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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  
Thursday, July 18, 2024  
8:27 a.m. EDT

Job No.: 540874  
Pages 1 - 189  
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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11            MARTIN MAO, BeiGene

12            MIKA McKEGAN, A/V Technician

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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

(Attached to the Transcript)

|                                                                                                                                                                                              |      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| SHOWALTER EXHIBIT                                                                                                                                                                            | PAGE |
| Exhibit 1 U.S. Patent No. 6,150,359                                                                                                                                                          | 31   |
| Exhibit 2 Article, "Discovery of BGB-8035,<br>a Highly Selective Covalent<br>Inhibitor of Bruton's Tyrosine<br>Kinase for B-Cell Malignancies<br>and Autoimmune Diseases," by<br>Guo, et al. | 79   |

EXHIBITS MARKED IN PRIOR SESSIONS

(Not attached)

|                                                        |      |
|--------------------------------------------------------|------|
| EXHIBIT                                                | PAGE |
| Exhibit 1001 U.S. Patent No. 11,672,803                | 134  |
| Exhibit 1003 Declaration of Hollis<br>Showalter, Ph.D. | 16   |

## EXHIBITS MARKED IN PRIOR SESSIONS - CONTINUED

| EXHIBIT      |                                | PAGE |
|--------------|--------------------------------|------|
| Exhibit 1005 | Dr. Rosen's Statement          | 87   |
| Exhibit 1036 | U.S. Patent Application No.    | 130  |
|              | 2020/0140432 A1                |      |
| Exhibit 1044 | 2021 Article by Brullo, et al. | 98   |
| Exhibit 1052 | Article by Ghose, et al.       | 73   |
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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, sir.

8 Q I'm David Frazier, I'm counsel for  
9 Pharmacyclics and AbbVie in this matter.

10 A Nice to meet you.

11 Q Likewise, likewise.

12 Have you been deposed before, sir?

13 A I have not been deposed before.

14 Q I'll go over just a few kind of ground  
15 rules that will help things go smoothly today.

16 First, as was mentioned, it will help if  
17 we don't speak at the same time. So I'll try to  
18 ask you a question, come to a full stop, and let  
19 you give your answer. But it helps the court  
20 reporter if we don't talk at the same time.

21 Do you understand?

22 A I understand.

1 I have a further question. How should I  
2 address you, Dr. Frazier?

3 Q Dr. Frazier, Mr. Frazier, either one is  
4 fine, yeah. I don't stand on formality.

5 A Okay. Neither do I.

6 Q Very good.

7 And you understand then that you're  
8 giving sworn testimony today, you're testifying  
9 under oath. Correct?

10 A I understand that.

11 Q And you understand that you must not  
12 discuss the substance of your testimony with your  
13 counsel during the deposition or at any breaks.

14 Correct?

15 A I understand that.

16 Q And you'll let me know if any such  
17 communications with counsel happen?

18 A I will. I will let you know that, yes.

19 Q But we don't anticipate there will be  
20 any.

21 And you're able to provide truthful  
22 testimony today, you're not suffering from any

1 condition or taking any medication that would  
2 affect your ability to give truthful testimony?

3 A No, I am not taking any medications that  
4 would affect my testimony.

5 Q Great. Now, in terms of breaks, I'm  
6 happy to accommodate a break at any time. So just  
7 let me know. The only thing I'd ask is if there's  
8 a pending question, that we go ahead and get the  
9 answer to that pending question, and then I'm  
10 happy to accommodate a break. All right?

11 A Fair enough.

12 Q And just if you can tell me where are you  
13 located today? Where are you Zooming from?

14 A So I'm Zooming from my home, which is in  
15 Harrisonburg, Virginia, which is in the  
16 northwestern part of the state, and most people  
17 associate Harrisonburg, Virginia, with James  
18 Madison University.

19 Q Okay. All right. Great. It's a lovely  
20 area. I've been down there a few times.

21 And so, and you are by yourself in the  
22 room where you're doing this deposition?

1           A     I'm by myself.

2           Q     And if you could just tell me, sir, if  
3 someone comes into the room while you're  
4 testifying.

5           A     I will let you know if that's the case.

6           Q     And you don't have any other lines of  
7 communication with your counsel. Correct?

8           A     Would you repeat that question, please?

9           Q     You don't have any other lines of  
10 communication with your counsel, just through this  
11 Zoom interface. Correct?

12          A     Just through the Zoom interface, yes.

13          Q     And you understand that you're not to be  
14 Googling or doing other types of research during  
15 the proceeding. Correct?

16          A     So understood.

17          Q     And what I would say is, I understand you  
18 have a collection of your declaration and the  
19 associated exhibits. We'll go through them one at  
20 a time. If there comes a point where you want to  
21 see something else that's cited in your  
22 declaration just let me know, and then we can get

1       that into the mix. But I just want to know what  
2       you're looking at.

3                     Is that fair?

4             A       That's fair.

5             Q       Okay. Great. And I think that's it for  
6       ground rules, then.

7                     The only other thing I'd say is if you  
8       don't understand any of my questions at any point,  
9       just let me know, I'll try to rephrase or  
10      understand what the misunderstanding is.

11     Otherwise I'll assume that you do understand my  
12     questions. Understood?

13             A       Understood.

14             Q       Great. How did you prepare for today's  
15     deposition?

16             A       So I, first of all, certainly reviewed  
17     the '803 patent. I went back over my own  
18     declaration, reviewed that. I reviewed Steve  
19     Rosen's declaration. I reviewed the AbbVie  
20     response to both mine and Dr. Rosen's  
21     declarations. I looked at the transcript of  
22     Dr. Rosen's deposition. And then last, I reviewed

1 the appeals board document.

2 Q Understood. All right. Other than your  
3 declaration and the materials that you've  
4 identified to me, was there anything that you  
5 reviewed that was not cited in your declaration?

6 A Do you want to repeat that question,  
7 please?

8 Q Yeah. So you've identified your  
9 declaration and some other materials that you  
10 reviewed.

11 Did you review anything else that was not  
12 cited in your declaration?

13 A So it turns out that following the  
14 submission of my declaration in October of last  
15 year I came across, in some literature searching,  
16 two examples of compounds that meet the structural  
17 limitations of the '803 patent claims that are  
18 actually -- these compounds are inactive.

19 Q When you say "inactive," what do you  
20 mean?

21 A So by "inactive" I mean they were assayed  
22 in a Btk assay, formatted assay, and these

1 compounds that are inactive have IC50s of greater  
2 than 1,000, which a POSA I think would agree that  
3 that high level of an IC50 would indicate  
4 inactivity. One wouldn't be interested in  
5 pursuing any compound that has an IC50 greater  
6 than 1,000.

7 Q When you say greater than 1,000, you mean  
8 greater than 1,000 nanomolar?

9 A Greater than 1,000 nanomolar, greater  
10 than 1 micromolar, yes.

11 Q So is it your opinion, then, that when it  
12 comes to kinase inhibitors, a person of ordinary  
13 skill would not be interested in an inhibitor that  
14 has an IC50 greater than 1 micromolar?

15 A That is my opinion. My opinion is that  
16 the -- a POSA would not further pursue a weak  
17 compound like that.

18 Q And do you feel that that has been the  
19 case since 2011?

20 A So I would say especially the case since  
21 2011, but even before 2011.

22 Q And that --

1           A     One of --

2           Q     That's a standard you've applied in your  
3     own work?

4           A     That's a standard I had when I was  
5     working with kinase in my own laboratory, that was  
6     the standard.

7                     I want to give you some details on these,  
8     where I found this information.

9                     Could I do that, please?

10          Q     Well, let me just -- we'll get through  
11     that. I was planning to focus mostly on your  
12     declaration. But maybe if you could just tell me  
13     first where did you -- or how did you come to  
14     locate these references?

15          A     So I was just doing general searching, as  
16     I often do. And, you know, use keyword searches  
17     or you use algorithms to come up with potential  
18     structures. And so I can't give you exact  
19     details. I do a lot of searching, you know. So  
20     in this process I came across these two papers, or  
21     two disclosures.

22                     One of which is in ACS Medicinal

1 Chemistry Letters, that would be year 2020, Page  
2 1863. So that would be the hard copy of ACS Med  
3 Chem Letters. That also published online earlier,  
4 I think December -- December -- December 11, I  
5 think, 2019.

6 And then the other disclosure was a  
7 patent. And this is also in 2019. I think this  
8 issued in 2019, if I recall July -- I think July  
9 23rd I think it is. And the patent number is a  
10 U.S. patent, Patent number is 10,358,446.  
11 10,358,446. And as I said, issued in July of  
12 2019, I think July 23rd.

13 Q And do you have notes that you're working  
14 from, or you committed those references, citations  
15 to memory?

16 A I worked on committing those to memory  
17 because I felt they were very important  
18 references.

19 Q Okay. All right.

20 A I hope I've given them to you correctly.

21 Q Okay. You don't otherwise have any notes  
22 in front of you besides the declaration and the

1 materials cited in the declaration. Correct?

2 A That's right. Just a pad here, scribble  
3 a couple notes.

4 Q But it's a blank pad at this point.  
5 Correct?

6 A Yeah, it's just a blank piece of paper  
7 that I can scribble some notes.

8 Q Okay. Great. Well, let's turn to your  
9 declaration.

10 So if we --

11 MR. FRAZIER: I guess that has been  
12 marked as Exhibit 1003 in this matter. And  
13 perhaps we can pull that up on screen.

14 (BeiGene Exhibit 1003, previously marked,  
15 not attached.)

16 A Yeah. Just give me a couple seconds  
17 here. So, yes, Exhibit 1003?

18 Q Yes. And I think we have it on the  
19 screen as well.

20 A Yeah.

21 Q And we can hand over control to you if  
22 you want to peruse through, and then we'll both be

1 looking at the same thing. It's usually the  
2 easiest way to do it. But, of course, if you have  
3 your own copy, that's okay as well.

4 A Yeah, I have my own copy, I can increase  
5 the font size and control it a little better for  
6 my own needs.

7 Q All right. So then the declaration,  
8 then, if we go to the page which is 134.

9 A So is this the PDF page or the actual  
10 document page?

11 Q The actual document page. But I see it's  
12 Page 137 in the PDF, if that's helpful.

13 A So as I see this page, it's the signature  
14 page?

15 Q Yes. And that's your signature on Page  
16 137 of Exhibit 1003?

17 A That is my signature.

18 Q Great. And since you submitted this  
19 document in October of 2023, have you identified  
20 any errors?

21 A There are very, very minor errors. And I  
22 can't even tell you where they are. There's I

1 would say no more than two or three errors.

2 Q And what's the nature of the errors that  
3 you have in mind?

4 A Yeah. So I'll just give you one specific  
5 error.

6 Q Okay.

7 A There's a discussion of the x-ray  
8 structures of Imbruvica and Brukinsa, and in one  
9 of those x-ray pictures that's within the -- my  
10 declaration here, it shows that there's a -- this  
11 is for Brukinsa -- shows that there is a donor  
12 hydrogen bond off of the Brukinsa  
13 six-membered ring, the NH, a donor hydrogen bond  
14 to the hinged region. It's described as a donor  
15 hydrogen bond, but it should have been described  
16 as an acceptor hydrogen bond.

17 Q Understood.

18 A Any POSA would have understood that the  
19 language there should have said acceptor instead  
20 of donor.

21 Q Any other errors that you're aware of?

22 A Just maybe a couple typos here and there,

1 but no major, you know, substantive errors that I  
2 think would make for invalidity of that particular  
3 sentence or section.

4 Q Understood. And anything else, then,  
5 that you would like to change in the report  
6 compared to how it was actually submitted?

7 A Nothing -- nothing that I can think of at  
8 this point.

9 Q And how did you go about preparing the  
10 declaration?

11 A So for legal matters -- you know, I'm not  
12 a lawyer. I consulted with Yi Zhang and Weil  
13 attorneys. And for scientific matters, this is  
14 all pretty much it's on my own. I did all the  
15 searching around, technical scientific issues, and  
16 that's reflected in my declaration.

17 Q And as for the documents that are cited,  
18 were some of those provided to you by the  
19 attorneys?

20 A They were provided only on request, my  
21 request.

22 Q And so did the attorneys provide you with

1 any of the documents that are cited in the report  
2 other than those that you requested? Did they  
3 give you kind of a package to begin with?

4 A No. They provided, as I recall, pretty  
5 much everything I asked for. These are, you know,  
6 for the most part they're all technical  
7 publications.

8 Q And so just to be clear, then, you worked  
9 on this document yourself. Correct?

10 A That's correct.

11 Q And you believe you were thorough in  
12 developing the opinions that are recited in the  
13 report?

14 A I think I'm pretty -- I think I'm pretty  
15 thorough.

16 Q And you included -- you understood that  
17 you were required to include all the bases for the  
18 opinions that you provided in the report?

19 A Would you -- would you repeat that  
20 maybe --

21 Q Yeah. So --

22 A -- provide --

1 Q Go ahead.

2 A I was going to say, just provide a little  
3 more detail there.

4 Q Yeah. So my question was, is it your  
5 understanding that you provided and were required  
6 to provide all the bases for the opinions that you  
7 provided in the report?

8 A All the bases? I'm not sure what you  
9 mean by "bases."

10 Q By bases I mean the evidence supporting  
11 the conclusions that you provided in the report.

12 A So the bases would have been the patents  
13 and manuscripts that I pulled from online or had  
14 my counsel provide to me upon request.

15 Q Right. And those were -- to the extent  
16 that you had a basis for an opinion in the report,  
17 you provided a citation to the document that  
18 formed the basis for that opinion. Correct?

19 A That's what I did, yes.

20 Q Now, you're offering opinions that the  
21 '803 patent in this case, which is for the record  
22 U.S. Patent 11,672,803, that that patent is

1       invalid.   Correct?

2           A       Those are the opinions that I'm offering.

3           Q       Right.   And you state that it's your  
4       opinion that the claims of the '803 patent are  
5       invalid under the written description and the  
6       enablement requirements of the patent law.

7                   Is that your understanding?

8           A       That's my understanding.

9           Q       Is it your view, then, that patent claims  
10      should not cover thousands of possible compounds?

11                   MS. PATEL:   Objection.   Foundation.

12          A       So it's my view -- repeat the question,  
13      please?

14          Q       My question is, is it your view, based on  
15      your understanding of the patent law -- which I  
16      understand was provided to you by the attorneys.

17                   Is that correct?

18          A       That's correct.

19          Q       So based on your understanding of the  
20      patent law, is it your understanding that claims  
21      of a patent should not cover many thousands of  
22      possible compounds?

1 MS. PATEL: Objection. Calls for a legal  
2 conclusion. Scope.

3 MR. FRAZIER: Counsel, let me just stop  
4 you there for a minute. It's my understanding  
5 that the objections in the PTAB are limited to  
6 objection to form. And I'd like if you could just  
7 refrain from giving other instructions.

8 Can we agree on that?

9 MS. PATEL: Counsel, I'm not limited to  
10 just objections to form. There are a number of  
11 other objections or bases for objection that I'm  
12 allowed to lodge per the PTAB's rules.

13 MR. FRAZIER: I disagree with that.

14 MS. PATEL: I don't think we can agree on  
15 that.

16 MR. FRAZIER: So it's your contention  
17 that you're allowed to provide additional verbiage  
18 besides "objection to form"? I just want to be  
19 clear on this because we may have to take further  
20 action if we can't reach agreement here.

21 Are you contending that you have a right  
22 during the deposition to say things other than

1 "objection to form" in terms of describing the  
2 basis for your objection?

3 MS. PATEL: Yes, that is correct. The  
4 practice notes for the PTAB, in our view, allow us  
5 to object beyond form. For example, privilege,  
6 foundation, relevance, scope --

7 MR. FRAZIER: How about legal  
8 conclusion --

9 MS. PATEL: -- and other such objections.

10 MR. FRAZIER: And the one actually that  
11 got my attention, you seem to be objecting on the  
12 grounds of a legal conclusion, and I just -- if  
13 you're withdrawing all the legal conclusions that  
14 Dr. Showalter has drawn, then I can agree to that  
15 objection and we'll move forward on that basis.

16 But otherwise, that would be an improper  
17 objection. All right?

18 MS. PATEL: We are -- to be clear, we are  
19 not withdrawing the opinions that Dr. Showalter  
20 has submitted in his declaration. But we disagree  
21 that we cannot object on the basis that you're  
22 asking him to provide a legal opinion.

1           MR. FRAZIER: That makes no sense.  
2     Either he's providing legal opinions today or he's  
3     not. Which is it?

4           MS. PATEL: As I said, he provided  
5     opinions in his declaration. Those opinions were  
6     informed by legal standards that we provided him.

7           But in terms of whether you can ask him  
8     about any aspect of the law or opinions outside of  
9     his declaration, we can object where you are  
10    asking him to provide legal conclusions.

11          MR. FRAZIER: Do you feel that asking him  
12    about the scope of the claims is outside of the  
13    scope of his declaration?

14          MS. PATEL: I don't believe that you  
15    asked him about the scope of the claims. You  
16    asked him whether it's his opinion that the law  
17    requires a certain number -- or would require that  
18    there not be a certain number of candidates  
19    claimed by a claim. That's a legal conclusion.

20          If you want to ask him the legal  
21    standards that he actually applied in his  
22    declaration, you can ask him about that.

1 MR. FRAZIER: All right.

2 MS. PATEL: But you can't ask him -- it's  
3 not a test on the law here, Counsel.

4 MR. FRAZIER: I disagree. I think that  
5 he's purporting to apply the law to the facts of  
6 this case. Correct?

7 THE WITNESS: Are you speaking to me?

8 MR. FRAZIER: I'm still speaking with  
9 counsel.

10 THE WITNESS: Okay.

11 MR. FRAZIER: Because we seem to have a  
12 point here where she's objecting to your providing  
13 testimony about the law. And I thought that's  
14 what you were doing in your declaration.

15 MS. PATEL: I'm objecting to questions  
16 you are asking him regarding what is the correct  
17 legal standard. He was provided a legal standard  
18 from counsel, that's how it always works. Those  
19 legal standards are in his declaration. And he  
20 applied those in providing his opinions.

21 MR. FRAZIER: Right. And I'm  
22 cross-examining on his understanding of the legal

1 standard, and that's perfectly proper. And it  
2 would be improper for you to object to his  
3 providing testimony on his understanding of that  
4 legal standard. Correct?

5 MS. PATEL: I disagree that it is  
6 improper for me to have objected in the moment  
7 that I did.

8 MR. FRAZIER: Well, let's move forward.

9 BY MR. FRAZIER:

10 Q So, Doctor, you were instructed on the  
11 legal standards in this case. Correct?

12 A I was instructed on legal standards.

13 Q And based on your instruction and the  
14 legal standards as you understand them, do you  
15 believe that patent claims should not cover  
16 thousands of possible compounds?

17 MS. PATEL: Objection. Foundation.

18 A So let me think about that a bit.

19 As I said, I'm not a lawyer. I depended  
20 on counsel to provide legal standard --

21 (Technical difficulty.)

22 Q I'm sorry, you cut out. Can I just ask

1 you to repeat what you said?

2 A Yeah. So I'm not a lawyer. I worked  
3 with counsel to understand legal standards, and I  
4 think I applied legal standards.

5 Regarding your question, I can't opine on  
6 that question, that's simply -- applied legal  
7 standards as I understood them from counsel.

8 Q And in applying the legal standards that  
9 you were provided by counsel, did you believe that  
10 it was improper for patent claims to cover many  
11 thousands of compounds?

12 MS. PATEL: Objection. Foundation.  
13 Asked and answered.

14 A So I guess maybe one way to sort of drill  
15 down on this question a bit is simply to look at  
16 my declaration. We could go to the pages of the  
17 declaration that relate to legal standards, and we  
18 can just look at -- look at what's stated in my  
19 declaration.

20 Q Let me find -- the legal standard section  
21 here is Pages 7 and 8. Actually, beginning at  
22 Page 6, if you want to turn there.

1           A     Okay, I'm there.

2           Q     And you understand then that the legal  
3 standards that you applied begin at Page 6 and go  
4 through Pages 7 and 8 of your declaration.

