were
represented by counsel at the deposition.

I further certify that the deposition of
HOLLIS SHOWALTER, Ph.D., occurred virtually, on
Friday, November 8, 2024, from 9:04 a.m. to 11:04
a.m. EST.

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

7
8 IN WITNESS WHEREOF, I have hereunto set my
9 hand this 8th day of November, 2024.

10
11 My commission expires:
12 October 31, 2027

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18 E-NOTARY PUBLIC IN AND FOR THE
19 COMMONWEALTH OF VIRGINIA
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Transcript of Hollis Showalter, Ph.D.
Conducted on November 8, 2024

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