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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BeiGene USA, Inc. and BeiGene, LTD.,
Petitioner

V.

Pharmacyclics LLC,
Patent Owner.

PGR2024-00009

Patent 11,672,803

Virtual Deposition of JAMES M. VEAL, Ph.D.
Friday, November 22, 2024
10:01 a.m. CST

Job No.: 560234
Pages: 1 - 243
Reported Stenographically by:
Tiffany M. Pietrzyk, CSR RPR CRR

1 Virtual deposition of JAMES M. VEAL, Ph.D.,
2 pursuant to notice, before Tiffany M. Pietrzyk, a
3 Certified Shorthand Reporter in the States of
4 Illinois, Texas, and California, Registered
5 Professional Reporter, Certified Realtime Reporter,
6 and a Notary Public in and for the State of
7 Illinois.

1 A P P E A R A N C E S

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19 ALSO PRESENT:

20 Jiang Lin (BeiGene)

21 Martin Mao (BeiGene)

22 Brian Krieger, Planet Depos Remote Tech

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C O N T E N T S

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E X H I B I T S

(Attached to transcript.)

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Exhibit 1 A document entitled "Kinase Inhibitor Drugs, Chapter 16: Practical Use of Computational Chemistry in Kinase Drug Discovery," authored by James M. Veal, dated 2009	51
Exhibit 2 Book chapter entitled "Kinases" from the book entitled "Protein Crystallography in Drug Discovery," authored by Jerry Adams and James Veal, dated 2004	101

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E X H I B I T S (cont'd)

(Not attached to transcript.)

PREVIOUSLY MARKED EXHIBITS	PAGE
Exhibit 1001 U. S. Patent 11,672,803	121
Exhibit 1060 A document entitled	139
"Discovery of Selective	
Irreversible Inhibitors for	
Bruton's Tyrosine Kinase,"	
authored by Pan, et al.,	
dated 2007, Bates numbers	
BeiGene Exhibit 1060.001 to	
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Exhibit 1106 Reply Declaration of James	22
M. Veal, Ph.D.	

1	EXHIBITS (cont'd)	
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3	Exhibit 1157 A document entitled	159
4	"Transition States and	
5	Energetics of Nucleophilic	
6	Additions of Thiols to	
7	Substituted α,β -Unsaturated	
8	Ketones: Substituent Effects	
9	Involve Enone Stabilization,	
10	Product Branching, and	
11	Solvation," authored by	
12	Krenske, et al., dated 2011,	
13	Bates numbers BeiGene	
14	Exhibit 1157.001 to .008	
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E X H I B I T S (cont'd)

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Exhibit 1158	A document entitled	160
	"Supporting Information for	
	Transition States and	
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3	Exhibit 2001 A document entitled,	150
4	"Structures of human	
5	Bruton's tyrosine kinase in	
6	active and inactive	
7	conformations suggest a	
8	mechanism of activation for	
9	TEC family kinases,"	
10	authored by Marcotte, et	
11	al., dated 2010, Bates	
12	numbers Exhibit 2001.001 to	
13	.0011	
14	Exhibit 2010 Declaration of Michael J.	190
15	Eck, M.D., Ph.D., in Support	
16	of Patent Owner's Response	
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1 P R O C E E D I N G S

2 (Witness sworn.)

3 MS. DANEK: Brenda Danek, for patent owner
4 Pharmacyclics.

5 MS. PATEL: Priyata Patel, for petitioner
6 BeiGene.

7 Actually, with me today is Kathryn Leicht,
8 from Weil Gotshal as well; and also on, petitioner
9 and representatives from our client team, Jiang Lin
10 and Martin Mao.

11 WHEREUPON:

12 JAMES M. VEAL, Ph.D.,
13 called as a witness herein, having been first duly
14 sworn, was examined and testified as follows:

15 EXAMINATION

16 BY MS. DANEK:

17 Q. Great. Dr. Veal, good morning.

18 A. Good morning.

19 Q. So I'm going to be asking you some questions
20 today regarding the declaration that you submitted
21 in support of BeiGene's reply brief concerning
22 U.S. Patent Number 11,672,803.