5                     Is that correct?

6           A     So starting with which paragraph?  
7                     Paragraph 17?

8           Q     Well, the section begins at Paragraph 14.

9           A     Yes, I see that.

10          Q     And then continuing through Paragraph 24,  
11 those are the legal standards that you applied in  
12 this matter. Correct?

13          A     Let me just look through this quickly.

14                     So go back to your question again.

15          Q     So then -- well, so my question initially  
16 was just that the legal standards that you applied  
17 in this matter run from Paragraph 14 through  
18 Paragraph 24 in your declaration. Correct?

19          A     Through 24? Yes, I think that's correct.

20          Q     And then the question that I was asking  
21 is, based on those legal standards that you were  
22 provided, is it your belief that patent claims

1     such as the claims in the '803 patent, should not  
2     cover thousands of possible compounds?

3             MS. PATEL: Objection. Form. Asked and  
4     answered.

5             A     So my belief is that the patent must  
6     cover within the specifications a description of  
7     enough of the, in this case, types of compounds  
8     that a POSA would be able to look at a list of  
9     let's say thousands of compounds as defined by the  
10    claims, and be able to identify any one of those  
11    thousands of compounds -- potentially identify any  
12    one of those thousands of compounds based on what  
13    is disclosed within the specifications.

14            Q     And based on the legal standards that you  
15    were provided, is it your understanding that a  
16    claim to a method of treating cancer should  
17    require clinical testing?

18            A     A method of treating cancer requires --  
19    repeat your question. I want to make sure I  
20    understand it.

21            Q     Right. My question is, based on the  
22    legal standards that you applied in this matter,

1 is it your understanding that a method of treating  
2 cancer, a claim to a method of treating cancer,  
3 should require clinical testing in the  
4 specification of the patent?

5 MS. PATEL: Objection. Scope.

6 A I think, yes, it would require some  
7 information regarding testing. You would have to  
8 test to prove that it would be -- a given agent  
9 would be efficacious.

10 Q Clinical testing?

11 A Certainly if you're talking about a drug,  
12 you know, you're talking about something that's  
13 going to be treating patients, so that implies  
14 clinical testing.

15 MR. FRAZIER: If we could get the  
16 document that we've marked by the court reporter  
17 as Tab 1, and I'd like to just mark this as  
18 Showalter Exhibit 1. And it's a copy of U.S.  
19 Patent 6,150,359.

20 (Showalter Deposition Exhibit 1 marked  
21 for identification and is attached to the  
22 transcript.)

1                   MR. FRAZIER: And if we could put that in  
2 the chat as well so that Ms. Patel can have it as  
3 well.

4                   (Discussion off the record with the A/V  
5 technician.)

6           A       I have it.

7           Q       And do you recognize the U.S. patent  
8 6,150,359?

9           A       I recognize this patent.

10          Q       Yes. And you are a co-author on this  
11 patent, or co-inventor?

12          A       I'm a co-inventor.

13          Q       And the patent relates to inhibition of  
14 protein tyrosine kinase and cell cycle kinases.

15                   Correct?

16          A       So it's been a long time. You're looking  
17 here at 24 years ago. So I'd really need to  
18 review this patent to give you the information you  
19 might be asking for.

20          Q       Well, if you want to take a moment to  
21 review it. My question is just, does it relate to  
22 inhibition of protein tyrosine kinase and cell

1 cycle kinase mediated cellular proliferation. But  
2 go ahead and review it, if you wish.

3 A Yeah, I'm going to take a few minutes  
4 here to review it.

5 Q Okay.

6 MS. PATEL: And I'll just note I haven't  
7 received the link on my chat. I think you might  
8 have just sent it directly to the witness.

9 (Discussion off the record with the A/V  
10 technician.)

11 A Okay, it's coming back. Let me just do  
12 some more scrolling here.

13 Okay, I think I'm ready to engage in  
14 further discussion.

15 Q And my question -- my first question was  
16 just, this patent relates to inhibition of protein  
17 tyrosine kinase and cell cycle kinase mediated  
18 cellular proliferation. Correct?

19 A That's correct.

20 Q Okay. And this is a general category of  
21 compounds called naphthyridinones?

22 A That's a proper -- that's a proper

1 chemical nomenclature, yes.

2 Q And if we turn to the claims, which are  
3 on PDF -- I'm just looking for the page here.  
4 Here we go. PDF Page 29.

5 A Okay, I'm there.

6 Q And so you understand that Claim 1 then  
7 begins on Column 55 on PDF Page 29 of this U.S.  
8 patent that I've marked as Showalter Exhibit 1?

9 A Yes, I see that.

10 Q And is it your understanding, based on  
11 the structure that's provided, can you give an  
12 estimate of the number of compounds that would be  
13 covered by this claim?

14 A So there are 30 different R groups. I  
15 can't give an estimate, but certainly -- I'm going  
16 to say I can't give an estimate, no.

17 Q It would be at least thousands, would you  
18 agree?

19 A It's hard for me, just sitting here  
20 looking at the structure, to know whether it would  
21 be any given -- any given number.

22 Q You think it would be at least thousands

1 of compounds, though. Correct?

2 A So I think I just answered that question.  
3 I'm not, you know -- I don't want to commit to a  
4 number, because I can't really tell looking at the  
5 structure. Or I can't make an estimate just  
6 looking at the structure as it's presented.

7 Q All right. If you turn to PDF Page 39.

8 Do you see PDF Page 39, Claim 55 is a  
9 method of treating cancer, the method comprising  
10 administering to a patient having cancer a  
11 therapeutically effective amount of a compound of  
12 Claim 1.

13 Do you see that?

14 A I see that.

15 Q Right. And is it your understanding that  
16 there was -- strike that.

17 Was there any clinical data that was  
18 provided in this patent, to your understanding?

19 A So my recollection here is that there is  
20 no -- there is no clinical data.

21 Q But when it came to your compounds, you  
22 were able to predict that every compound that

1 would be covered by Claim 1 would be capable of  
2 treating cancer.

3 Is that correct?

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

6 A So I want to hear your question again.  
7 Restate it.

8 Q My question is that with respect to your  
9 patent, the '359 patent that we marked as  
10 Showalter Exhibit 1, and Claim 55, is it your view  
11 that you were able to predict that every single  
12 compound of Claim 1 would treat cancer as claimed  
13 in the method of treating cancer in Claim 55?

14 MS. PATEL: Objection. Form.

15 A My view is that I as a POSA would not  
16 have been able to predict -- or guess, let me say  
17 guess -- that a compound would be able to treat  
18 one of the -- treat a patient clinically.

19 Q So you're saying that even though your  
20 patent claims a method of treating cancer with the  
21 compounds of Claim 1, that you are -- you think  
22 that you or a POSA would have been unable to

1 predict whether that was actually something that  
2 could be done by those compounds?

3 A So I think a POSA could surmise that  
4 maybe -- that a compound could treat a patient  
5 clinically, but that's the extent I think to which  
6 a POSA would be able to make any statements  
7 regarding clinical application.

8 Q And it's your understanding the work  
9 that's reflected in the '359 patent, Showalter  
10 Exhibit 1, was conducted in the late 1990s.

11 Is that correct?

12 A As I recall, that's when we did the work.

13 Q One additional question. We talked  
14 earlier about the inhibition by an inhibitor. And  
15 I believe you told me that the inhibition of one  
16 micromolar -- of higher than one micromolar would  
17 be considered insufficient inhibition by a person  
18 of ordinary skill in the art.

19 Do you recall that?

20 A Yes.

21 MS. PATEL: Objection. Form.

22 Q And if I were to go through this patent,

1 would I see a consistent treatment of that, that  
2 inhibition of 1 micromolar or higher would be  
3 deemed in your patent to be inactive?

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

6 A So I think one has to view this in  
7 context. So in 2000 -- correct -- scratch that.

8 In the late 1990s the standard for  
9 activity was different from the standard later.  
10 So in 1995 discoveries were being made around  
11 tyrosine kinase and protein kinase inhibitors.  
12 And this was based on the screening of chemical  
13 libraries.

14 So a compound that was discovered through  
15 screening might have an IC50 of 1 micromolar.  
16 That would be a good starting point for conducting  
17 an SAR campaign.

18 But as more information was derived from  
19 SAR campaigns the standard changed, because  
20 compounds of increasing potency were being  
21 discovered.

22 So I would say as of 2010, 2011, the

1 standard still was that to have an active compound  
2 you had to be less than 1 micromolar IC50 in a  
3 kinase assay.

4 Q Respectfully, sir, that's not what you  
5 told me at the beginning of this deposition.

6 Correct?

7 MS. PATEL: Objection. Form.

8 Argumentative.

9 A So at the beginning of the declaration I  
10 indicated, when you asked this question, that  
11 these were 2019, 2020 disclosures. In that time  
12 period, 2019, 2020, the standard for activity was  
13 that anything greater than 1,000 nanomolar, 1  
14 micromolar, would have been deemed by a POSA as  
15 inactive.

16 Q Let's move on.

17 MR. FRAZIER: Let me mark --

18 Q Actually, let me ask you a question  
19 before we mark another exhibit.

20 MR. FRAZIER: We can go ahead and take  
21 down Showalter Exhibit 1.

22 Q So in performing the research that you

1 did in connection with your declaration, which is  
2 Exhibit 1003, did you attempt to educate yourself  
3 about the state of the art with respect to the  
4 structure of Btk?

5 A I did. I did reading on the structure of  
6 Btk.

7 Q And did you also attempt to educate  
8 yourself about what was known about kinase  
9 inhibition of Btk in the art as part of the work  
10 that you did in preparing your declaration,  
11 Exhibit 1003?

12 A Repeat your question, please?

13 Q Yeah, my question is, did you attempt to  
14 educate yourself about the state of the art of  
15 kinase inhibition of Btk as part of the work you  
16 did in preparing your declaration, Exhibit 1003?

17 A So I read a number of papers, and I think  
18 some of the early publications were around maybe  
19 as early -- I don't exactly remember, but I think  
20 in the late '90s.

21 So, and then I followed those  
22 publications with more recent publications on the

1 state of the art. So if I think a fairly broad  
2 understanding of the state of the art of Btk from  
3 over about a 25-year period.

4 MR. FRAZIER: Let's pull up -- I believe  
5 we have a document that's marked as Exhibit 2001.

6 (Pharmacyclics Exhibit 2001, previously  
7 marked, not attached.)

8 A Just a second here, I'll pull mine up.  
9 Exhibit -- what did you say the exhibit is?

10 Q 2001.

11 A Two zero zero one?

12 Q Yes. It's actually on the screen as  
13 well.

14 A Okay, I'm not finding it in my hard  
15 drive. Okay.

16 MR. FRAZIER: And if we could then put  
17 that in the chat then for the doctor and counsel.

18 Q Just let me know when you're able to open  
19 that, Dr. Showalter.

20 A Okay. It's open.

21 Q And do you recognize this document that  
22 we've marked as Exhibit 2001 as a 2010 article by

1 Marcotte, et al., about the structure of Btk?

2 A I recognize this, this paper.

3 Q Now, is this an article that you were  
4 aware of when you were preparing your declaration?

5 A So this is an article that I drew from  
6 for my declaration.

7 Q And to your understanding, was it cited  
8 anywhere in your declaration?

9 MS. PATEL: Objection. Foundation.

10 A It's cited in my declaration, I just  
11 can't remember where. At least I believe it's  
12 cited in my declaration.

13 Q But do you have -- well, let me put it  
14 this way: To my knowledge, it is not cited in  
15 your declaration. If you have a particular place  
16 in mind, perhaps you could point me to that.

17 A So I'm aware of this, I was aware of this  
18 document.

19 Q Are there any other documents that you  
20 were aware of and considered in preparing your  
21 declaration but did not include either in the  
22 declaration itself or in some sort of list of

1 materials that you considered?

2 MS. PATEL: Objection. Form. Asked and  
3 answered.

4 A I'm not aware of any such documents.

5 Q And to the extent that this document is  
6 not cited in your declaration, we can conclude it  
7 did not form part of the basis of your opinions.

8 Correct?

9 MS. PATEL: Objection. Form.

10 A So this document was -- I was aware of  
11 this document actually before putting my  
12 declaration together. And so this document would  
13 have informed some of my views on Btk and Btk  
14 inhibitors. And I drew from some of that  
15 information I had in my head. It's possible that  
16 I simply formed my opinions based on this but  
17 failed to include this in my list of references,  
18 of disclosed information that was out there in the  
19 public domain.

20 Q You agree that this Marcotte 2010  
21 document, which is Exhibit 2001, would have been  
22 important information for a person of ordinary

1 skill in the art who was developing an inhibitor  
2 of Btk?

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

5 A This document would have been a helpful  
6 document. I don't -- I submit that it wouldn't --  
7 that a POSA would have been able to -- a POSA  
8 would be able to imagine inhibitors of Btk without  
9 having seen this document.

10 Q Do you agree that by 2010 and the  
11 publication of this document, that a PDB 3GEN  
12 crystal structure was available for Btk?

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

15 A So the crystal database would have had a  
16 structure for Btk, but that structure would have  
17 been determined as early as -- again my memory may  
18 not be perfect on this, but as early as 2000.

19 Q And you agree also that there would have  
20 been a 3GEN crystal structure of Btk together with  
21 the inhibitor known as B43. Right?

22 MS. PATEL: Objection. Foundation.

1 Form.

2 A Again, from my knowledge in this area, I  
3 was aware even before putting the declaration  
4 together that a crystal structure of B43 would  
5 have been -- of B43 with Btk would have been  
6 available.

7 Q Right. And B43 is a reversible inhibitor  
8 that is an analog of ibrutinib. Correct?

9 MS. PATEL: Objection. Form.  
10 Foundation.

11 A So I would -- I would state that  
12 differently.

13 I would say that ibrutinib is an analog  
14 of B43.

15 Q And you understand, then, that the  
16 Marcotte publication, Exhibit 2001, provides a  
17 crystal structure of B43 bound to the Btk active  
18 site. Correct?

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

21 A So I would agree that as shown in Figure  
22 2 here, B43 crystalized with Btk was available as

1 of, let's say -- I forget the date on this  
2 publication, but would have been available likely  
3 I think sometime around 2005, 2008, something like  
4 that.

5 Q And just for clarity, the article is --  
6 has a 2010 publication date.

7 A So that means -- I agree. That means  
8 that the experiments, the science in this article,  
9 would have been performed prior to that date over  
10 maybe a two- to three-year period. So mid two  
11 thousand -- 2005 on, let's say, to 2008.

12 Q And just for clarity, as you sit here  
13 today you are not aware of having cited this  
14 Marcotte Exhibit 2001 in your declaration.

15 Correct?

16 A So I was not aware that I had not  
17 included this. Again, I was drawing from prior  
18 information that I had on B43. I was quite aware  
19 of B43 and its structure and its  
20 co-crystallization with the enzyme.

21 Q And you agree that a POSA would consult  
22 this structural information about how B43

1       interacted with Btk to illuminate the binding mode  
2       of a compound if they were investigating the  
3       inhibitors disclosed in the '803 patent?

4               MS. PATEL:  Objection.  Form.

5           A       So I as a POSA would have been aware of  
6       this, of this article, and would have been  
7       interested in the co-crystal structure of B43 with  
8       Btk.

9           Q       And that's because having that structure  
10      would inform you about the binding mode of an  
11      inhibitor having the B43 structure.  Right?

12               MS. PATEL:  Objection.  Form.  Asked and  
13      answered.

14          A       So the structure would have provided  
15      information on a reversible compound, not an  
16      irreversible compound as is the case for  
17      Imbruvica, or Brukinsa.  This informs a POSA on a  
18      reversible compound.  So useful information, but  
19      insufficient information.

20          Q       And you're aware that BeiGene also  
21      consulted the binding mode of B43 as part of its  
22      development of zanubrutinib?

1 MS. PATEL: Objection. Form. Calls for  
2 speculation. Foundation.

3 A So the answer to that is I don't know.

4 MS. PATEL: Counsel, we've been going for  
5 about an hour now. Is it all right if we take a  
6 break?

7 MR. FRAZIER: Sure.

8 MS. PATEL: All right.

9 (A recess was taken.)

10 BY MR. FRAZIER:

11 Q So, Dr. Showalter, let's go back to your  
12 declaration, Exhibit 1003, and I'll refer you to  
13 Paragraph 7.

14 A Paragraph 7. Okay, I'm there.

15 Q And Paragraph 7 is in a section of your  
16 declaration called Qualifications. Correct?

17 A Correct, that's the section, yes.

18 Q All right. And in Paragraph 7 you say  
19 that your research, background, and interests  
20 include organic and heterocyclic synthesis  
21 methodology, designing physicochemical properties  
22 into high-throughput screen hits which confer

1 drugability, (e.g., conformity to Lipinski rules,  
2 absence of toxicophores).

3 Do you see that? It goes on from there?

4 A Yes, I see that.

5 Q And could you tell me what are the  
6 Lipinski rules that you refer to in Paragraph 7.

7 A So the -- well, the Lipinski rules were  
8 first articulated, first published I think in the  
9 year 1999. And this was by -- I'm not recalling  
10 the first -- the given name, but Lipinski, who was  
11 a computational medicinal chemist at Pfizer, he  
12 published a list of what he called rules in a  
13 paper I think in 1999.

14 And that paper had such wide readership,  
15 the initial article was republished in 2001. So  
16 let's get to what the rules are. These are what  
17 have been referred to as the rule of five.

18 So the rule of five states that no  
19 compound will have more than -- would have a  
20 molecular weight no higher than 500, a compound  
21 would not have a C LogP, which is a measure of  
22 lipophilicity of a compound, of greater than 5.

1 And these are -- these relate to what I  
2 indicated -- relate to issues of drugability,  
3 whether a compound had drug-like characteristics.

4 And then the other requirement is that  
5 the compound would not have more than ten total  
6 hydrogen bond acceptors or donors. And within  
7 those rules I think you wouldn't have more than  
8 five hydrogen bond donors.

9 So that's sort of the gist of the rules.

10 Q And so certainly by June of 2011 a POSA  
11 would have been aware of the Lipinski rules?

12 A A POSA would have been aware as of 2011  
13 of the Lipinski rules. But there was  
14 reinterpretation of those rules, and Lipinski  
15 himself agreed to the three interpretation. He  
16 said these rules are really too rigid. We're  
17 going to call these guidelines.

18 So there was never any followup  
19 computation. That I'm aware of, by Lipinski that  
20 show how these rules morph in the guidelines.

21 Q And as far as the use of the Lipinski  
22 rules, they would have been helpful to a POSA in

1 guiding the selection of properties for orally  
2 bioavailable compounds. Correct? In 2011.

3 A A POSA would have been aware of these  
4 rules, yes.

5 Q And would have found them useful in  
6 guiding their efforts?

7 A Useful? They would have found them  
8 helpful, perhaps, yes, I think a POSA, as I said,  
9 would have been aware of these rules. Wouldn't  
10 necessarily adhere to all these rules. It depends  
11 on what you're trying to achieve in your drug  
12 discovery program.

13 Q Let's turn to Paragraph 29 of your  
14 declaration.

15 A Paragraph 29. Okay, I'm there.

16 Q In Paragraph 29 you indicate that a group  
17 of scientists at a company called Celera  
18 discovered using BTKIs, Btk inhibitors such as  
19 CRA-032765, to covalently bind the kinase domain  
20 (specifically Cys481 in that domain) and could  
21 inhibit district activity.

22 Do you see where I'm reading?

1           A     I see where you're reading, yes.

2           Q     And you cite there to Exhibit 1060.

3                   Do you see that?

4           A     Yes, I see that.

5                   MR. FRAZIER: Let's go ahead and pull up  
6 Exhibit 1060 at this point.

7                   (BeiGene Exhibit 1060, previously marked,  
8 not attached.)

9           Q     And, Dr. Showalter, you recognize Exhibit  
10 1060 then as an article by Pan, et al., from 2007?

11          A     I recognize this article.

12          Q     And you understand that Pan made his  
13 discoveries through a virtual docking model using  
14 the crystal structure of the active site of Btk  
15 and the related kinase L-C-K, LCK?

16                   MS. PATEL: Objection. Form.  
17 Foundation.

18          A     So I'm aware that Pan drew from a model  
19 of these two kinases, a homology model.

20          Q     And they included in Figure 1 an  
21 illustration of how their compound would fit in  
22 the Btk binding site. Correct?

1 MS. PATEL: Objection. Form.

2 A So that -- that model, yes, shows, at  
3 least with respect to the homology model they were  
4 using, how this compound would bind into Btk.

5 Q And you understand that this picture then  
6 shows a reversible inhibitor in the binding  
7 pocket. Correct?

8 A This is a reversible inhibitor.

9 Q Right. But that then there's data in Pan  
10 that indicates that by adding a Michael acceptor  
11 to that compound, that they're able to achieve an  
12 irreversible inhibition. Correct?

13 MS. PATEL: Objection. Form.

14 Foundation.

15 A So they added a different moiety to this  
16 compound, and that moiety would have been a linker  
17 and warhead. And the linker is different from the  
18 linker shown here in Figure 1. And then, of  
19 course, as you add the warhead, it becomes even  
20 more different.

21 Q And the functional data then shows that  
22 the warhead is indeed close enough to functionally

1 and irreversible inhibit Btk. Correct?

2 MS. PATEL: Objection. Form.

3 A Would you repeat that question, please?

4 Q Right. The functional data shows that  
5 attaching the linker and warhead results in  
6 confirmation that's close enough to functionally  
7 and irreversibly inhibit Btk. Correct?

8 MS. PATEL: Objection. Form.

9 Foundation.

10 A So the data show that the molecule can  
11 form irreversibility to Btk, and specifically trap  
12 cysteine 481. But it gives no details on how  
13 structurally that occurs.

14 Q It provides you Figure 1 which shows the  
15 structure of the irreversible inhibitor, and then  
16 it makes a direct connection between that  
17 structural binding and the resulting irreversible  
18 inhibition, doesn't it?

19 A So you said irreversible inhibitor in  
20 Figure 1. You meant reversible, I think?

21 Q Let me just state that again.

22 So it provides in Figure 1 a diagram of a

1 reversible inhibitor which Pan and the co-authors  
2 then connect to the binding mode of an  
3 irreversible inhibitor. Correct?

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

6 A So one cannot speculate as to whether a  
7 pose such as shown in Figure 1 will translate into  
8 a similar pose for an irreversible inhibitor,  
9 because you're changing too many aspects of the  
10 molecule itself, the molecule that is shown here  
11 in Figure 1.

12 Q You agree that if we look at Page 2, that  
13 the document itself describes a series of  
14 irreversible inhibitors that were synthesized  
15 based on the Figure 1 confirmation. Correct?

16 A Are you referring to Table 3?

17 Is that what you're referring to?

18 Q I'm looking at below Table 2.

19 A Yes, the structures -- the series of  
20 structures from Compound 4 to Compound 13 -- or  
21 15, is that what you're referring to?

22 Q Right.

1           A     So, yes, there were a series of compounds  
2 synthesized and tested.

3           Q     I'm just looking for a section here.

4                     Right. So if we start at Page 1 carrying  
5 over on to Page 2 --

6           A     You mean Page 1 --

7           Q     You see the paragraph on Page 1 that  
8 begins, "We realized that these two kinases"?

9           A     I'm sorry, Page 1 PDF or --

10          Q     Page 1060.001. There is a number down in  
11 the bottom right-hand corner.

12          A     Yes. Okay.

13          Q     All right. If we look at Page 1060.001,  
14 there is a paragraph that begins at the bottom  
15 right-hand corner.

16                     Do you see that?

17          A     I see that.

18          Q     All right. And it refers to the idea  
19 that they could develop inhibitors based on their  
20 proposal to develop a selective inhibitor through  
21 an electrophilic center capable of irreversibly  
22 inactivating the target. Right?

1 MS. PATEL: Objection. Form.

2 A Could you actually read the specific  
3 sentence that says that?

4 Q Yeah. It goes over on to the next  
5 paragraph. So for example, it says, the last line  
6 of Page .001 going on to .002 says, "Based on  
7 sequence alignments of 491 kinases, there are only  
8 ten kinases with a cysteine at this position," and  
9 it recites all of those. And it says, "This  
10 result reinforced our initial proposal to develop  
11 a selective inhibitor for Btk through an  
12 electrophilic center capable of irreversibly  
13 inactivating the target."

14 Do you see that?

15 A Let me just -- changing pages here.  
16 "This result reinforced our initial proposal to  
17 develop a selective inhibitor for Btk through an  
18 electrophilic center capable of irreversibly  
19 inactivating the target."

20 So the result -- let's see here. Yeah, I  
21 see that.

22 Q Right. And so you understand then that

1 the authors of the Pan 2007 Exhibit 1060 used the  
2 structural information that was available as  
3 reflected in Figure 1 to design irreversible  
4 inhibitors that would place the warhead close  
5 enough to the cysteine target for the warhead, the  
6 cysteine 481, to irreversibly inhibit Btk. Right?

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

9 A So Pan states that he is aware of other  
10 kinases that have cysteine 481. And so he's --  
11 he's looking to -- he's looking to build on that  
12 information by attempting to synthesize an  
13 inhibitor that would trap cysteine 481. Realizing  
14 that there are -- relative to, you know, the whole  
15 domain of kinases, tyrosine kinase, only nine  
16 others that have that same cysteine 481 within the  
17 same -- same part of the protein structure.

18 So he's hoping -- in my view he's hoping  
19 to develop an inhibitor that will provide some  
20 selectivity.

21 Q And then he shows functionally that,  
22 indeed, he can create that inhibition. Correct?

1 MS. PATEL: Objection. Form. Asked and  
2 answered.

3 A So through experimentation he was able to  
4 generate analogs that showed good potency against  
5 Btk. But he does not show data relative to how he  
6 actually proved that he was inhibiting Btk through  
7 a Michael acceptor interaction with cysteine 481.

8 It's possible that these inhibitors could  
9 have been interacting in a reversible fashion.

10 Q Just a moment. I seem to have kicked  
11 myself out of the case view. Just a moment.

12 If you go to the top of Page 2, in the  
13 top right-hand corner.

14 A So I think I'm on the right page, is  
15 opposite the proposed binding mode figure?

16 Q Yeah.

17 A Yeah.

18 Q You see the sentence that says, "We  
19 confirm the irreversibility of these compounds  
20 using two methods," and it goes on from there?

21 A Okay. So I'll correct my prior  
22 testimony.

1                   So there was -- there was proof. I  
2 simply had forgotten these details.

3           Q       Okay. There was proof of the  
4 irreversibility?

5           A       These would be two methods of determining  
6 irreversibility.

7           Q       All right. Now, you understand then by  
8 2011 it was known that a kinase inhibitor would be  
9 more potent against kinases where it could form a  
10 covalent bond and irreversibly inhibit, as  
11 compared to a kinase lacking the cysteine where it  
12 could make only reversible interactions. Correct?

13                   MS. PATEL: Objection. Form.

14           A       So I disagree with that statement. There  
15 were, in 2011 and later, compounds -- and even  
16 today, compounds that are reversible inhibitors  
17 that are just as potent as irreversible inhibits.

18           Q       The benefit of the irreversible inhibitor  
19 here was the selectivity that was generated for  
20 the cysteine-containing kinases. Correct?

21                   MS. PATEL: Objection. Form.

22           A       So that would be a benefit. But that

1 doesn't necessarily mean it would translate into  
2 better clinical efficacy.

3 Q Well, it did translate into high-affinity  
4 binding to Btk, correct, as reflected in Table 3?

5 A As reflected in Table 3, that's a case  
6 for the number of the compounds synthesized, but  
7 not necessarily all compounds.

8 And I might note that from the -- our  
9 earlier discussions on the two references that I  
10 came across, those are examples of compounds that  
11 are what I would term adenine mimetics. So they  
12 would have a lot of similarity to the structure,  
13 the core structure, that's in Pan.

14 And, of course, those compounds that I  
15 have referred to earlier as inactive have very  
16 high IC50s. They have the linker warhead of  
17 ibrutinib. So I don't think that one can affirm  
18 that just because you have an irreversible  
19 inhibitor it is going to be more potent or more  
20 effective.

21 Q You agree that all of the irreversible  
22 inhibitors that are recited in Table 3 show

1 high -- or shall we say potent inhibition of Btk.

2 Correct?

3 A Most of these show, I would assert to  
4 have good to excellent potency, with maybe the  
5 exception of Compound 5, that's still good  
6 potency.

7 Q All right. Let's turn to Paragraph 33 of  
8 your declaration.

9 A I'm there.

10 Q And at Paragraph 33 you say -- you are  
11 referring to the Btk inhibitors generally.

12 Correct?

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

15 A Repeat that statement, please.

16 Q Let me go back up.

17 So starting at Paragraph 30, you give  
18 some general statements about Btk inhibitors.

19 Right?

20 MS. PATEL: Objection. Form.

21 A There are a number of statements being  
22 made about Btk inhibitors, yes.

1           Q     Right. And you're speaking generally,  
2     you actually say it at the beginning of Paragraph  
3     30, "Generally speaking, BTKIs can be classified  
4     into two types," and then you go on from there.

5                     Right?

6           A     I so state, yes.

7           Q     Yeah. Okay.

8                     So then going from there you say,  
9     "Certain irreversible BTKIs are generally  
10    understood to comprise four components," and then  
11    you list the four components. Right?

12          A     So the four components are the  
13    hydrophobic moiety or the back pocket moiety,  
14    heterocyclic core, a linker which occupies what's  
15    known in the art as a sugar pocket, and then a  
16    terminal warhead group that typically contains a  
17    Michael acceptor group. Those are the four  
18    components.

19          Q     Right. And you then say that "Typically  
20    the structure of the heterocyclic core is an  
21    optionally substituted fused heterocyclic ring  
22    system, for example the Z'-structure as prescribed

1 in the challenged claims."

2 Correct?

3 A So that's what I'm stating.

4 Q Right. And so that's a generalized  
5 understanding that a person of skill in the art  
6 would have had?

7 A Yes, a POSA would have that  
8 understanding.

9 Q And then you say that the principle --  
10 these principle components, going on to Paragraph  
11 33, "These principle components are interrelated,  
12 their structures and the interrelationship between  
13 them affect the pharmacological properties and  
14 functions of the Btk inhibitors, including those  
15 functions recited in the challenged claims."

16 Do you see that?

17 A I see that.

18 Q And you don't actually have a citation  
19 for that statement in particular. Correct?

20 A I do not have a citation.

21 Q So your support for that is in the  
22 following paragraphs.

1                   Is that correct?

2           A       So let's look at the following  
3 paragraphs.

4                   So we're looking at the principal  
5 components as shown in the structure of Imbruvica,  
6 which is -- this would be 1003.17.

7           Q       Right. And what I'm asking is, given the  
8 absence of a citation in Paragraph 33, are we to  
9 assume that the support for Paragraph 33 is found  
10 in Paragraphs 34 or 35, 36, and 37?

11                   MS. PATEL: Objection. Form.

12           A       Yes, those additional paragraphs provide  
13 support for the statement.

14           Q       Looking at Paragraph, I guess it's 39,  
15 spanning from Page -- Exhibit 1003.20 to 1003.21,  
16 you see at the top of Page 1003.21, the structures  
17 of Imbruvica and Brukinsa?

18           A       I'm scrolling down.

19                   So those are not the structures of  
20 Imbruvica and Brukinsa. Those represent the core,  
21 the Z', with respect to the '803 claims. Those  
22 respect -- let me back up.

1           Those represent the Z', especially the  
2 parts of those structures that are bolded.

3           Q     And I think maybe we're talking past each  
4 other. I'm looking at the two structures above  
5 Paragraph 40 that I think associate with Paragraph  
6 39.

7           A     Ah, okay.

8           Q     So spanning from Page 20 to 21.

9           A     Yeah, sorry. Those are the two  
10 structures.

11          Q     So we have there at the top of Page  
12 1003.21 the structures of Imbruvica and Brukinsa.

13                   Correct?

14          A     Those are the structures of each of those  
15 agents.

16          Q     And you agree that they are structurally  
17 very similar compounds. Correct?

18          A     I agree that they have similarities, but  
19 I would not agree that they're very similar.

20          Q     And you agree that Brukinsa is derived  
21 from Imbruvica?

22                   MS. PATEL: Objection. Lacks foundation.

1 Form.

2 A So I do not agree that Brukinsa is  
3 derived from Imbruvica. What I do agree to is  
4 that Brukinsa has some structural features that  
5 are the same as found in Imbruvica.

6 Q And that's not by chance. Right? That's  
7 the scientists who made Brukinsa were aware of the  
8 features of Imbruvica and incorporated them into  
9 Brukinsa, to your knowledge. Right?

10 MS. PATEL: Objection. Foundation.  
11 Form.

12 A So if you look in my appendix, it  
13 describes 1750-plus core modifications represented  
14 by Z' in the Markush structure of the '803 claims.  
15 1750 modifications. And those encompass, each one  
16 of those represents a different Z'.

17 So a POSA wouldn't necessarily have out  
18 of just thin air chosen the Z' for Brukinsa.

19 Q Well, I'm not talking about the Z' at the  
20 moment. It's obvious that the phenoxyphenyl, the  
21 back pocket binder, and the linker and warhead are  
22 identical between Imbruvica and Brukinsa.

1 Correct?

2 A So the linker -- scratch that.

3 The back pocket substituent is identical.

4 But the linker warhead I would submit is not  
5 identical.

6 The linker in and of itself shown in  
7 purple is a piperazine six-membered ring with  
8 nitrogen. But Imbruvica and Brukinsa attach that  
9 linker at different points of the -- attach the  
10 linker at different points of that ring system.

11 And so that is going to have implications  
12 on how the inhibitor is going to position the  
13 warhead such that it can capture cysteine 451.

14 So I disagree that the linker is the  
15 same. It is not the same. And it's also not  
16 attached in a similar fashion for each of those  
17 two compounds.

18 Q The warhead is the same. Correct?

19 A The warhead is the same.

20 Q And the warhead is attached to, I believe  
21 you said a piperazine ring, right, a six-membered  
22 ring with a nitrogen?

1           A     That is the same.

2           Q     Right. And what you're saying is  
3     different is simply the way in which it's attached  
4     to the Z' portion of the molecule. Correct?

5           A     Yes, it's different in two ways.  
6     Actually, in three ways. It's different in terms  
7     of the position of attachment onto the -- onto the  
8     linker.

9                     It's different in terms of the  
10    stereochemistry of attachment from the  
11    heterocyclic core's ring system to the linker.  
12    And it's different with respect to the position of  
13    attachment onto the core.

14                    In Imbruvica the attachment is off of a  
15    pyrazole ring, the five-membered ring. In  
16    Brukinsa the attachment is off of a six-membered  
17    ring. So I view these as markedly different  
18    compounds.

19          Q     And yet you certainly couldn't say that  
20    it's mere coincidence that the Brukinsa molecule  
21    has the same phenoxyphenyl back pocket, for one.

22                    Correct?

1 MS. PATEL: Objection. Asked and  
2 answered. Foundation. Form.

3 A So a POSA would have been aware certainly  
4 of the back pocket substituent. But a POSA  
5 wouldn't have just settled on a back pocket  
6 substituent with a Z' in mind and make one  
7 compound. A POSA would have made a whole series  
8 of compounds, including the back pocket  
9 substituent found in Imbruvica.

10 Q And all I'm getting at, Doctor, is that  
11 you raise a lot of theoretical differences, and  
12 yet these two molecules have exactly the same  
13 warhead, connected to a piperazine ring, and they  
14 have exactly the same back pocket. And that's  
15 obviously not by coincidence.

16 Do you agree with me?

17 MS. PATEL: Objection. Asked and  
18 answered. Foundation.

19 A So what I'm saying is that for these two  
20 compounds, you need to view them holistically.  
21 You need to view each compound as a sum of its  
22 parts.

1           And a sum of its parts, when viewed  
2           holistically, will -- in terms of inhibition of  
3           the enzyme in forming a covalent bond of cysteine  
4           481, will determine the bioactive confirmation  
5           such that either one of these inhibitors will be  
6           able to capture cysteine 481.

7           Q       Right. And so by saying that the  
8           molecules are the sum of their parts, you  
9           acknowledge that the structure which is the  
10          phenoxyphenyl back pocket binding portion is  
11          important to the arrangement and binding of both  
12          Brukinsa and Imbruvica in its active site.

13                 Correct?

14                 MS. PATEL: Objection. Form. Asked and  
15          answered.

16          A       So the back pocket diphenyl ether is  
17          important. It's -- in the case of both of these  
18          compounds it's necessary, but it's not sufficient.

19          Q       And likewise, the presence of the warhead  
20          attached to the piperazine ring is an important  
21          component for each of these compounds and their  
22          function as an irreversible inhibitor of Btk.

1 Correct?

2 A You need a suitable electrophile, a  
3 suitable Michael acceptor, to capture cysteine  
4 481. And it turns out in the case of these two  
5 compounds that Michael acceptor is the same.

6 Q Now, you say in Paragraph 41 that the  
7 differences in the aromaticity and saturation  
8 state of the rings, the five- and six-membered  
9 rings, would be expected to meaningfully affect  
10 the interactions with Btk. Correct?

11 A Yes, I state that.

12 Q But you don't include a citation for that  
13 statement in Paragraph 41. Correct?

14 A Yeah, I don't see a citation there.

15 Q And you agree that by 2011, by June of  
16 2011, there were many different aromatic and  
17 nonaromatic heterocyclic hinge binding scaffolds  
18 that were known to make hydrogen bonds to kinase  
19 gatekeeper residues. Right?

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

22 A So across the domain of kinase inhibitors

1 as of 2010, 2011, most, as the -- of the  
2 heterocyclic systems would have been classified as  
3 aromatic, aromatic fused systems. And a subset of  
4 those would have been -- would have been of the  
5 six-five bicyclic double-fused aromatic systems as  
6 found in Imbruvica. But very few, and I'm not  
7 aware of any, that would have been -- let me back  
8 up.

9 Imbruvica has an aromatic system of  
10 pyrazole pyrimidine, which is very similar to  
11 adenine. So, you know, one would classify that as  
12 an adenine mimetic. And a number of other  
13 inhibitors in the literature at that point would  
14 have been adenine mimetics.

15 But I'm not aware of any that would have  
16 been what we call an aro aromatic, nonaromatic  
17 type system.

18 In this case the aromatic part of  
19 Brukinsa is the pyrazine ring, and the nonaromatic  
20 part is the piperazine ring.

21 Q Let's look at Exhibit 1052.

22 (BeiGene Exhibit 1052, previously marked,

1 not attached.)

2 A Okay, I'm there.

3 Q And Exhibit 1052 you recognize as a 2008  
4 article by Ghose, et al.?

5 A I recognize that.

6 Q Right. And that's an article that you  
7 selected and relied on in preparing your  
8 declaration?

9 A That's a very -- yeah, that's a very  
10 important article from 2008.

11 Q And according to the Ghose article, there  
12 were known many different types of hinge binding  
13 scaffolds that could form appropriate hydrogen  
14 bonds with the kinase molecules. Correct?

15 MS. PATEL: Objection. Foundation.  
16 Form.

17 A So Ghose shows a big list of the kinases  
18 which had been crystallized. So these are kinases  
19 that were crystallized without a ligand. Okay?  
20 So these are so-called apo crystal structures, no  
21 ligand. And these are -- these crystal structures  
22 encompass a wide range of kinases as of 2008.

1                   Interestingly enough, he doesn't include  
2                   Btk in this list.

3                   Q       And then also included are structures of  
4                   a large number of cores and kinase inhibitors that  
5                   would, in fact, create what he refers to as the  
6                   gk+3 and gk+1 hydrogen bonds. And I'm looking for  
7                   example at Table 3.

8                   MS. PATEL: Objection. Form.

9                   A       So I'm looking at Table 3 also.

10                  Q       And so Table 3 shows the structures of  
11                  many different inhibitor molecules that are  
12                  capable of hinge binding and making appropriate  
13                  hydrogen bonds with what Ghose describes as the  
14                  gatekeeper gk+3 and gk+1. Correct?