1 Do you recall submitting a declaration in
2 support of BeiGene's reply?

3 A. I do.

4 Q. And if I refer to patent number 11,672,803
5 as the '803 patent, will you understand what I'm
6 referencing?

7 A. Yes.

8 Q. Can you please state your full name for the
9 record?

10 A. James Veal.

11 Q. And have you been deposed before?

12 A. I have not.

13 Q. Have you ever testified at trial?

14 A. I have not.

15 Q. So let's take a few minutes to go over a
16 couple of ground rules, just to make sure we're all
17 on the same page as we proceed with today's
18 deposition. I'm going to be asking you a series of
19 questions. My questions and your answers to those
20 questions will be recorded by the court reporter,
21 who has joined us here today. The court reporter
22 cannot record, sort of, physical gestures, nodding

1 or shaking your head, so please provide verbal
2 responses to my questions.

3 Is that okay?

4 A. Yes.

5 Q. And it's very important that we do not speak
6 over one another because, again, the court reporter
7 is going to be recording everything that we say. So
8 I'll do my best to wait for you to complete a
9 response to a question before asking another
10 question if you'll do your best to wait for me to
11 finish my question before beginning your response.

12 Is that fair?

13 A. Yes.

14 Q. If you do not understand my question, please
15 let me know, and I will try to clarify or rephrase.
16 But if you answer my question, I'm going to assume
17 that you understood my question, and you're
18 responding to my question with that assumption that
19 you understand.

20 Is that fair?

21 A. Yes, that's fair.

22 Q. If you need a break at any time, please let

1 me know, and we can, you know, break for whenever
2 you need to. I just ask that if there's a pending
3 question, that you answer the question before we
4 take any break.

5 Is that okay?

6 A. Yes.

7 Q. Okay. Now, during the course of any breaks,
8 you understand that you cannot speak about the
9 substance of your testimony with your attorney.

10 Do you understand that?

11 A. I do.

12 Q. And during the deposition, your counsel may
13 make objections, but unless you are instructed not
14 to answer the question, you still need to provide a
15 response to my question.

16 Do you understand that?

17 A. I do.

18 Q. And you understand today that you are under
19 oath and obligated to testify truthfully?

20 A. Yes.

21 Q. And that's the same as if you were
22 testifying before any court of law?

1 A. Yes, I understand.

2 Q. Is there any reason that you cannot provide
3 full and accurate, truthful testimony today?

4 A. No.

5 Q. If at any time you need to clarify or amend
6 any answer that you've given to a question, please
7 let me know so that we can make sure that the record
8 of your testimony is complete and accurate. Okay?

9 A. Yes. That's good.

10 And Ms. Danek, I do have three
11 clarifications before -- to my declaration before we
12 start.

13 Q. Okay.

14 A. So I just want to make sure those are
15 addressed ahead of time.

16 Q. Sure.

17 What's the first one?

18 A. So -- and I'm just reading a written copy of
19 the clarification. So paragraph 118.

20 Q. One second.

21 Yes.

22 A. And footnote 6 of paragraph 118.

1 Q. Uh-huh.

2 A. So for clarity, I just want to indicate that
3 compound 7 of Zhang should also be included in the
4 list of compounds that I modeled. I did provide a
5 screenshot, which is included in Exhibit 1146.

6 Q. Okay. And does the rest of the substance of
7 footnote 6 also apply to compound 7?

8 A. Yes.

9 Q. Okay. And what's the second correction that
10 you need to make?

11 A. So the second correction is with respect to
12 paragraph 146.

13 Q. One second. Let me get there.

14 Okay.

15 A. So there is an "it" in the sentence
16 "Modeling suggests that structure E2 is inactive,
17 however, because it does not form any H-bonds to
18 Btk's hinge region."

19 I just want to clarify that the "it" in that
20 sentence refers to the biaryl core ring system and
21 does not include the amine substitution.

22 Q. Okay.

1 A. And similarly in paragraph 149, same thing.
2 I state in paragraph 149 that "Modeling suggests
3 that structure E3 is inactive, however, because it
4 does not form a hydrogen bond to Btk's hinge
5 region."

6 I want to clarify that the "it" in that
7 sentence refers to the biaryl core ring system. It
8 does not include the amine substitutions.

9 Q. Okay. And you mentioned that you are
10 looking at a written document, written notes
11 concerning these corrections?

12 A. So all I have is a printout of those
13 specific clarifications just as I read them.

14 MS. PATEL: Brenda, just so you know, we're
15 happy to provide those to you if you would like.
16 Yeah.

17 MS. DANEK: That would be great, yeah.
18 Please do produce the written copy of what you're
19 referring to as you provide your testimony.