15                  MS. PATEL: Objection. Form.

16                  A       So just a little more clarity on the  
17                  nomenclature. Gk means gatekeeper. So gk+1 would  
18                  be the amino acid residue next to the gatekeeper.  
19                  So these are really looking at hydrogen bond  
20                  patterns to both the residue next to the  
21                  gatekeeper and then the residue that's three amino  
22                  acids from the gatekeeper.

1                   And so he shows -- yes, he shows a number  
2 of structures.

3           Q       Right. And those structures include  
4 structures that have nonaromatic heterocycles.  
5 Correct?

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

8           A       So let me -- let me just scroll down here  
9 on this list, and we can talk about any examples  
10 with nonaromatics. Let's see.

11                   So in Table 2 he doesn't show any  
12 examples with nonaromatics, as far as I can tell.

13           Q       I was focusing on Table 3. Can you  
14 review that.

15           A       Table 3. Okay.

16                   So the first nonaromatic that I see in  
17 Table 3 is Structure 30. My comment on that is  
18 that that structure is far removed from the  
19 structural limitations of the '803 Markush  
20 structure.

21                   There may be others further down.  
22 Thirty-one -- 31 is nonaromatic, has a nonaromatic

1 moiety. And there's others. But by and large,  
2 there are almost no -- there are no structures  
3 which have any resemblance in terms of their core  
4 structure to either Imbruvica or Brukinsa.

5 Q You agree that the structure 33 also has  
6 a nonaromatic component that makes part of the  
7 hydrogen bonding to those gatekeeper adjacent  
8 residues?

9 MS. PATEL: Objection. Form.

10 A Thirty-three is shown -- shows a  
11 bicyclic, six-six bicyclic ring system, not a  
12 six-five as you would see in Brukinsa.

13 And interestingly enough, it's hard to  
14 derive information because he designates one  
15 position as A. What is A? That doesn't -- that's  
16 not very helpful in terms of whether this forms  
17 the hydrogen bonding pattern that he shows.

18 Q And any others in Table 33 that you could  
19 characterize as having nonaromatic components in  
20 the portions that bind to the gk+3 and gk+1 cites?

21 A So just scrolling down here, 37 is  
22 nonaromatic. Thirty-nine would be also classified

1 as nonaromatic. Forty-two -- or 43 is a very  
2 bizarre structure, and it appears that he's not  
3 showing any hydrogen bonds being formed to the  
4 hinge region with this compound. There's no  
5 heterocycles that the -- that the graphic there is  
6 pointing to.

7 So I think that's it for 43.

8 Q Okay.

9 A So there's not -- there's very little  
10 learning here with respect to forming hydrogen  
11 bonding patterns to nonaromatic moieties that a  
12 POSA would be able to extrapolate to a structure  
13 such as Brukinsa.

14 Q All right. Let's put that one aside for  
15 now.

16 MS. PATEL: Counsel, it's been about an  
17 hour. I don't know if you want to take a break  
18 before you turn to another exhibit.

19 MR. FRAZIER: Oh, we can. I was about to  
20 switch gears, so sure.

21 MS. PATEL: All right. Great.

22 (A recess was taken.)

1 BY MR. FRAZIER:

2 Q Let's turn to a document that is Tab 9.

3 MR. FRAZIER: If we could pull that one  
4 up and put it in the chat as well. It's an  
5 article by Guo from 2023.

6 (Showalter Deposition Exhibit 2 marked  
7 for identification and is attached to the  
8 transcript.)

9 Q Dr. Showalter, if you would let me know  
10 when you have a copy of this.

11 A So I have this. It's uploaded.

12 Q And so the document that we've marked as  
13 Showalter Exhibit 2, are you familiar with this?

14 A I am not familiar with this article. I  
15 don't recall seeing it. If I saw it, I didn't --  
16 I didn't look at it in depth.

17 Q I just wanted to -- we're not going to go  
18 through it in detail, but there are just a couple  
19 of things. I wanted to start with just Figure 1,  
20 because it illustrates the approved irreversible  
21 Btk inhibitors.

22 Do you see that on Page 4026?

1           A     4026? Yeah, I see that.

2           Q     And it shows the five approved  
3     irreversible Btk inhibitors. And you see that in  
4     the sentence right below Figure 1, it actually the  
5     first word of the sentence is on the prior page.  
6     It says, "Although these inhibitors show excellent  
7     efficacy, suboptimal kinase selectivity leads to  
8     some adverse events such as skin rash and diarrhea  
9     (well established for the EGFR inhibitors) or  
10    platelet dysfunction (shown for TEC and SRC  
11    kinases). These off-target activities may be  
12    acceptable for cancer treatment due to the severe  
13    nature of the disease and limited time frame of  
14    the treatment."

15                Do you see that?

16          A     I see that.

17          Q     And you agree that in considering the  
18    safety and off-target effects of a molecule, one  
19    would have to account for the severity of the  
20    disease that's being treated?

21          A     That's my understanding.

22                MS. PATEL: Objection. Objection.

1 Scope.

2 Q And you understand that these five  
3 modules are, in fact, the approved irreversible  
4 Btk inhibitors as of 2023?

5 A I recognize certainly the first four.  
6 I'm not as familiar with -- I'm familiar with  
7 Structure 5. I'm not familiar with its approval  
8 status, tirabrutinib. But it's in my report. It  
9 is an approved agent, yes.

10 Q And you've specifically analyzed in this  
11 case ibrutinib and zanubrutinib. Correct?

12 A I have analyzed those two in my  
13 declaration.

14 Q And have you also considered  
15 acalabrutinib binding?

16 A So I'm familiar with acalabrutinib as  
17 another agent that treats various cancers,  
18 especially B cell type cancers. And I'm familiar  
19 with the fact that its core structure is related  
20 to the core structure of ibrutinib. It's an  
21 adenine mimetic. And I'm familiar with the fact  
22 that it has good clinical effects when -- for

1 cancer patients.

2 Q And you agree that all five approved Btk  
3 inhibitors have similar hinge binding to ATP?

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

6 A I'm not aware of the hinge binding  
7 pattern of Structure 4. It's a monocyclic core  
8 region. So I don't know how that binds to the  
9 hinge.

10 Q But you then agree that at least  
11 Compounds 1, 2, 3, ibrutinib, acalabrutinib, and  
12 zanubrutinib, all have similar hinge binding,  
13 similar to ATP?

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

16 A So they have some similar binding  
17 patterns to the hinge region, but not necessarily  
18 the exact same binding patterns.

19 Q And their similarities are similar to the  
20 hinge binding of ATP. Correct?

21 MS. PATEL: Objection. Foundation.  
22 Form.

1           A     For the most part, to the extent I know  
2     all the hinge binding -- the hinge binding found  
3     in acalabrutinib, I would say yes, they have  
4     similar hinge binding patterns to ATP.

5           Q     So then if you go down to the bottom of  
6     the first column, you see where it says,  
7     "Moreover, five approved Btk inhibitors all have  
8     similar hinge binding to ATP."

9                     You agree with that statement. Correct?

10          A     Where are you -- where are you?

11          Q     The bottom of Page 426, 4026, on the  
12     left-hand column.

13                     You see there's a sentence that says,  
14     "Moreover, five approved Btk inhibitors all have  
15     similar hinge binding to ATP," and then it goes on  
16     from there.

17          A     Okay.

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

20          A     I see that sentence.

21          Q     And you have no reason to quarrel with  
22     it?

1 MS. PATEL: Same objections.

2 A So -- excuse me. So based on the Ghose  
3 article, I think I could agree with this  
4 statement.

5 Q Let's turn, if we could, to Exhibit 1076.  
6 (BeiGene Exhibit 1076, previously marked,  
7 not attached.)

8 Q Do you have Exhibit 1076 in front of you,  
9 Mr. Showalter?

10 A I just launched the document.

11 Q Just let me know when you have it.

12 A Yeah, I have it.

13 Q And you recognize Exhibit 1076 as a 2021  
14 article by Zhang, et al. And this is also one  
15 that you cited in your declaration. Correct?

16 A This has been cited.

17 Q And if you look at -- if I can refer you  
18 to Page 1076.005.

19 A Okay, I'm on that page.

20 Q You agree, then, with the statement that  
21 says, "To mimic the intermolecular interactions  
22 between ATP, adenine, and the hinge region, all

1 Btk inhibitors possess a heterocycle core to  
2 maintain similar" action -- "interactions with the  
3 hinge residues."

4 I'm reading right at the end of the first  
5 paragraph of Section 2.2, if that's helpful.

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

8 A So I agree with that statement to some  
9 degree.

10 I don't agree that they maintain -- the  
11 key word here is similar interactions. They can  
12 be different.

13 Q You agree that zanubrutinib is mimicking  
14 the interaction of ATP or adenine?

15 MS. PATEL: Objection. Foundation.  
16 Form.

17 A So as I recall from the crystal structure  
18 which was determined I believe around 2015 of  
19 Brukinsa with Btk, it showed similar but not the  
20 same hydrogen bond donor interactions with the  
21 hinge region as ATP.

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

1 declaration, if we could.

2 A Okay, I'm back.

3 Q And you talk there about substitutions  
4 that can also impact the aqueous solubility of a  
5 Btk inhibitor, thereby affecting its other  
6 pharmacological properties such as  
7 bioavailability.

8 Do you see that?

9 A So which -- which page are we on?

10 Q I'm sorry, Paragraph 45.

11 A So read that again, please?

12 Q Yeah. So Paragraph 45 says,  
13 "Additionally, the substitutions can also impact  
14 the aqueous solubility of a Btk inhibitor, thereby  
15 affecting its other pharmacological properties,  
16 such as bioavailability."

17 Do you see that?

18 A I see that.

19 Q And so you refer to two things in support  
20 of that statement. One is Exhibit 1005, Paragraph  
21 69. And that's Dr. Rosen's declaration?

22 A Okay. Yeah.

1 Q Let's just look at that.

2 MR. FRAZIER: If we can pull up Exhibit  
3 1005.

4 (BeiGene Exhibit 1005, previously marked,  
5 not attached.)

6 A So I have pulled it. I have pulled it  
7 up.

8 Q Okay. If you look at Exhibit 1005, Page  
9 33, it's .0033. And going on to Page .034, this  
10 is Dr. Rosen's statement that you're citing there  
11 in your Paragraph 45.

12 A 033, 034. And you're starting with which  
13 paragraph?

14 Q Sixty-nine, which is the paragraph you  
15 cite.

16 A Okay. So let me read that paragraph.

17 Q Okay.

18 A "For example, I understand from  
19 Dr. Showalter's declaration that Brukinsa and  
20 Imbruvica have different Z'-structures, including  
21 their substitution patterns. I also understand  
22 from Dr. Showalter's declaration that the

1 substitution pattern of the Z'-structure impacts a  
2 BTKI's solubility. The solubility of the drug,  
3 the solution, and its GI permeability are  
4 essential factors that control the amount of  
5 absorption and absorption speed, along with the  
6 bioavailability of the drug. A necessary factor  
7 involved in absorption after a drug's oral  
8 administration is the aqueous solubility of the  
9 therapeutics. This demonstrates that the  
10 Z'-structure impacts the pharmacological  
11 properties of BTKI."

12 Q So when you say it affects -- the aqueous  
13 solubility affects the pharmacological properties  
14 of the drug, you simply are referring to  
15 absorption and drug bioavailability?

16 MS. PATEL: Objection. Form.

17 A So a drug needs to be -- when orally  
18 administered, needs to be absorbed in the gut. So  
19 physicochemical aspects of a drug, that  
20 "physicochemical," meaning structural features  
21 that relate to drugability, are very important.  
22 And if you get -- you have to have absorption

1 through the gut before you are going to be  
2 bioavailability, so that's important.

3 Q But there is a wide range of solubility  
4 that will allow for those features. Right?

5 A So there is not necessarily a wide range  
6 of solubilities. You would have to determine  
7 solubilities, of course, through experimentation.  
8 And based on that, plus you would also need to do  
9 what's called permeability experiments. So those  
10 two experimental -- types of experiments will give  
11 you some estimate of whether a drug is going to be  
12 orally -- bioavailable orally.

13 Q But the -- as you indicate, Imbruvica is  
14 practically insoluble in water, and yet it's an  
15 effective oral compound. Right?

16 MS. PATEL: Objection. Form.

17 A So a compound can be -- can have poor  
18 solubility in water. It does not necessarily  
19 preclude it from being a good clinical agent. It  
20 just means you've got to -- you've got to play  
21 more games, if you will, in terms of making that  
22 compound have oral bioavailability.

1                   This gets into something I don't want to  
2 elaborate on, but it gets into formulation  
3 studies.

4           Q     All right. If we go to Paragraph 51.

5           A     So this is still Rosen?

6           Q     No. I'm sorry. Paragraph 51 of your  
7 declaration, going back to Exhibit 1003.

8           A     Okay. So I'm reading it.

9           Q     You say that, "In fact Imbruvica and the  
10 other BTKIs (except Brukinsa) comprise a core that  
11 mimics adenine."

12                   But Brukinsa also has a core that mimics  
13 adenine. Right?

14                   MS. PATEL: Objection. Form. Asked and  
15 answered.

16           A     So we've discussed this before. I think  
17 I answered in the nonaffirmative.

18           Q     I think you said that the binding between  
19 Brukinsa and adenine, that they were similar but  
20 not identical, was what I had understood you to  
21 say.

22                   Do you agree with that?

1           A     Would you repeat your statement?

2           Q     Yes. I thought I had understood you to  
3 say that the binding of Brukinsa and adenine are  
4 similar, albeit not identical.

5           A     So you mean the heterocyclic binding to  
6 the hinge region is similar?

7           Q     Correct.

8           A     I wouldn't -- I wouldn't say that the  
9 binding actually of those two compounds are  
10 similar. I would say within the hinge region.  
11 The binding has more to do than just with the Z'  
12 core, overall binding to Btk.

13          Q     You agree that Brukinsa is, in fact,  
14 mimicking adenine in its binding. Correct?

15               MS. PATEL: Objection. Asked and  
16 answered. Form.

17          A     Brukinsa does not exactly mimic adenine.  
18 Some of the -- some of the binding, some of the  
19 hydrogen bond donor acceptor interactions, are the  
20 same, but some are not the same.

21          Q     And so based on the fact that it has some  
22 that are the same and some that are not the same,

1       you're concluding that it does not mimic adenine?

2           A       It does not exactly mimic adenine.

3           Q       You're adding the word "exactly" to your  
4       statement in Paragraph 51.

5                   Is that correct?

6           A       Let's scratch "exactly," and let's just  
7       say it does not mimic adenine.

8           Q       You told me a few different things.  
9       Final answer, does it mimic adenine or does it not  
10      mimic adenine?

11          A       It does not mimic adenine in all of  
12      the -- in its hydrogen binding properties.

13          Q       But it's very similar because it shares  
14      certain hydrogen binding properties. Right?

15                  MS. PATEL: Objection. Objection. Asked  
16      and answered.

17          A       It depends. It depends what you mean by  
18      "similar."

19          Q       Well, for example, we looked at the Guo  
20      article from 2023. Right? And it said that all  
21      five approved Btk inhibitors have similar hinge  
22      binding to ATP. Right?

1                   So all of them are similar, and all of  
2                   them are mimicking adenine. Right?

3                   MS. PATEL: Objection. Asked and  
4                   answered.

5                   A        So I think I've addressed that question  
6                   already.

7                   Q        Your counsel is just wasting time by  
8                   saying "asked and answered." You actually have to  
9                   answer my questions.

10                  And so the question was, you agree that  
11                  all five approved Btk inhibitors all have similar  
12                  hinge binding to ATP. Correct?

13                  MS. PATEL: Same objections.

14                  A        They all form interactions with the hinge  
15                  region, and those interactions include binding to  
16                  the g+1 as described by Ghose, and g+3. But some  
17                  of them also involve binding to the gatekeeper  
18                  residue creatinine 474. So there are some same  
19                  interactions with the residues along the -- along  
20                  the hinge, but there are some that are different.

21                  Q        You understand that Guo 2023 article was  
22                  published by BeiGene. Right?

1 MS. PATEL: Objection. Foundation.

2 Form.

3 A You just showed that to me. I didn't  
4 even look at where it came from.

5 Q Yeah. Do you want to go back to that?  
6 It's Showalter Exhibit 2. If you still have that  
7 in front of you, maybe we could just --

8 A I don't. I already closed it.

9 Q I will represent to you that the Guo 2023  
10 article was published by BeiGene. And it says  
11 five approved Btk inhibitors all have similar  
12 hinge binding to ATP.

13 Do you agree or disagree with that  
14 statement?

15 A So it depends. Again, it depends on your  
16 definition of "similar."

17 As I have just testified to, some are  
18 similar, but some are dissimilar.

19 Q Okay. Let's go back to your declaration  
20 at Paragraph 57.

21 A Okay.

22 Q In Paragraph 57 you talk about it being

1 critical that Btk has the proper bioactive  
2 orientation?

3 A Yes, I discuss that.

4 Q And -- but you don't provide any  
5 citations in Paragraph 57 for the opinions that  
6 are discussed. Correct?

7 A I do not provide any citations.

8 Q All right. You agree that by 2011 it was  
9 known that the Cys481 amino acid in the Btk  
10 binding site is solvent exposed?

11 MS. PATEL: Objection. Foundation.  
12 Form.

13 A Repeat that question, please?

14 Q Do you agree that by 2011 a POSA would  
15 have understood that the Cys481 is solvent  
16 exposed -- is a solvent exposed moiety?

17 MS. PATEL: Same objection.

18 A I can't answer that question. I don't  
19 remember.

20 Q Let's go back to the Marcotte  
21 publication. Well, strike that. Since you didn't  
22 cite Marcotte, so I'll move on.

1                   Can you pull up the Pan article, which is  
2                   your Exhibit 1060.

3                   A       Okay, I have the Pan article on my  
4                   desktop.

5                   Q       And if we turn then to Table 3 in Pan,  
6                   which we looked at before, which is the various  
7                   linker warhead combinations and their resulting  
8                   Btk inhibition activity.

9                   Do you see that?

10                  A       I see those.

11                  Q       And you agree with me that in -- for  
12                  example, Compounds 11 and 12 and 13 and 14 show  
13                  that the particular standard of chemistry  
14                  orientation does not substantially alter the Btk  
15                  inhibition of the compounds?

16                  MS. PATEL: Objection. Lacks foundation.  
17                  Form.

18                  A       So I would agree in the context of the  
19                  data presented here that the stereochemical  
20                  orientation does not have a major impact.

21                  But that's -- this data is -- has to be  
22                  viewed in the context that we're looking at a

1 single core, single Z' relative to the '803 claim  
2 section. We're looking at a single core.

3 Q Within the orientation that was presented  
4 in the Pan publication, a POSA would conclude that  
5 those -- that the stereochemistry differences  
6 between Compounds 11 and 12 and between Compounds  
7 13 and 14 don't substantially alter the potency.

8 Right?

9 MS. PATEL: Objection. Form.  
10 Foundation. Asked and answered.

11 A So a POSA would conclude that with the  
12 pyrrolo pyrimidine core structure found in  
13 Imbruvica for these sets of substituents, linker  
14 warhead substituents that were evaluated, that the  
15 stereochemistry off of the core is not producing  
16 major differences in IC50 values.

17 That's all -- I think that's all a POSA  
18 could conclude.

19 Q Let me jump to then Paragraph 59 in your  
20 declaration. So if we go back then to Exhibit  
21 1003.

22 A Okay, I'm there.

1           Q     And in 1003 you cite to an article which  
2     is Exhibit 1044.

3           MR. FRAZIER:   If we can look at that one  
4     now as well.

5           (BeiGene Exhibit 1044, previously marked,  
6     not attached.)

7           A     Okay, I have launched the article.

8           Q     So you recognize Exhibit 1044 as a 2021  
9     article by Brullo, et al?

10          A     I recognize that.

11          Q     And as we indicated, this is one that you  
12     cited in your declaration.   Right?

13          A     It's -- yes, it's been cited.

14          Q     And you agree then that on the basis of  
15     the crystallographic data, ibrutinib and  
16     zanubrutinib share similar bioactive conformations  
17     within wild-type Btk binding site?

18          MS. PATEL:   Objection.   Form.

19          A     So again, it depends on what you mean by  
20     "similar."

21          Q     I'm just asking if you agree or disagree  
22     with the statement.

1 MS. PATEL: Objection. Form.

2 A So overall I disagree with the statement.

3 Q Okay. If you look at the bottom of Page  
4 1044.003?

5 A Okay.

6 Q You see in this article by Brullo that  
7 you cited in your declaration they say, "On the  
8 basis of the crystallographic data available,  
9 ibrutinib and zanubrutinib share similar bioactive  
10 conformations within the wild-type Btk binding  
11 site."

12 Do you see that?

13 A Where is that statement?

14 Q At the very bottom of Page 1044.03, below  
15 where it says Approved Btk Inhibitors. It's about  
16 six lines up from the bottom, beginning, "On the  
17 basis of"?

18 A I see this.

19 Q So that's how Brullo, et al.,  
20 characterized the bioactive confirmations of  
21 ibrutinib and zanubrutinib as similar within the  
22 wild-type Btk binding site. Correct?

1           A     So that's their conclusion. My  
2 conclusion is not the same as their conclusion.

3           Q     Okay. If we go to your Paragraph 60 then  
4 in Exhibit 1003.

5           A     Paragraph 60. Okay. Let me back up  
6 here.

7                     Okay, I'm there.

8           Q     So in Paragraph 60 you describe the  
9 active site of the Btk kinase. Right?

10          A     So that's -- that's the description  
11 that's there.

12          Q     And the active site of Btk is where ATP  
13 binds. Correct?

14          A     That's a well-known fact.

15          Q     Now, if we go back to Exhibit 1052, which  
16 was the Ghose article that we were looking at  
17 earlier, if you still have that one around.

18          A     I'll have to pull it up again.

19          Q     Sure.

20          A     You're referring to the 2008 J Med Chem  
21 article?

22          Q     That's correct, Exhibit 1052.

1           A     Okay. I have pulled that up.

2           Q     All right. And if you look at Page 002.

3           A     Okay, I'm there.

4           Q     And you see that in 2008 Ghose described  
5     that -- how understanding of the ATP binding site  
6     compressed into 2D is very helpful since medicinal  
7     chemists do and will continue to use simple  
8     sketched structures either on paper or computer to  
9     conceive of and design new inhibitors.

10                  Do you see that?

11          A     I don't. Could you direct me to where.

12          Q     I'm sorry. Yeah. It's on the right-hand  
13     column in the second full paragraph beginning, "An  
14     understanding of the ATP binding site."

15          A     Okay, I'm there. Let's look at it again.

16          Q     Go ahead and read it. It says, "An  
17     understanding of the ATP binding site compressed  
18     into 2D is very helpful since medicinal chemists  
19     do and will continue to use simple sketched  
20     structures either on paper or a computer to  
21     conceive of and design new inhibitors."

22                  Do you understand that that was certainly

1 something that a POSA would be aware of by 2011.

2 Correct?

3 A Yes, a POSA would have been aware of  
4 this.

5 Q And then also of the next sentence in  
6 that same paragraph where Ghose, et al., say, "It  
7 is therefore very practical to introduce a  
8 simplified 2D schematic of the active site, see  
9 Figure 2, for the purpose of visualizing the  
10 binding poses of various kinase inhibitors."

11 Do you see that?

12 A Yes, I see that.

13 Q And that's also something that a POSA  
14 would have been aware of by 2011. Right?

15 A A POSA would have been aware of this,  
16 yes.

17 Q And therefore he concludes at the end of  
18 that, the next paragraph at the end of that  
19 column, "The high degree of structural similarity  
20 of the ATP binding site and the presence of key  
21 interaction sites for ligand recognition lend  
22 itself to an informatics-driven analysis of

1 protein ligand interactions across the kinome."

2 Do you see that?

3 A So let me read this again. Structural  
4 similarity of the ...

5 Yes, I see that.

6 Q So what Ghose is referring to there is  
7 the use of an informatics-driven analysis as a way  
8 of understanding and predicting protein ligand  
9 interactions across protein kinases. Right?

10 MS. PATEL: Objection. Form.

11 A So this is -- this is what he states.

12 Q And you agree that the active site in  
13 kinases including Btk is a conserved region.

14 Correct?

15 A So it's known in the science of protein  
16 kinases that, yes, the active site has a degree,  
17 it has conserved -- conserved amino acid residues.

18 Q And Btk, for example, belongs to the  
19 large kinases family known to have conserved  
20 active sites. Right?

21 A So I'm not an expert on the structural,  
22 actual structural aspects of protein kinases.

1 That's more in the realm of a protein chemist, but  
2 that is my understanding.

3 Q Okay. And if we look on that same page  
4 of the Ghose article, if you look at Figure 2,  
5 Figure 2 is describing the general features of the  
6 conserved ATP binding site in the kinases.

7 Correct?

8 A So that's the description which is  
9 portrayed.

10 Q Right. And one of the features that's  
11 portrayed there in the bottom right-hand corner is  
12 the hydrophobic pocket.

13 Do you see that?

14 A I see that.

15 Q And by 2011 the developers of kinase  
16 inhibitors understood that including a moiety that  
17 could occupy the back pocket on a kinase inhibitor  
18 would contribute to the inhibitor's selectivity  
19 and potency. Right?

20 MS. PATEL: Objection. Form.

21 A So I think there was -- at that point  
22 there was sufficient advancement in the state of

1 the art of protein kinases that a POSA would  
2 understand that the back pocket would contribute  
3 certainly to potency and possibly also to  
4 selectivity.

5 Q Let's look also then at Paragraph 2 -- or  
6 at -- yeah, the same page here, at Exhibit 1052,  
7 Page.002. You see the heading that says Kinase  
8 ATP Binding Site As a Target For Ligand Design?

9 A Yes, I see that.

10 Q And you agree that certainly by 2011 it  
11 was understood that the kinase hinge region  
12 usually has one hydrogen donor and two hydrogen  
13 acceptors?

14 A Repeat your statement, please.

15 Q Yeah. That it was understood certainly  
16 by 2011 that the kinase hinge region usually has  
17 one hydrogen donor and two hydrogen acceptors?

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

20 A One -- yeah, the hydrogen -- sorry, the  
21 hinge region has one hydrogen bond donor and two  
22 acceptors, is that your --

1 Q Right. Right.

2 A So the hinge region would have at least  
3 one of those. It could also have another hydrogen  
4 bond acceptor which would be the gatekeeper  
5 residue itself.

6 Q So looking at the second paragraph under  
7 that heading Kinase ATP Binding Site As a Target  
8 For Ligand Design, it's on the left column of Page  
9 2.

10 A Yes.

11 Q Do you see it says there, The ATP binding  
12 site is a narrow hydrophobic pocket located  
13 between the two lobes which are linked by a  
14 flexible hinge region. The hinge region usually  
15 has one hydrogen donor flanked by two hydrogen  
16 acceptors derived from the protein backbone.

17 Do you agree with that?

18 A So the key word here is "usually," but  
19 not always. And it depends on -- I'll just make  
20 another statement. Not all hinge regions have the  
21 same residues, so that will dictate whether he  
22 would have -- whether this statement is valid.

1           Q     Let's look also at the -- at Exhibit  
2     1073.  If we could pull that one up.

3                     (BeiGene Exhibit 1073, previously marked,  
4     not attached.)

5           A     Okay, I have it on my desktop.

6           Q     And you recognize Exhibit 1073 as an  
7     article by Uckun and Qazi from 2010?

8           A     Yes, I recognize that.

9           Q     And it is also one that you cited and  
10    relied on in your declaration?

11          A     I did.  I did rely on this publication.

12          Q     And if we look at Page 2, so 1073.002.

13          A     Okay.

14          Q     So this actually carries over from the  
15    prior page.  Where it says, "Figure 1B shows a  
16    model of the ternary complex of Bruton's tyrosine  
17    kinase."

18                     So I'm looking at the left-hand column  
19    going from Page 1 on to Page 2.

20          A     Okay.

21          Q     You see it says, Figure 1C is a schematic  
22    illustration of the active site?

1           A     Figure 1C. Let me look at.

2                     Okay. I see Figure 1C.

3           Q     And there -- and it says that "There are  
4     two hydrogen acceptors and one hydrogen donor from  
5     the backbone carbonyl and amide groups of the  
6     hinge region, potentially forming hydrogen bonds  
7     with the inhibitors (as indicated by arrows in B)  
8     which align with the ATP-binding cleft to  
9     determine the orientations of protein kinase  
10    inhibitors."

11                    Do you see that?

12          A     Let me go back up to the statement.

13                    And where did you quote that statement?

14          Q     It is right there at below the box on the  
15    left-hand column, right above where it says Btk,  
16    that whole paragraph.

17          A     Okay.

18          Q     So you agree then that by 2011 a POSA  
19    would have understood that Btk itself has two  
20    hydrogen acceptors and one hydrogen donor, similar  
21    to other kinases. Right, in the hinge region?

22                    MS. PATEL: Objection. Objection. Form.

1           A     This -- this figure is a little bit  
2     confusing. It's showing three residues here, and  
3     it doesn't indicate what those residues are.

4           Q     You're looking at Figure 1C?

5           A     I'm looking at 1C. It would be helpful  
6     if they actually indicated what these residues are  
7     in the hinge region, whether, you know, it's as --  
8     as per Ghose definitions, as whether these are  
9     gk+1 or gk+2, 3. Okay? Because the way it's --  
10    this figure is shown here, you might interpret  
11    this to be gk+1 and gk+2. Ghose doesn't talk  
12    about any gk+2s.

13          Q     Well, certainly the sequence of Btk was  
14    known by 2011. Correct?

15          A     The sequence of Btk was known by 2011.  
16    So these are very generic -- it's a very generic  
17    schematic, Figure 1C. And so it leads me to some  
18    confusion as to which residues are actually  
19    forming hydrogen bonds.

20          Q     You see that Figure 1C is there in the  
21    context of Figure 1A and 1B, and 1B actually does  
22    include more details on the particular residues

1 involved?

2 A Uh-huh.

3 Q 1C is just a schematic.

4 A So 1A and 1B, these are very difficult,  
5 at least for me, to ascertain what these residues  
6 actually are. Especially in 1B.

7 Q Presumably you were able to read and  
8 understand it when you cited it in the  
9 declaration, though?

10 A So let me blow this -- blow this up  
11 maybe.

12 Okay. I can see the residues now. D  
13 would be -- D -- I'm just looking here. D521,  
14 that's not -- am I reading it right?

15 I'm looking for a glutamic acid residue  
16 in the hinge region. And many of this is a matter  
17 of numbering. So there is a glutamic acid I see  
18 here, which is, as I can read it, 521. And then  
19 next to that should be a tyrosine residue. So  
20 that would correspond to gk+2 in Ghose  
21 nomenclature.

22 And then there would be a methionine next

1 to that, that would be the sequence.

2 So based on my general knowledge of hinge  
3 region residues, I would have had certainly some  
4 understanding of 1C.

5 Q Okay. Great. And so you agree that by  
6 2011 it was known that the adenine of the kinase's  
7 ligand ATP forms the hydrogen bonds with the  
8 kinase hinge region, that was something that was  
9 understood by a POSA?

10 A That was well established.

11 Q Okay. Going back then to what a POSA  
12 would understand about inhibitors within the --  
13 within the hinge region. We agree then that in  
14 general most kinase inhibitors would have been  
15 expected to form two and some even three hydrogen  
16 bonds with the hinge region involving one hydrogen  
17 acceptor flanked by one or two hydrogen donors?

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

20 A So a POSA would -- a POSA would be  
21 knowledgeable about hinge region binding patterns  
22 from x-ray crystallography data. That would --

1 that would have been the best source of  
2 understanding what these hinge region binding  
3 patterns actually look like.

4 Q All right. If you go back to Exhibit  
5 1052, which is the Ghose article, again.

6 A Okay, I am back at the Ghose article.

7 Q Actually, I take that back. Maybe we'll  
8 jump ahead here. Sorry. All right. Let's look  
9 at Exhibit 1053, if we could.

10 A Okay. I'll need to bring that up.

11 Okay. I have launched the article.

12 Q So if we look at Figure 3 of Exhibit  
13 1053, I think this is what you were referring to  
14 previously that there was an error in the  
15 declaration, but I just want to clarify.

16 For zanubrutinib, which are the hydrogen  
17 bond donors and which are the hydrogen bond  
18 acceptors? And if it's helpful, we can look at  
19 Paragraph 61 of your declaration, is where you  
20 discuss this.

21 A Yeah. So I think it depends on the x-ray  
22 crystallography data for Brukinsa.

1           One crystal structure shows that there's  
2   two hydrogen bond donors that you attribute to the  
3   NH<sub>2</sub> of the amide, and then there's one hydrogen  
4   bond acceptor attributed to the carbonyl of the  
5   amide.

6           Q     And focusing on Figure 3, which you have  
7   reproduced in your declaration at Paragraph 61  
8   then, the connection there that you're referring  
9   to, the donor is the red that's at the top? You  
10   put a box around the relevant section in your  
11   declaration. Correct?

12          A     Let me go back to my declaration.

13          Q     Yeah, if you can just compare.

14          A     So where are we in the declaration?

15          Q     The declaration at Paragraph 61 on Page  
16   32. I'm sorry. It's Exhibit 1003, .035.

17          A     Yes. And let me correct the record. I  
18   misspoke. There is also a hydrogen bond donor  
19   function in Brukinsa, that is the six-membered  
20   ring that's NH, a six-membered ring.

21          Q     Right.

22          A     That's fused to the pyrazole. There's

1     also a hydrogen bond there. So depending on the  
2     interpretation of the x-ray crystallography data,  
3     there's either two or three hydrogen bonds.

4           Q     And specifically in the hinge region  
5     here, it's identifying two hydrogen -- in Btk two  
6     hydrogen bond acceptors and one donor from the  
7     perspective of Btk.

8                     Is that correct?

9           A     That's what the x-ray crystallography  
10    data shows.

11          Q     Okay. Great. Let's go to Paragraph 63  
12    in your report.

13          A     Okay, I'm there.

14          Q     And Paragraph 63 you say, Based on the  
15    same crystallography data -- well, you ultimately  
16    conclude in Paragraph 63 that Exhibit 1044  
17    supports that Imbruvica and Brukinsa have  
18    different hydrogen bond formation patterns with  
19    Btk. Correct?

20          A     That's what's stated.

21          Q     And we were looking -- I think we looked  
22    at 1044 earlier. Right. And so your conclusion

1 is different than the article that you cite, this  
2 Exhibit 1044 by Brullo, in that Brullo says on the  
3 basis of the crystallographic data available,  
4 ibrutinib and zanubrutinib share similar bioactive  
5 conformations within the wild-type Btk binding  
6 site.

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

9 Q And that -- yeah, that's on -- that's on  
10 again Exhibit 1044, Page 003.

11 A I lost you there. Could you --

12 Q So I'm just comparing -- so at Paragraph  
13 63 of your report, you conclude that Exhibit 1044  
14 supports that Imbruvica and Brukinsa have  
15 different hydrogen bond formation patterns with  
16 Btk. And that's your conclusion.

17 But the conclusion of the article itself  
18 is that ibrutinib and zanubrutinib share similar  
19 bioactive conformations within the Btk binding  
20 site.

21 MS. PATEL: Objection. Form.

22 A So the fact that they have different --

1     that they have different hydrogen -- did you say  
2     different or the same? You said the same.

3           Q     No. They have different -- your  
4     conclusion in Paragraph 63 is that they have  
5     different hydrogen bond formation patterns with  
6     Btk. And if we look at 1044, which is what you're  
7     talking about here, 1044 says at the bottom of  
8     Page .003, On the basis of the crystallographic  
9     data available, ibrutinib and zanubrutinib share  
10    similar bioactive conformations within the  
11    wild-type Btk binding site.

12          A     So the fact that they have different  
13    binding patterns does not mean that the binding  
14    patterns don't have some similarity. The binding  
15    patterns have similarity, but they are different.

16          Q     Okay.

17                MS. PATEL: Counsel, is this -- we're  
18    almost at noon. Can we break for lunch maybe for  
19    30 minutes or so?

20                MR. FRAZIER: If you'd like, yeah.  
21    Whenever you want lunch is fine with me.

22                (A discussion was held off the record.)

1           Q     So going on from there then, Paragraph 64  
2     says, "The understanding of hydrogen bond  
3     formation, its impact on Btk binding can be gained  
4     from crystallography data of known compounds, the  
5     SAR of hydrogen bonding and how it impacts Btk  
6     binding and off target binding for unknown and  
7     uninvestigated compounds would be unpredictable."

8                     Do you see that?

9           A     I see that.

10          Q     But you would agree with me that it is  
11     common and would have been common for a POSA in  
12     2011 to extrapolate from the binding of known  
13     compounds in the available data to other related  
14     compounds. Correct?

15                     MS. PATEL: Objection. Form.

16          A     So a POSA, based on x-ray crystal  
17     structures, would be able to make some guesses  
18     based on the binding patterns to the hinge region,  
19     would be able to make some guesses as to maybe  
20     which compounds yet to be discovered would bind in  
21     the same fashion to the hinge region.

22          Q     All right. If you look at your Paragraph

1 65, it's on Pages .038 and .039 of your  
2 declaration. And you say that "Crystallography  
3 data available in 2008 reveals that kinase  
4 inhibitors having a Z'-structure that falls under  
5 the structural limitations which are discussed  
6 below present distinct orientations relative to  
7 the hinge region of a kinase as a result of subtle  
8 changes in the substitution pattern of the  
9 Z'-structure."

10 Do you see that?

11 A I see that.

12 Q Okay. Now, you've put a portion of Table  
13 2 from the Ghose reference in your declaration at  
14 Paragraph 64 and -- 65 rather, Paragraph 65, but  
15 you've cut off a portion of the Table 2 as well.

16 Right?

17 A I did cut off a portion of Table 2  
18 because I thought the examples I present are most  
19 relevant to this issue of hinge region binding,  
20 especially for compounds that fall within the  
21 structural limitations of the '803 patent claims.

22 Q But you agree that the different

1     orientations that are presented there are also --  
2     are the result of differences in the different --  
3     the different kinases, not the structure of the  
4     molecule itself. Right?

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

7             A     So many of the kinases that are in the --  
8     excuse me, in Table 1 that are cited in Table 1  
9     crystal structures, have a fair amount of -- let  
10    me back up. Have conservation within the hinge  
11    region. So in that context I would argue that the  
12    orientations shown here apply to many of the  
13    kinases but not necessarily to all the kinases.

14             And recall Table 2 does not include  
15    Btk -- or Table 1. Table 1 does not include Btk.

16             Q     Yeah, I guess I was looking in particular  
17    at -- right there on Page .039, you make a point  
18    about the different orientations of the molecules.  
19    But those orientations are dependent on the  
20    particular kinases that are involved in -- with  
21    respect to that data.

22             MS. PATEL: Objection. Form.

1           A     So that's one criteria. The other  
2 criteria would be the substitution pattern -- or  
3 is the substitution pattern.

4                     If you look at the table that I  
5 presented, 1, you look at that particular  
6 orientation to the hinge region for ATP -- and if  
7 you go to 1A, it shows a different orientation.  
8 That orientation is going to be due not -- in this  
9 case not to the substitution, the compounds are  
10 the same, but to a different hinge region  
11 sequence.

12                    And if you go down to 1B, you can see yet  
13 another orientation of the adenine to the hinge  
14 region, but this is simply adding on three  
15 phosphate groups. So I would say substitution is  
16 also very important.

17           Q     But the Ghose authors themselves actually  
18 attribute the difference to the PIM1 kinase that  
19 is binding there.

20                    Do you agree with that?

21                    MS. PATEL: Objection. Foundation.  
22 Form.

1           A       So they discuss the different hinge  
2       region interactions in PIM1 kinase?

3           Q       Right.

4           A       But I think, again, that sort of -- that  
5       undergirds my argument that when you have  
6       different sequences of amino acids along the  
7       backbone of the hinge region, that will affect the  
8       orientation of the -- of the heterocycle, in this  
9       case adenine.

10          Q       Right. But you're not saying that Btk  
11       has the same sequence as PIM1 in that region.

12                   Correct?

13          A       No. I'm not saying that. Btk has a  
14       different -- a different sequence.

15          Q       So if we look at -- back to Page 2 in the  
16       Ghose article, you see that at the top left-hand  
17       column there's the paragraph that begins, "If  
18       proteins change their structures"?

19                   Do you see that?

20          A       I see that.

21          Q       Okay. And there's a little introduction.  
22       And then I want to focus, there's a sentence that

1 begins about halfway down, "As a consequence,  
2 through an analysis of the binding modes of  
3 different types of kinase ligands, one can  
4 anticipate the binding mode of a related ligand  
5 with kinase inhibitor features."

6 Do you see that?

7 A Yes, I see that.

8 Q All right. And you agree with that.  
9 Correct?

10 MS. PATEL: Objection. Form.

11 A So the key word there is "anticipate."  
12 But I think you need to read the next sentence  
13 also. Okay. No. Scratch -- scratch that  
14 comment.

15 Q Okay. I was going to say, I agreed with  
16 you that the -- because the next sentence says,  
17 "Such an analysis is extremely useful in deciding,  
18 for instance, where to place a hydrogen acceptor  
19 or donor atom, install a solubilizing group, or  
20 include a hydrophobic modification."

21 So Ghose is saying a person of ordinary  
22 skill could use this information to guide where to

1 place a hydrogen acceptor or donor atom in an  
2 inhibitor molecule. Right?

3 MS. PATEL: Objection. Form.

4 A So Ghose is saying you can use this  
5 information. But if you look -- I want to go a  
6 little bit further down to the -- some of his  
7 conclusion remarks. If you go to -- go to Ghose  
8 1002 .20.

9 Q Okay.

10 A And starting with the last sentence on  
11 that page. I'll read this. The medicinal  
12 chemists may find the prediction rules devised  
13 herein helpful to quickly formulate a binding mode  
14 hypothesis for a potential ligand. Likewise, a  
15 substructure searchable database combining a  
16 simplified representation of scaffolds, et cetera,  
17 et cetera, may also prove useful. For  
18 computational chemists, such a database may help  
19 in picking the, quote, correct ligand pose one  
20 expects to observe experimentally from among the  
21 many generated by various ligand docking programs.  
22 A cross-breeding ligand hybridization methodology

1 coupled with sophisticated ligand affinity  
2 prediction tools can be a useful hit/lead  
3 generation strategy; however, all of the  
4 aforementioned uses of a kinase knowledge base  
5 should be considered suitable only for idea  
6 generation rather than the routine prediction of  
7 high affinity ligands. And then they talk about  
8 addressing off-target activities.

9 Further down in the -- in that same  
10 paragraph. A benchmark for physicochemical  
11 property profile for kinase inhibitors in drug  
12 discovery is still evolving, since only a limited  
13 number of kinase drugs have been approved thus  
14 far. So therefore, kinase inhibitor design should  
15 leverage a property profiles of oral drugs,  
16 et cetera. We've discussed some of this already.  
17 And then the last sentence I think is very key.  
18 "Knowledge-based drug discovery is an excellent  
19 way in ligand design to mate privileged structural  
20 components with exploratory moieties.  
21 Paradoxically, the advantages of knowledge-based  
22 drug discovery depend critically on an increase in

1 information that can only come from speculative  
2 approaches and serendipitous results."

3 So I read that to mean that, yes, making  
4 estimates or guesses on a candidate molecule based  
5 on known ligand -- known ligand hinge region  
6 interactions is useful. It's useful, but it  
7 cannot estimate or even predict precisely given  
8 target compounds.

9 Q Okay.

10 MR. FRAZIER: Maybe now would be a good  
11 time to go ahead and take a lunch break, if that  
12 would be okay.

13 THE WITNESS: I agree, let's take a  
14 break.

15 (A recess was taken.)

16 BY MR. FRAZIER:

17 Q So, Dr. Showalter, let's turn to  
18 Paragraph 73 of your declaration, which was  
19 Exhibit 1003. And this is page .045.

20 A Seventy-three. Got it.

21 Q And in this paragraph you say that the  
22 published empirical data of Brukinsa's and its

1 R-isomer's Btk binding potency also confirms that  
2 the chirality in Brukinsa's linker affects the Btk  
3 binding activity.

4 Do you see that?

5 A Yes, I see that.

6 Q And you cite to the article which is  
7 Exhibit 1053 by Guo, et al. Maybe pull that up as  
8 well.

9 A Got it. Yeah, that's the -- that's the J  
10 Med Chem article?

11 Q Yes, from 2019.

12 A Yes. So I have the article.

13 Q And I think you've reproduced Table 6 of  
14 the article in your declaration, so you can look  
15 at Table 6 either in the declaration or in the  
16 article itself.

17 A Okay, I am back on my declaration now.

18 Q But you would agree with me that the --  
19 what you're illustrating here is a compound with  
20 different chiral presentations, either a mixture  
21 for an S orientation or an R orientation, and then  
22 the Btk binding characteristics of those three

1 categories. Correct?

2 A Yes, I see that.

3 Q And you would agree with me that in each  
4 case the result is high affinity inhibition of  
5 Btk. Correct? Or potent inhibition of Btk?

6 A So the data in and of themselves agree  
7 with your statement. But I think what you need to  
8 look at here is the factor of -- the difference,  
9 there's a -- if I do my math right, let's see,  
10 there's at least a five-fold difference, whatever  
11 the math is there, between the R and the S.

12 So as opposed to the data in Pan that  
13 showed both the R and S being essentially  
14 equivalent in potency, here there's a -- you know,  
15 there's a multifold difference in IC50. Which  
16 tells you that, at least from the data in Pan, you  
17 can't extrapolate any one given results from a  
18 publication on a given Z' core, you can't  
19 extrapolate from one publication to another one  
20 like this one where we have a different Z' core.

21 Q You can't extrapolate to determine the  
22 precise IC50 for inhibiting Btk. But in fact, it

1 does align in that both are still high-potency  
2 inhibitors. Right?

3 MS. PATEL: Objection. Form.

4 A So as of 2020, 2019, when this paper  
5 was -- 2019 when this paper was published, a POSA  
6 would look at this and say Compound 31 is very  
7 highly potent, it's less than 1 nanomolar. They  
8 would say the -- so -- sorry. Not Compound 31.  
9 31A, the S isomer, 31B the R isomer is 11. That  
10 would have been a high level of potency as of  
11 2010, 2011.

12 But the standards for potency change over  
13 time. And here one wouldn't say that 11 was  
14 necessarily high potency; they would say it's  
15 potent.

16 Q Okay. While we still have the Exhibit  
17 1053 out, if you could look at Page 002 in that  
18 article.

19 A Okay, I'm on that page.

20 Q And do you see that on the right-hand  
21 column there's a sentence about halfway through  
22 the first paragraph that says, "To illuminate the

1 binding mode of early lead Series 1," or I, "the  
2 binding mode of I2 without warhead was established  
3 and aligned to that of B43"?

4 A I see that statement.

5 Q All right. And so you understand that  
6 B43 was the inhibitor that Marcotte had provided  
7 the structure of Btk bound to that inhibitor back  
8 in 2010. Right?

9 A That's -- as I recall, that's what's in  
10 Marcotte.

11 Q And so even during the development of  
12 zanubrutinib, the scientists at BeiGene looked to  
13 the Marcotte structure to inform them about the  
14 binding mode of their early lead series I.

15 Correct?

16 A So I need to look back to --

17 MS. PATEL: Objection. Form.  
18 Foundation.

19 A Yes, I think scientists at BeiGene would  
20 have looked at any information in the literature  
21 relating to binding to Btk.

22 Q Okay. And specifically here they call

1 out that they were looking at the B43 Marcotte  
2 information. Right?

3 A That's --

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

6 A So that's what's stated in this article.

7 Q All right. Let's jump to your Paragraph  
8 76, then.

9 In Paragraph 76 you refer to a patent  
10 publication from 2020 which you indicate shows  
11 that altering substitutions of the Z'-structure  
12 has an unpredictable effect on the IC50, which is  
13 a measurement of Btk inhibition activity.

14 Do you see that in Paragraph 76?

15 A I see that.

16 Q All right. Let's then take a look at  
17 Exhibit 1036 that you cite there.

18 (BeiGene Exhibit 1036, previously marked,  
19 not attached.)

20 A Exhibit 1036. This is the patent. Okay,  
21 I have pulled up the patent.

22 Q And am I correct in understanding that

1     you have taken structures from this patent,  
2     Exhibit 1036, and reproduced them on Page .047 of  
3     your declaration?

4           A     So let me look in my declaration to make  
5     sure we're talking about the same thing here.

6                   Those six structures were taken from the  
7     patent.

8           Q     And then below them you have put IC50  
9     information that shows their IC50 for inhibition  
10    of Btk. Correct?

11          A     These are Btk data.

12          Q     Right. And those are data also from the  
13    patent, I assume?

14          A     If I correctly reproduced from the  
15    patent, those would be the data. And I think I  
16    did.

17          Q     And again, you would agree with me that  
18    all of these are showing potency or high potency  
19    against Btk. Correct?

20                   MS. PATEL: Objection. Form.

21          A     So I would argue, again based on our  
22    discussion earlier, that this is -- you have to

1 look at the context of the time period when  
2 these -- when a series is discovered.

3 2010, 2011, these would all be classified  
4 as highly potent or let me just say potent. As of  
5 2019 the standard had changed and, therefore, some  
6 of these data I would view as not representing  
7 necessarily highly potent compounds. They are  
8 potent, but not highly potent.

9 Q Okay. All right. If you turn in your  
10 declaration, just below that you begin a section  
11 called Off-Target Binding and Adverse Side  
12 Effects.

13 Do you see that?

14 A I see that.

15 Q All right. And it's your understanding  
16 that while there may be differences in the extent  
17 of off-target binding, both zanubrutinib and  
18 ibrutinib demonstrate some degree of off-target  
19 binding.

20 Is that correct?

21 A So based on their package inserts, that  
22 information is shared. The information shared

1 argues that there are off-target effects.

2 Q Of both compounds?

3 A Both compounds.

4 Q And then you indicate at -- well, let me  
5 just stop there, then.

6 Are you an expert in the side effects of  
7 Btk inhibitors?

8 A I am not an expert.

9 Q So that's something we should look  
10 perhaps to Dr. Rosen for?

11 A That would be my recommendation.

12 Q Let's jump forward to Paragraph 102 in  
13 your declaration.

14 A Okay, I'm there.

15 Q And you say in Paragraph 102 that, "The  
16 only compounds that are explicitly disclosed in  
17 the specification and that satisfy the structural  
18 limitations are Brukinsa and its positional and  
19 chiral isomers."

20 Do you see that?

21 A I see that.

22 Q And what do you mean by "its positional

1 and chiral isomers"?

2 A So ibrutinib -- Imbruvica would have as  
3 one of its isomers, instead of the R  
4 stereochemistry of the linker, you would have the  
5 S stereochemistry.

6 A positional isomer would be where the  
7 linker itself, the piperidine linker, is linked to  
8 the pyrazole pyrimidine core either through the 4  
9 position of the piperidine linker or, as in  
10 Imbruvica, the 3 position.

11 Q So then would you agree that all of those  
12 are inhibitors of Btk, potent inhibitors of Btk?

13 MS. PATEL: Objection. Form.

14 A So I'm recalling the data from Pan. And  
15 I think all of those isomers are represented in  
16 Pan. And we agreed that those as of 2010, 2011,  
17 would be considered potent inhibitors.

18 Q Okay. Great. Let's look now at the '803  
19 patent, which is Exhibit 1001.

20 (BeiGene Exhibit 1001, previously marked,  
21 not attached.)

22 A Okay, yeah, I have launched the document.

1           Q     So when you get the document up, if you  
2     can look at Column 15.  Actually, not Column 15.  
3     I think it's Column 62, rather.

4           A     Okay.

5           Q     Hang on one second while I'm closing some  
6     windows on my Adobe here so I can handle this  
7     patent.

8                     All right.  And I want to refer you then  
9     to Paragraph 115 in your declaration at the same  
10    time where you're referring to the disclosure of  
11    the '803 patent.  You say, "At most, the  
12    specification states that, in some embodiments,  
13    the ball structure of Formula (E) is one of the  
14    below substituted fused biaryl moieties (Formula  
15    (E) ring systems)."

16          A     Which paragraph are you on?

17          Q     115.

18          A     Okay, I see that.

19          Q     And so you're referring in Paragraph 115  
20    to the statement at the bottom of Column 62, where  
21    it says, "In some embodiments, the circle is a  
22    substituted fused biaryl moiety selected from"?

1           A     I say that.

2           Q     And is that what you're referring to in  
3 Paragraph 115?

4           A     So I'm referring to Formula (E) in  
5 Paragraph 115.

6           Q     Right. And you say, "At most, the  
7 specification states that, in some embodiments,  
8 the ball structure is one of the below substituted  
9 fused biaryl moieties."

10                  Do you see that?

11          A     I see that.

12          Q     And I'm asking, by that language are you  
13 referring to the portion of the patent beginning  
14 at Line 44 on Column 62?

15          A     Line 44. I see this, yes.

16          Q     And so that's what you're referring to in  
17 Paragraph 115. Correct?

18          A     That's what I'm -- that's what I'm  
19 looking at, yes.

20          Q     And so you see that that sentence begins,  
21 "In some embodiments the circle is a substituted  
22 fused biaryl moiety." Right?

1           A       That is -- that is what's stated in the  
2 patent.

3           Q       Right. And so it does not say that in  
4 all embodiments the circle is a substituted fused  
5 biaryl moiety. Right?

6           A       The language is "in some embodiments."

7           Q       Okay. And so that implies to you and  
8 would imply to a person of skill in the art that  
9 not every embodiment is a substituted fused biaryl  
10 moiety. Correct?

11                   MS. PATEL: Objection. Form.

12           A       States your question again?

13           Q       Yeah, is it your view that a person of  
14 ordinary skill, reading this portion of the patent  
15 in Column 62, would conclude that not every  
16 embodiment of the circle in Formula (E) would be a  
17 substituted fused biaryl moiety selected from the  
18 group below?

19                   MS. PATEL: Objection. Form.

20           A       So the language specifies some  
21 embodiments. It doesn't specify all embodiments.

22           Q       Okay. And if you go up to the Formula

1 (E) definition around Line 15, it gives the  
2 structural formula. And then at Line 15 it says,  
3 "Wherein the circle is a moiety that binds to the  
4 active site of a kinase, including a tyrosine  
5 kinase, further including a Btk kinase cysteine  
6 homolog."

7 Do you see that?

8 A Yes, I see that.

9 Q And we have already looked at a number of  
10 publications, including, for example, the Ghose  
11 publication, from prior to June of 2011 that  
12 showed different types of moieties that would bind  
13 to the active site of a kinase. Correct?

14 MS. PATEL: Objection. Form.

15 A So the Ghose article says that there are  
16 certain types of structures that will bind to a  
17 kinase based on the heterocyclic ring system. But  
18 it doesn't say anything about Btk kinase.

19 Q But you agree that in 2011, by June of  
20 2011, a POSA would know of many different cores  
21 that could bind to a tyrosine kinase. Correct?

22 MS. PATEL: Objection. Form.

1 Foundation.

2 A So as of 2010, 2011, there were many  
3 cores in the literature described as kinase  
4 inhibitors. There were not many cores described  
5 as Btk inhibitors.

6 Q Okay.

7 A So adding to that point, the two cores  
8 that were described as binding to Btk were  
9 essentially the one elucidated in Marcotte and the  
10 one that's elucidated in Pan, pyrrolo pyrimidine  
11 and pyrazolo pyrimidine.

12 Q And I guess the question is, did you look  
13 for other literature to identify additional cores  
14 that would have been known to bind to either  
15 kinases or Btk kinases?

16 A So I've followed over the last couple of  
17 years fairly closely the literature of Btk  
18 inhibitors. And as of 2010, 2011, the cores that  
19 I just described to you were the ones that I came  
20 across as being Btk inhibitors either in a  
21 reversible, or in the case of Pan, irreversible,  
22 compounds.

1           Q     In the patent at -- if we go to Column 15  
2     you see there is a definition of aryl?

3           A     "The term 'aryl' refers to an aromatic  
4     ring when each of the atoms forming the ring is a  
5     carbon atom."

6           Q     Yes. And it goes on from there.

7                     Correct?

8           A     There's additional description.

9           Q     Right. And you see it then has example  
10    of aryl groups include but are not limited to?

11   And the examples that it includes include  
12   molecules that are partially aryl and partially  
13   not aryl. Correct?

14          A     Would you -- would you direct me to which  
15   of the groups that description applies to.

16          Q     How about fluorenyl?

17          A     Fluorenyl has two benzene rings attached  
18   to each other by a single bond. And then off of  
19   those benzene rings those -- those two rings get  
20   connected by a single carbon which is -- which is  
21   not aromatic. That ring is not aromatic.

22          Q     So the definition of aryl in the patent

1 includes compounds that have some rings that are  
2 aromatic and one that's not, in the context of  
3 fluorenyl?

4 MS. PATEL: Objection. Form.

5 A So this -- it depends. It depends if you  
6 view the definition of ring as specifying a single  
7 ring or a ring system. So the definition here  
8 says aryl rings can be formed at five, six, seven,  
9 eight, nine, or more than nine carbons. It  
10 doesn't specify that all these carbons have to  
11 make up a single ring system as in fluorenyl.

12 Q So I'm just interested in your view on  
13 this. Are you then saying that in your view an  
14 aryl in the '803 patent has to refer to an  
15 aromatic ring, or it can include compounds that  
16 include both aryl and nonaryl rings?

17 A So the definition in the patent does not  
18 comply with organic chemistry principles. But in  
19 terms of the definition given, a compound that has  
20 one aryl ring, I guess this would -- this would  
21 suffice to say that the definition could include a  
22 definition different from what we found in an

1 organic textbook.

2 Q Let's jump forward to Paragraph 136 in  
3 your declaration. And you see you have a section  
4 that actually begins at Section 134 about a person  
5 of ordinary skill in the art.

6 Do you see that?

7 A Yes, I see that.

8 Q And at 136 you indicate that it's your  
9 opinion that a POSA would have been part of a team  
10 that included at least a member that had at least  
11 a Ph.D. in chemistry, organic chemistry, or  
12 related field, with training as a medicinal  
13 chemist.

14 Do you see that?

15 A I see that.

16 Q And you agree that such a person in the  
17 2010, 2011 time frame would have had training or  
18 experience with computerized docking models?

19 A So --

20 MS. PATEL: Objection. Form.

21 Q You can go ahead.

22 A So I don't agree with that. In 2010,

1 2011, docking models were not readily available  
2 for any member of a -- of a research team. And  
3 docking, molecular docking, is a highly  
4 specialized area. So that would require somebody  
5 with full-time dedication to actually doing the  
6 modeling. And the member, the POSA member, would  
7 be someone most likely trained in a subspecialty  
8 of organic chemistry. I would say either  
9 theoretical organic chemistry, physical organic  
10 chemistry, one of the subspecialties.

11 Q And they would certainly have experience  
12 in reading and interpreting the structural data  
13 like we've seen in the Pan article of x-ray  
14 crystal structures bound to ligands.

15 Do you agree?

16 A So a POSA -- a POSA would likely be  
17 working with specialists in molecular docking or  
18 in, say, x-ray crystallography or computational  
19 modeling, that sort of thing. So they would have  
20 had some interaction with one of those members of  
21 the team, but not -- not actually doing  
22 calculations or crystallizations themselves.

1           Q     All right. If we jump forward in your  
2     declaration to Paragraph 141, you have a section  
3     entitled Breadth of the Claims.

4           A     Okay, I'm there.

5           Q     And then in talking about this, let's  
6     also have available the '803 patent, Exhibit 1001,  
7     at Column 151, so we can see Claim 1 of that  
8     patent.

9           A     Which column are you talking about?

10          Q     Column 151 of the '803 patent. Where it  
11     says, "what is claimed is," about Line 32, I  
12     guess.

13          A     Okay, I'm there.

14          Q     All right. And in understanding -- in  
15     reading the '803 patent, you purported to come up  
16     with a number of compounds that would be  
17     encompassed within the claims for use in this  
18     method. Correct?

19          A     I did the calculations.

20          Q     And in coming up with your estimate, did  
21     you give weight to all the words in the claims?

22                MS. PATEL: Objection. Form.

1 A Repeat your question, please?

2 Q Right. So the question is, did you give  
3 weight, in determining the number of compounds,  
4 did you give weight to all of the words in the  
5 claims, or did you just take the structure out  
6 separately from the claim language?

7 A No; I gave --

8 MS. PATEL: Object to form.

9 A I gave weight to all of the language in  
10 the claims.

11 Q All right. So you understand then that  
12 the claims would be limited to irreversible  
13 inhibitors of Btk that are small organic  
14 molecules. Right?

15 A So my question would be, what is the  
16 definition of a small organic molecule?

17 Q I would ask you that question, given  
18 you're the one who made the calculation.

19 So what did you define as a small organic  
20 molecule in performing your calculations?

21 A So it depends on the nature of the  
22 organic molecule being considered. For an orally

1 available, orally administered drug, the molecular  
2 weight would have to be smaller, for a small  
3 organic molecule, then for a class of drugs like  
4 polypeptides which usually -- just usually are not  
5 administered orally because of proteases are  
6 breaking them down. So my definition of a small  
7 organic molecule is one that you could administer  
8 orally and it is taken up by the gut and gets into  
9 the bloodstream.

10 Q And did you have in mind a particular  
11 molecular weight or weight range?

12 MS. PATEL: Objection. Form.

13 A So that depends. As of 2010, 2011,  
14 investigators sort of hung their hat onto  
15 Lipinski's rules. But Lipinski later modified his  
16 definition. He says molecular weight 500 is not a  
17 requirement, it can be higher. And if you look,  
18 you know, in the literature, other so-called small  
19 organic molecules that have a molecular weight  
20 considerably greater than 500 that are orally  
21 available, you can look to something like -- just  
22 thinking here, like certain antibiotics would be

1 considered small organic molecules but have much  
2 higher molecular weight than 500.

3 Q So in considering your calculations, what  
4 did you have in mind as the high end of a  
5 molecular weight?

6 A I would view a molecular weight of -- a  
7 maximum molecular weight of 1500.

8 Q Okay. And in determining the structures  
9 that one would pursue, is it your understanding  
10 that a POSA would not try to make random billions  
11 of molecules; that they would seek to design in a  
12 particular direction?

13 MS. PATEL: Objection. Form.

14 A So "design in a particular direction,"  
15 tell me what you mean by "direction."

16 Q I mean, do you agree that a POSA would be  
17 more likely to begin with -- to look at, for  
18 example, cores that were, as the patent says,  
19 known to bind to tyrosine kinases?

20 MS. PATEL: Objection. Form.

21 A So the cores that a POSA could consider,  
22 1700 -- 1750 of which I draw out in my -- in the

1     appendix, those would be cores that might be  
2     considered by a POSA, amongst others. And that  
3     list of 1750 is actually conservative. It could  
4     have been a much larger list. But I applied  
5     principles of stability, aqueous and otherwise,  
6     to -- before I included any of these cores in the  
7     list of 1750.

8           Q     So let's look -- so you're referring to  
9     your Exhibit A, is that right? Or Appendix A?

10          A     Appendix.

11          Q     Appendix A?

12          A     Yeah.

13          Q     All right. And where did you get the  
14     structures that are cited in Appendix A?

15          A     These structures can be found in numerous  
16     heterocyclic chemistry textbooks or in a  
17     generalized organic -- sorry, heterocyclic  
18     chemistry books that discuss various heterocyclic  
19     cores. And these are also available from online  
20     searching, the ones that are a little more -- that  
21     have possible instability effects. And the ones I  
22     deemed would be unstable I did not include in my

1 list of 1750 cores.

2 Q But you also didn't cite any references  
3 as the source for your 1750 cores in Appendix A.

4 Correct?

5 A There are no references cited in the  
6 appendix.

7 Q As you sit here today, are you able to  
8 determine -- rather, are you able to tell me which  
9 of these cores would bind to a tyrosine kinase  
10 inhibitor or Btk?

11 A So that would depend on the substituents,  
12 the moieties attached to the cores, and in what  
13 relationship the attachments, the substitutions  
14 have to each other, are they attached next to each  
15 other, are they attached several -- you know,  
16 three or four positions away from each other.

17 So I also considered substituent effects.

18 Q But you have not identified in Appendix A  
19 which of these cores have been found to bind to  
20 tyrosine kinase or act as tyrosine kinase  
21 inhibitors. Right?

22 MS. PATEL: Objection. Form.

1           A       The only way you could determine whether  
2       they're tyrosine kinase, specifically Btk  
3       inhibitors, would be to make -- to make those  
4       cores with substituents that one would hypothesize  
5       would result in proper orientation of the  
6       molecule, such that it could trap cysteine 481 if  
7       the cores had incorporated a Michael acceptor, so.  
8       And then it would take extensive experimentation  
9       to actually verify that any one of these cores  
10      with the appropriate substituents to target  
11      cysteine 481 actually performed -- performed the  
12      function -- the function they're designed for.

13          Q       Have any of these cores been used in  
14      inhibitors of tyrosine kinases?

15                 MS. PATEL: Objection. Form.  
16      Foundation.

17          A       So I would have to look at the list.  
18      It's just too many compounds to remember which  
19      have or have not been utilized in the design of  
20      tyrosine kinase inhibitors. It's a very big list,  
21      and I simply don't remember.

22          Q       Well, when you were pulling the

1 references -- I assume you actually came up with  
2 this, with the list in Appendix A; it wasn't just  
3 provided by the attorneys?

4 A You sort of faded out there.

5 Q I'm sorry. Yeah. Just confirming, as I  
6 understand it, you're saying that you generated  
7 the list of compounds in Appendix A, it was not  
8 provided to you by the attorneys?

9 A I did not get assistance from the  
10 attorneys.

11 Q And so when you were studying the  
12 literature to identify these, were any of the  
13 references that you used references that described  
14 the inhibition properties of compounds including  
15 these cores against tyrosine kinase inhibitors?

16 MS. PATEL: Objection. Form.

17 A So I looked at not necessarily -- I did  
18 not look at medicinal chemistry literature to  
19 confirm that these cores had been utilized to make  
20 tyrosine kinase inhibitors. These are cores that  
21 fit the structural specifications as outlined in  
22 the Claims 1 and 8 that they be an optionally

1 substituted fused heterocyclic ring system  
2 comprising from two to four nitrogen atoms. And  
3 then from that definition drew up a list of  
4 various subgenera that would fit that definition.

5 So this would -- this included the  
6 aromatic -- aromatic subgenus. And then another  
7 subgenus was aromatic in the six-membered ring,  
8 nonaromatic in the five-membered ring. A third  
9 genus aromatic in the five-membered ring and  
10 nonaromatic in the six-membered ring. And then a  
11 fourth genus was -- or is bicyclic systems meeting  
12 the definition here of two to four nitrogen header  
13 atoms that are -- wherein both rings are  
14 nonaromatic.

15 So based on that definition I could draw  
16 out ring systems almost ad nauseam.

17 Q And so I guess that's one question, is  
18 did you just draw them out, or did you actually  
19 find every one of the structures that you had here  
20 in the literature as a ring system that existed in  
21 the literature?

22 MS. PATEL: Objection. Form.

1           A     So there are a number of heterocyclic  
2     texts out there that contain many of the -- well,  
3     most of the ring systems that I outline in the  
4     appendix. And then others, if I had doubts, I  
5     checked them out online to see if they presented  
6     any issues around especially instability. Those  
7     were instantly reflected.

8           Q     So you looked for instances of  
9     instability, but you don't recall looking to see  
10    if any of them were part of tyrosine kinase  
11    inhibitors that were known in the literature?

12          A     So some of the ones that are listed I was  
13    aware when I drew up the list, especially the  
14    first category, the aromatic-aromatic. Because  
15    based on the definition here, a lot of those would  
16    be adenine type mimetics, so I was aware that  
17    these -- that these are found in the tyrosine  
18    kinase literature as inhibitors.

19          Q     So you just said that a person of  
20    ordinary skill, looking at this, would have to do  
21    this extensive testing and so forth. But it's  
22    also the case that a person of ordinary skill

1 could look to the literature to find out the  
2 existing properties of these compounds in the  
3 context of tyrosine kinase inhibition as well.

4 Right?

5 A All of the -- all of the -- all of the Z  
6 primes that I draw in the appendix would have been  
7 publicly available to any POSA.

8 Q Okay. And do I understand correctly then  
9 that Appendix A formed the basis for your  
10 calculations of the breadth of the claims?

11 A The basis formed for the breadth of the  
12 claims were -- was on the Z'-structure encompassed  
13 in Brukinsa. So my calculations, as you can see  
14 in my declaration, are based on 21 variables which  
15 are -- or 21 substituent classes which are  
16 specified, which are outlined in the  
17 specifications.

18 So of the 1750 cores which I outline in  
19 the appendix, I chose one. I chose the Brukinsa  
20 core. And since the patent specifies that any Z'  
21 can be substituted, I included generic  
22 substituents, or substituents off of the core of

1     Brukinsa, and then applying -- applying 21  
2     different possibilities for each one of those  
3     positions. You can see from the calculations that  
4     I came up with -- I don't have the number in front  
5     of me, but I think around 5 billion possibilities  
6     just -- just for the Brukinsa core. And that's an  
7     undercount. I didn't include various isomers,  
8     positional isomers and other sorts of isomers.

9           Q     All right. If you -- so it's your  
10    contention that there are billions of species with  
11    respect to a single core.

12                   Is that correct? Or billions of species  
13    including all the cores in your Appendix A?

14           A     So my calculations were done with one  
15    core, the core that makes up -- that is  
16    encompassed in Brukinsa. Those calculations,  
17    based on a relatively low number of possible  
18    substituents that you could adorn that core with,  
19    computes to 4 to 5 billion as I recall for just --  
20    just the Brukinsa core.

21                   So cores are going to have different  
22    possibilities for substitution. The more the

1 aromatic-aromatic type cores of course are going  
2 to have less positions for substitutions, so those  
3 numbers won't be as high.

4 But on the other hand, the nonaro-nonaro  
5 cores, nonaromatic and nonaromatic bicyclic cores,  
6 will have more positions for substitution than  
7 what I showed for the Brukinsa core.

8 So on average maybe at least a billion  
9 for every core.

10 Q How did you go about using the knowledge  
11 that a POSA would have about the structure of  
12 ibrutinib and the structure of Btk in coming up  
13 with your number of compounds that were  
14 encompassed by the claims?

15 MS. PATEL: Objection. Form.

16 A I'm not sure I understand your question.  
17 Could you rephrase it, maybe reframe it?

18 Q Yeah. So we agree that a person of  
19 ordinary skill certainly in the 2010 and 2011 time  
20 frame would -- and having the '803 patent in front  
21 of them, would have the knowledge of the patent,  
22 certainly the structure of ibrutinib, you'll have

1 the benefit of the structural information in the  
2 Pan article, the benefit of the structural  
3 information in the Marcotte article, as well as a  
4 lot of other information known about tyrosine  
5 kinase and kinase interactions more generally as  
6 reflected in Ghose and others.

7 And so you would agree that that would  
8 inform their decisions on how to substitute any of  
9 these cores. Correct?

10 MS. PATEL: Objection. Form.

11 A So a POSA, based on the literature as of  
12 2010, 2011, would have been aware of aromatic --  
13 aromatic-aromatic cores, fused ring systems in  
14 which both -- in which both rings are aromatic.  
15 And that would be a likely starting point for the  
16 POSA. The POSA would have been aware of ring  
17 systems that had already been investigated toward  
18 generating tyrosine kinase inhibitors that were  
19 not irreversible but were reversible.

20 So it would have been certainly kind of  
21 an easy transition to go from a reversible to an  
22 irreversible inhibitor simply from what was known

1 in the literature regarding various cores which  
2 were reversible inhibitors. And most of these  
3 would have been -- or many of these -- not most of  
4 these, but many of these would have been  
5 adenine-type mimetics.

6 Q And in performing your calculations,  
7 then, you assumed that a person of skill would not  
8 substitute to a point that led to a molecular  
9 weight of greater than 1500?

10 MS. PATEL: Objection. Form.

11 A So 2010, 2011, you would -- you would  
12 likely have been influenced -- would have likely  
13 been influenced by Lipinski rules. So they would  
14 have wanted to maintain lower molecular weight  
15 compounds.

16 Q And likewise, that would influence  
17 whether they were -- the types of substitutions  
18 that they would make and the extent to which they  
19 were done recursively. Correct?

20 MS. PATEL: Objection. Form.

21 A That would have been a consideration.  
22 But let me just make an addendum to your

1 statement.

2 If you look at the list of 21  
3 substituents in these specifications that are  
4 drawn from, yes, many of those would involve  
5 recursive types of substituents. And that would  
6 get you into an infinite number of possibilities.

7 But if you take any one of those 21  
8 substituents and within the definition of the  
9 substituent chose the lowest molecular weight  
10 substituent for each of the positions specified as  
11 for substitution, that would give you a  
12 molecular -- lower molecular weight compound  
13 falling within a -- whatever you wanted to define  
14 as your cutoff for molecular weight. And that  
15 would get you into certainly compounds that have  
16 oral -- oral activity.

17 And so if you do that -- and I don't have  
18 a list of substituents in front of me. I think  
19 you could do a calculation just on the lowest  
20 molecular weight substituents possible, and you  
21 could come up with reasonable molecular weights.  
22 And still -- still that would compute still to, in

1 the case of the example I gave, that would compute  
2 to billions of compounds.

3 Q I'm looking at Paragraph 162 of your  
4 declaration. And it says that the substitutions  
5 themselves may be further substituted recursively,  
6 and these further substitutions are not defined or  
7 limited, therefore the number of substitutions  
8 permitted by optionally substituted can be  
9 potentially infinite.

10 Do you see that?

11 A I see that.

12 Q But that doesn't take into account the  
13 understanding of a person of ordinary skill that  
14 they don't want the molecule of infinite size.  
15 Right? That's -- they would never really just  
16 keep substituting and substituting recursively to  
17 make a molecule that was practically large?

18 A So a POSA wouldn't want to make something  
19 that would not be -- be active in an initial,  
20 let's say, kinase assay. But I think this is just  
21 simply adding -- Paragraph 162 is indicating that  
22 if you substituted recursively, that the number of

1       substituents would be unlimited.

2           Q       But again, as we've discussed, a person  
3       of ordinary skill would be wanting to follow  
4       Lipinski and to have an orally bioavailable  
5       compound and something that's a realistic  
6       compound, so they wouldn't do that. Right?

7           A       So I think a POSA would realize that you  
8       wouldn't want to generate every compound in the  
9       universe.

10          Q       Right.

11          A       But they would also realize that if you  
12       substituted with small substituents as I have just  
13       discussed, you could still be looking at millions,  
14       billions of compounds for a given core, a given  
15       Z', depending on which, you know, Z' you'd want to  
16       evaluate.

17          Q       Can you tell me in your Appendix A your  
18       definition of aro versus nonaro, what definition  
19       you're using?

20          A       So the definition is simple. One ring of  
21       the fused ring system is aromatic, according to  
22       rules of aromaticity. The other one -- the other

1 one would be nonaromatic; that is to say, it  
2 doesn't have the double-bond configuration within  
3 the ring system that fits the definition of  
4 aromatic. It might have a double bond, but not be  
5 considered aromatic according to rules of  
6 aromaticity.

7 Q And by rules of aromaticity are you  
8 talking about whether the carbons are oriented as  
9 SP3 or SP2, for example?

10 A So rules of aromaticity -- and I think  
11 this is delineated in the specification. There's  
12 a statement somewhere in the specification saying  
13 that rules of aromaticity follow the formula  $4N$   
14 plus 2, where  $N$  is an integer. And these are of  
15 Pi electrons.

16 So for benzene, for instance, you have  
17 three double bonds. That's a total of six Pi  
18 electrons. So that fits a formula  $4N$  plus 2  
19 wherein  $N$  is 1.

20 So it's quite easy to determine whether a  
21 ring is aromatic or not aromatic, and a POSA would  
22 be able to do that.

1 Q Okay.

2 MS. PATEL: Counsel, is this a good time  
3 to take a break? We've been going for over an  
4 hour.

5 MR. FRAZIER: Yeah. Okay. Sounds good.

6 (A recess was taken.)

7 BY MR. FRAZIER:

8 Q So, Dr. Showalter, in considering your  
9 Appendix A, you have not done an analysis to  
10 determine which of the bicyclic five-six systems  
11 you cite would be more or less likely to be  
12 functional inhibitors of Btk if they were appended  
13 as the claims describe with a phenoxyphenyl back  
14 pocket binder and the linker warhead structure  
15 that's in Claim 1. Right?

16 MS. PATEL: Objection. Form.

17 A I have not done such an analysis.

18 Q If you look at the '803 patent again, if  
19 we look at -- well, first of all, if you look at  
20 Claim 1, you see that it requires as the linker  
21 the piperazine ring that we discussed earlier, the  
22 six-membered ring with one nitrogen.

1                   Is that correct?

2           A       So the language says, The irreversible  
3   inhibitor Btk is a small molecule organic -- small  
4   organic molecule having the structure and in the  
5   Markush as shown where Z' is an optionally  
6   substituted fused heterocyclic ring system  
7   comprising from two to four nitrogen heteroatoms.

8                   So that means you can have as few as two  
9   nitrogens and as many as four nitrogen heteroatoms  
10   spread across those two rings.

11                  But additional language specifies certain  
12   types of patterns that you must have. Where the  
13   optionally substituted fused heterocyclic ring  
14   system consists a five-membered ring comprising at  
15   least -- and let me go back up here -- at least  
16   one nitrogen heteroatom fused to a six-membered  
17   ring comprising at least one nitrogen heteroatom.

18                  So regardless of where you place your  
19   nitrogens within the fused bicyclic ring system,  
20   each one of those rings has to have at least one  
21   nitrogen atom, and a sum total of all the nitrogen  
22   atoms cannot be more than four.

1           Q     And you do understand that -- or we  
2     agree, perhaps, that the five-six heterocycle  
3     structure is a structural commonality with  
4     ibrutinib. Correct?

5                     MS. PATEL: Objection. Form.

6           A     So ibrutinib is a five-six aro,  
7     aromatic-aromatic system.

8           Q     Okay. And then I was actually asking my  
9     question before your last answer, which actually  
10    was a helpful answer, I appreciate you going  
11    through that, but my question is about the linker  
12    then in Claim 1. So after the Z'-structure, then  
13    attended to the Z'-structure is a six-membered  
14    ring with one -- with one of the apexes being  
15    nitrogen.

16                    Is that your understanding?

17          A     Please state that again.

18          Q     That -- well, how would you characterize  
19    this six-membered ring with the nitrogen in Claim  
20    1 that's appended to the Z'?

21          A     So the six-membered ring would be in  
22    ibrutinib, Imbruvica, it would be the piperidine

1 ring which has two nitrogen atoms.

2 Q I think we are still talking past each  
3 other. I am asking now about the piperazine ring  
4 that's connected to the warhead.

5 A Connected to the warhead or to the  
6 linker?

7 Q Connected to the warhead.

8 A Okay. I got you.

9 Q So if I could point, I'd point you to  
10 what I was --

11 A Okay. To the linker.

12 Q So I have moved away from Z' now, and I  
13 just wanted to ask you some questions about the  
14 other remaining parts on the bottom of the  
15 molecule.

16 A Okay.

17 Q And so let's talk about the ring there,  
18 it's a six-membered ring with the one nitrogen.  
19 And I believe you referred to it as piperazine.

20 Is that correct?

21 A Piperidine.

22 Q Piperidine. Okay. And so that's the --

1 and so that is the linker molecule, or linker  
2 moiety I'd say, in this molecule that's claimed in  
3 the Claim 1 method. Correct?

4 A That is the linker.

5 Q And then if you go to Column 52.

6 A Column 152.

7 Q Just 52.

8 A Fifty-two. So I've got to go all the way  
9 back to 52?

10 Q Yeah.

11 A Okay.

12 Q And you recognize then that at the bottom  
13 of Column 52 and into the top of Column 53 is a  
14 group of ring structures including the one we were  
15 just looking at from Claim 1 that are recited as  
16 potential linker structures?

17 A So are you looking at the line -- what is  
18 it, Line 49? The squiggly?

19 Q That's right.

20 A Down to Y? And so Y would be the linker.

21 Q Okay. All right. Let's move forward to  
22 Paragraph 238 and 239 of your report.

1           A     Okay, I'm there.

2           Q     Okay. And you indicate that in Paragraph  
3     238 that "a POSA might use some modeling or  
4     virtual screening to identify potentially viable  
5     compounds, but it would not appreciably reduce the  
6     number that would need to be synthesized and  
7     tested due to the limitations of the available  
8     methods."

9                     Do you see that?

10          A     I see that.

11          Q     And I just wanted to go through -- well,  
12     what available methods did you have in mind in  
13     Paragraph 238?

14          A     So when we say "modeling," talking about  
15     the sort of modeling that Pan describes in his  
16     article, 2008 I think it was. So you take a known  
17     crystal structure of a kinase. You know the  
18     coordinates of that. And then you set up -- you  
19     set up a program, a modeling program, in which you  
20     can bring in a candidate ligand. So you have to,  
21     of course, convert that structure into a digital  
22     structure, and then carry out the modeling.

1           And it's not a simple exercise, as I  
2 understand it. It takes work to generate a model  
3 that you might have confidence in.

4           Virtual screening would relate to  
5 something that's a little bit different. There  
6 you would be looking at a library of candidate  
7 compounds. And you wouldn't necessarily be  
8 focusing in on a given -- on a given potential Btk  
9 inhibitor, but you would be looking at a wide  
10 range of potential inhibitors. And you'd just  
11 simply again do that. It's a different algorithm,  
12 as I understand it.

13           You have a algorithm that can now look  
14 quickly. It's sort of a yes/no type answer you  
15 get, to look quickly at maybe a given pose to a --  
16 to a model of a given kinase, and you use that to  
17 determine whether one might want to progress  
18 toward further studies. Actually, you would be  
19 looking to do synthesis at that point. And that  
20 would be -- all of this would be very  
21 labor-intensive and would require many, many  
22 hours, days, months, years to screen the

1 potential -- potential number of compounds,  
2 billions of compounds you'd want to look at.

3 Q Well, why would you want to look at  
4 billions of compounds?

5 A You'd want to look at -- when you're  
6 talking about 1750 possible -- possible species in  
7 terms of just possible cores with different  
8 substituents, and you're looking to select the  
9 best one towards an improved inhibitor or to get  
10 IP space, you might not be looking at billions,  
11 but you might be looking -- if your technology is  
12 good enough, you can look at maybe a hundred  
13 thousand, but that's still a lot. You want to  
14 winnow this down to a smaller list that you would  
15 then want to look at by synthesis. But even that  
16 smaller list, let's say you winnow the list down  
17 to a hundred compounds that model really well,  
18 that -- you're still looking at months, years,  
19 decades of synthesis, depending on the nature of  
20 the candidate compound and the information in the  
21 literature on the synthesis of such a compound or  
22 compounds. And then you've got to work out all

1 the steps.

2 It's -- it's a daunting process.

3 Q Okay. I guess first of all, do I  
4 understand then that in connection with your  
5 enablement analysis, part of your analysis is  
6 based on how long it would take to make the full  
7 scope of compounds that fall within the claims?

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

10 A That's part of the analysis. I think  
11 that also takes into consideration that you would  
12 be able to use modeling or virtual screening or  
13 other related technologies to winnow down your  
14 list to something that is manageable. As of 2010,  
15 2011, the technology was pretty primitive relative  
16 to two thousand -- you know, later 2020, for  
17 instance, towards winnowing down this list.

18 Q If we look at, you actually cite to Zhang  
19 2009 here, which is Exhibit 1077.

20 MR. FRAZIER: If we could pull that up.

21 (BeiGene Exhibit 1077, previously marked,  
22 not attached.)

1           A     Okay. It's on my desktop.

2           Q     And so Zhang states then that in addition  
3 to guiding analog synthesis, structure and form  
4 design is used in diverse way to facilitate  
5 inhibitor discovery and optimization.

6                     Do you see that?

7           A     Where are you reading that from?

8           Q     The bottom of Page 7. I'm sorry, I just  
9 jumped in the middle. Yeah, so let's look at Page  
10 007. There's a section called Structure-Informed  
11 Design?

12          A     Structure-Informed Design on the left  
13 side. I see that.

14          Q     And so you see it says, "In addition to  
15 guiding analog synthesis, structure-informed  
16 design is used in diverse way to facilitate  
17 inhibitor discovery and optimization. And perhaps  
18 the most frequent use is to determine the key  
19 interactions formed between the inhibitor and the  
20 active site and to learn where functionality may  
21 be introduced to modulate potency or selectivity."

22                     And then it says the second says,

1 "Alternatively, crystal structures can be used to  
2 design hybrid compounds in which a portion of one  
3 inhibitor is grafted onto a portion of another  
4 guided by superimposition of the bound  
5 structures."

6 And it says, "This can be an especially  
7 effective way to create new Type 2 inhibitors by  
8 generating molecular amalgams."

9 And so those are examples of the types of  
10 structure-informed design that could be done at  
11 the time?

12 Is that correct?

13 MS. PATEL: Objection. Form.

14 A Yes, that's -- those are some of the  
15 possibilities using modeling and crystal  
16 structures.

17 Q Right. Then if we go down to Page 009.

18 A Okay, I'm on 009.

19 Q You see that on 009 down in the  
20 right-hand corner there's a section that's called  
21 Perspectives?

22 A I see that.

1           Q     All right. And there Zhang says,  
2     "Indeed, much of current kinase inhibitor  
3     discovery takes place through rational drug design  
4     rather than through high-throughput screening and  
5     empirical optimization on the basis of  
6     structure-activity relationships."

7                     Do you see that?

8                     MS. PATEL: Objection. Form.

9           A     I see that.

10          Q     And so that is the way Zhang  
11     characterized the state of the art and how someone  
12     would pursue a kinase investigation in this time  
13     period of 2009. Correct?

14                     MS. PATEL: Objection. Form.

15          A     So that appears to be his point of view.

16          Q     All right. And likewise, then, if you go  
17     to the next page, so Page 010, again on the  
18     left-hand side, he says, "It is fair to say that  
19     the chemical challenge of making potent and  
20     selective inhibitors with good pharmacological  
21     properties can be overcome for most kinases of  
22     interest using currently available technologies."

1           A     I just caught up with you.  Would you  
2     read that again?

3           Q     Yeah.  So he says, "It is fair to say  
4     that the chemical challenge of making potent and  
5     selective inhibitors with good pharmacological  
6     properties can be overcome for most kinases of  
7     interest using currently available technologies."

8                     Do you see that?

9           A     I see that.

10          Q     And you agree with that at this time  
11     frame by 2011?

12          A     So from the previous section that you  
13     wrote, he seems to be maybe contradicting himself.

14          Q     He's citing several ways that you could  
15     pursue a rational approach based on available  
16     technologies.  Correct?

17                     MS. PATEL:  Objection.  Form.

18          A     So I guess when he says, despite these  
19     advances, he's referring to the technologies that  
20     he discussed earlier.  So he says, a number of  
21     significant challenges remain, and then he goes  
22     on.

1           Q     Right. And the challenges he identifies  
2 are, first, mutants could arise. Right?

3           A     That's one, that would have been one  
4 challenge.

5           Q     Right. And then unexpected toxicity?

6           A     That would be another challenge.

7           Q     And then predictability of tumor models?

8           A     Especially in the 2010-'11 time period,  
9 that would have been a major challenge.

10          Q     And then finally would be kinase  
11 signaling cascades?

12          A     So that -- that's a correct statement,  
13 and it's still true. These are very complex  
14 signaling cascades, and new information around  
15 details of these cascades is continually being  
16 filled in by molecular biologists.

17          Q     But you would agree that the '803 patent  
18 had addressed the signaling cascade issue and that  
19 it had shown that inhibition of Btk actually does  
20 correlate with treatment of disease. Right?

21               MS. PATEL: Objection. Foundation.  
22 Form.

1           A       So as best as I can assess, the  
2 translation of inhibiting Btk irreversibly through  
3 trapping of cysteine 481, and how that correlates  
4 to actual treatment of disease and whether that  
5 particular mechanism accounts for the effect of  
6 the inhibitor to the disease or disease models  
7 you're looking at, I'm not really qualified to  
8 speak to that issue. That's more Dr. Rosen's  
9 area.

10           Q       Okay. It seems that Zhang also addresses  
11 that issue on -- going back again to Pages 6 to 7.  
12 Exhibit 1077, Page 006 to 007. Do you see it says  
13 "Inhibitor discovery efforts usually precede the  
14 determination of a crystal structure, homology  
15 models developed from one or more of the hundreds  
16 of other kinase ligand co-crystal structures are  
17 often used to predict a binding mode of the  
18 inhibitor to a three-dimension homology model of  
19 the kinase." That's in the paragraph that goes  
20 from Page 6 over to Page 7.

21                   Do you see that?

22           A       Is it the paragraph starting with,

1 "Analog synthesis"?

2 Q That's right. It's the last sentence in  
3 that paragraph.

4 A Starting with "however"?

5 Q Yes.

6 A "However, as inhibitor discovery efforts  
7 usually precede the determination of a crystal  
8 structure, homology models developed from one or  
9 more of the hundreds of other kinase ligand  
10 co-crystal structures are often" -- scrolling  
11 down. "Are often used to predict a binding mode  
12 of the inhibitor to a three-dimensional homology  
13 model of the kinase."

14 So what's your question around that?

15 Q The question is, again, doesn't that  
16 suggest that the way a person of ordinary skill  
17 would pursue making any given inhibitor in this  
18 system would be to look at a homology model of the  
19 known information, ibrutinib, or ibrutinib analog,  
20 in the context of Btk, and use that to inform  
21 which molecules to synthesize, both in terms of  
22 what core to use as well as any substitutions on

1       that core?

2                   MS. PATEL:  Objection.  Form.

3       Foundation.

4           A       So to the extent there was crystal --  
5       well, to the extent that there was information  
6       regarding homology models, and there was in the  
7       Pan article, one would use that information to  
8       look at other candidate ligands toward making a  
9       new inhibitor.

10          Q       If we go to -- let's jump to -- well, let  
11       me ask you this question:  Are you aware of a  
12       software package called Glide that was available  
13       before June of 2011?

14          A       I'm not aware.

15          Q       Let's go back to the Ghose article,  
16       Exhibit 1052.

17          A       Okay, I have the Ghose article.

18          Q       And then if we go to Page 22 in that  
19       article.  .022 down in the right hand.

20          A       Is this the page with the reference  
21       listings?

22          Q       Yeah.  Actually, it's -- we'll do this

1 backwards from the way I was planning to.

2 But if you see -- while we're here, if  
3 you look at 19, 20, and 21, you see there are  
4 three articles that are cited there. The first  
5 one is called -- is titled "Glide: A new approach  
6 for rapid, accurate docking and scoring."

7 Second one is, "Extra Precision Glide:  
8 Docking and scoring incorporating a model of  
9 hydrophobic enclosure for protein-ligand  
10 complexes.

11 And the third, 21, is "Glide: A new  
12 approach for rapid, accurate docking and scoring."

13 And so those are publications concerning  
14 a software package called Glide. And if we go  
15 back up to -- maybe it's back up on Page 1 is  
16 where this appears. If we look where it's --  
17 yeah.

18 A Did you say Page 1?

19 Q Yes, Page 1.

20 And so Page 1 then, you see at the bottom  
21 right-hand corner it says, "Although many  
22 approaches are aimed at correcting the known

1 limitations of docking including scaling of ligand  
2 and receptor atomic radii," and he cites to 19 to  
3 21 there.

4 A So I'm not following where you are.

5 Q The bottom right-hand corner on the first  
6 page of the Ghose article.

7 A Okay. Somehow I skipped over 2. I'm  
8 starting. Current State Of Structure-Aided Ligand  
9 Design, is that it?

10 Q Yes. Right at the bottom of that.  
11 There's a sentence that begins, "Although many  
12 approaches are aimed at correcting" --

13 A Okay. I got you.

14 Q So one of those -- yeah, including  
15 scaling of ligand and receptor atomic atom radii,  
16 and it refers to 19 to 21, which we just looked at  
17 are the Glide -- and actually, yeah, all three of  
18 those are related to Glide.

19 A Yeah, I see that.

20 Q So one of the approaches then that Ghose  
21 mentions is the use of a software to help inform  
22 structure function relationships.

1                   Is that correct?

2           A       According to what he says here. I  
3       presume that's correct.

4           Q       And then are you aware of a design  
5       program called Pymol?

6           A       Say that again?

7           Q       Are you aware of a computer structure  
8       design program called Pymol?

9           A       Pymol?

10          Q       Yeah. P-Y-M-O-L, used for looking at  
11       chemical structures in the context of protein  
12       binding, for example?

13          A       So I'm -- the program name rings a bell,  
14       but I've been away too long from structural  
15       biologist to have even a vague idea what that  
16       program does.

17          Q       Okay. All right. Then let's go, are you  
18       familiar with ChemDraw?

19          A       I'm familiar with ChemDraw.

20          Q       All right. And that was available prior  
21       to 2010, 2011, to your knowledge?

22          A       The initial releases of ChemDraw I think

1       were sometime around 1995 or thereabouts.

2           Q       Okay. All right. One more. A program  
3       called Maestro or Schrödinger? Are you familiar  
4       with that?

5           A       Schrödinger rings a bell. I have never  
6       heard of Maestro.

7           Q       If we look in this, while we have Ghose  
8       here still in front of us, if you look at Page  
9       003, under Alignment of Protein Structures you see  
10      here it's -- it says under Alignment of Protein  
11      Structures, "All qualifying files from the  
12      previous step were read into Maestro  
13      www.Schrödinger.com and examined visually to  
14      determine if the coordinate set contains a fully  
15      solved kinase domain," and then it goes on from  
16      there.

17                   And so my question is just, do you agree  
18      that Maestro/Schrödinger was available prior to  
19      June of 2011?

20          A       So according to -- according to what he  
21      states here, this is a 2008 publication, and some  
22      of the references that he uses to support his

1 statements here, it seems to me that these  
2 programs were available prior to 2010 and '11.

3 Q And do you have any recollection or  
4 understanding of what the Maestro/Schrödinger  
5 package would do?

6 A So I'm not a structural biologist and  
7 don't deal in that realm. So I am not informed as  
8 to the capabilities, the capabilities of these  
9 programs.

10 Q Okay.

11 MR. FRAZIER: Why don't we take a  
12 five-minute break, and I may be about ready to  
13 wrap up.

14 MS. PATEL: All right.

15 (A recess was taken.)

16 BY MR. FRAZIER:

17 Q So if you look at Paragraph 221 of your  
18 report?

19 A 221?

20 Q Yes. Paragraph 221.

21 A Okay, I'm there.

22 Q And you see there's a section that

1 begins, Dependent claims, and then it calls out  
2 Claim 2, Claim 3 to 7, Claim 12, and Claim 20 as  
3 you go forward?

4 A Yes, I see that.

5 Q All right. And my question is, are there  
6 any new or additional arguments that you're making  
7 for those dependent claims that are not part of  
8 the analysis that you did on the independent  
9 claims?

10 So as I read it, it looks like you're  
11 just saying there's nothing in the dependent  
12 claims that would cause them to be analyzed  
13 differently. But if you have additional arguments  
14 for the dependent claims, if you could just point  
15 them out to me?

16 MS. PATEL: Objection. Form.

17 Q A simpler version of the question is to  
18 say, for the dependent claims, do you have  
19 arguments that you're making about written  
20 description that are in addition to the arguments  
21 that you're making about the written description  
22 of the independent claims?

1 MS. PATEL: Objection. Form.

2 A No, I don't -- I don't have any  
3 additional arguments. These are certainly  
4 directed more to clinical issues. But I stand by  
5 the statements I made.

6 Q All right. And the same then if we jump  
7 to Paragraph 259 is where you address the  
8 dependent claims with respect to your analysis of  
9 enablement. And the same question there. Did you  
10 have any new arguments for the dependent claims  
11 beyond those that you made for the independent  
12 claims?

13 A So the same -- the same answer applies  
14 that I just gave you.

15 Q Okay. Okay.

16 MR. FRAZIER: All right. I have no  
17 further questions.

18 MS. PATEL: Okay. One moment.

19 We have no redirect.

20 MR. FRAZIER: Great.

21 (Off the record at 2:58 p.m. EDT.)

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ACKNOWLEDGMENT OF DEPONENT

I, HOLLIS SHOWALTER, Ph.D., do hereby  
acknowledge that I have read and examined the  
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.

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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  
Thursday, July 18, 2024, from 8:27 a.m. to 2:58 p.m.  
EDT.

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 19th day of July, 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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| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                   |                                                                                                                                                                 |                                                                                                                                                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>a1</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 184:12, 185:19,<br>185:21                                                                                         | <b>acids</b>                                                                                                                                                    | 109:21, 110:6,<br>112:3, 112:7,<br>120:17, 135:2,<br>142:4, 143:5,<br>143:21, 148:3,<br>150:9, 150:11,<br>151:1, 152:18,<br>165:8, 165:9,<br>169:18, 171:18,<br>176:19, 179:22,<br>181:17 |
| 6:5                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>above</b>                                                                                                      | 75:22, 121:6                                                                                                                                                    | <b>ad</b>                                                                                                                                                                                 |
| <b>abbvie</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 66:4, 108:15                                                                                                      | <b>acknowledge</b>                                                                                                                                              | 152:16                                                                                                                                                                                    |
| 7:9, 11:19                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <b>absence</b>                                                                                                    | 71:9, 187:3                                                                                                                                                     | <b>add</b>                                                                                                                                                                                |
| <b>ability</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 49:2, 65:8                                                                                                        | <b>acknowledgment</b>                                                                                                                                           | 53:19                                                                                                                                                                                     |
| 9:2                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>absorbed</b>                                                                                                   | 187:1                                                                                                                                                           | <b>added</b>                                                                                                                                                                              |
| <b>able</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 88:18                                                                                                             | <b>across</b>                                                                                                                                                   | 53:15                                                                                                                                                                                     |
| 8:21, 30:8,<br>30:10, 35:22,<br>36:11, 36:16,<br>36:17, 37:6,<br>41:18, 44:7,<br>44:8, 53:11,<br>59:3, 71:6,<br>78:12, 110:7,<br>117:17, 117:19,<br>149:7, 149:8,<br>162:22, 171:12                                                                                                                                                                                                                                                                                          | <b>absorption</b>                                                                                                 | 12:15, 14:20,<br>61:10, 72:22,<br>103:1, 103:9,<br>139:20, 164:10                                                                                               | <b>addendum</b>                                                                                                                                                                           |
| <b>about</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 88:5, 88:7,<br>88:15, 88:22                                                                                       | <b>acs</b>                                                                                                                                                      | 158:22                                                                                                                                                                                    |
| 19:9, 24:7,<br>25:8, 25:12,<br>25:15, 25:22,<br>26:13, 27:18,<br>31:11, 31:12,<br>37:14, 40:3,<br>40:8, 40:14,<br>41:3, 42:1,<br>46:22, 47:10,<br>48:5, 62:18,<br>62:22, 67:19,<br>76:9, 78:16,<br>78:19, 86:3,<br>94:22, 99:15,<br>109:12, 111:12,<br>111:21, 116:7,<br>119:18, 122:1,<br>124:7, 128:21,<br>129:13, 131:5,<br>138:18, 140:16,<br>142:4, 144:5,<br>144:9, 144:11,<br>156:10, 156:11,<br>157:4, 162:8,<br>165:11, 166:3,<br>166:13, 166:17,<br>168:14, 170:6, | <b>acalabrutinib</b>                                                                                              | 14:22, 15:2                                                                                                                                                     | <b>adding</b>                                                                                                                                                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 81:15, 81:16,<br>82:11, 83:3                                                                                      | <b>act</b>                                                                                                                                                      | 53:10, 92:3,<br>120:14, 139:7,<br>160:21                                                                                                                                                  |
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