20 BY MS. DANEK:

21 Q. Do you have any other written materials with
22 you to assist you with your testimony today?

1 A. So I have my declaration electronically on a
2 second screen. Then also a directory that provides
3 access to all the exhibits that are unmarked. And
4 then I have a printout of the table of contents of
5 my declaration.

6 Q. When you say that you have a -- you have
7 "access to exhibits that are unmarked," what
8 unmarked exhibits do you have access to?

9 A. Sorry. By that, I was told that for any
10 exhibits, I should not, like, you know, have
11 highlighted any paragraphs or that sort of thing.
12 So all the exhibits are, you know, unmarked in that
13 fashion.

14 Q. So they're clean copies of the --

15 A. Correct.

16 Q. Okay. And so do you have access to any
17 documents that are not exhibits that have already
18 been labeled as exhibits for this proceeding?

19 A. I do not.

20 Q. And do you have any other windows or
21 applications open and available to you for assisting
22 you in the course of providing your testimony today?

1 A. I do not. I had my Gmail window open to be
2 able to log into the Zoom link, and so that's it.
3 So ...

4 Q. Okay. If you at any point access any
5 windows, applications, or other materials beyond the
6 already labeled exhibits for this proceeding during
7 the course of your testimony, please let me know
8 what materials you are reviewing. Okay?

9 A. Yes. And I do not plan to do that.

10 Q. Dr. Veal, what did you do to prepare for
11 today's deposition?

12 A. So I had a series of meetings with counsel
13 to discuss the nature of the case, if you will. And
14 then I reviewed Dr. Eck's deposition and also
15 Dr. Showalter's deposition. I glanced briefly at
16 Dr. Scott's deposition. And then, you know, over
17 the course of meetings with my attorneys, you know,
18 became familiar with the case and the matters of the
19 case and then ultimately, that led to preparation of
20 my deposition. I'm sorry. My declaration.

21 Q. Okay. So let me break that out because my
22 question was what did you do for your -- to prepare

1 for your deposition today. I'll ask you about your
2 preparation of your declaration in a minute.

3 But specifically, to prepare for today's
4 deposition, did you -- did you do anything in
5 particular to prepare for providing testimony on
6 your declaration for -- at the deposition today?

7 A. I mean, I reviewed my declaration and also
8 exhibits that were referenced in the declaration.
9 That's primarily it. And discussed with my
10 attorneys, you know, basically how to prepare for
11 the --

12 MS. PATEL: Dr. Veal, I'm gonna just make
13 sure you -- just make sure you don't reveal any
14 privileged information while you're describing how
15 you prepared.

16 THE WITNESS: I see.

17 A. Yes. And so, you know, matters like if
18 there was an objection for foundation or an
19 objection for form.

20 MS. PATEL: Dr. Veal, you can -- I'm gonna
21 instruct you not to reveal any privileged
22 information, including any conversations that we

1 had.

2 THE WITNESS: Okay. Okay.

3 A. So I'll leave it at that then.

4 BY MS. DANEK:

5 Q. Okay. So in preparation for today's
6 deposition, you reviewed your declaration and
7 materials, exhibits that you cited in your
8 declaration; is that correct?

9 A. Yes.

10 Q. And you also had conversations or meetings
11 with counsel to discuss the deposition; is that
12 correct?

13 A. Yes.

14 Q. How many times did you meet with counsel
15 in -- specifically to prepare for your deposition?

16 A. We've had, I guess, three or four meetings.

17 Q. Okay. And about how long were the meetings?

18 A. They were, you know, a few hours in length.

19 Q. So you had three or four meetings, and each
20 were three hours in length?

21 A. Yes. Or I think in total, it was, you know,
22 probably I would say -- I'm trying to calculate off

1 the top of my head -- I'd say 16 hours of
2 preparation or meetings.

3 Q. And outside of these 16 hours of meetings
4 with counsel, about how long did you spend reviewing
5 the -- your declaration and the materials cited in
6 your declaration?

7 A. I would say several days overall.

8 Q. So several full, like, workdays, so three,
9 eight-hour days?

10 A. Yes, that's fair, in entirety from
11 preparation of my declaration and reviewing the
12 documents as part of that preparation and then, you
13 know, reviewing them again once the declaration was
14 submitted.

15 Q. So the three eight-hour days of reviewing
16 materials, that included the time you spent writing
17 the declaration, or is that just time you spent
18 after you wrote the declaration to prepare for the
19 deposition?

20 A. I would say -- so it was probably, you know,
21 I would say, you know, one of the days perhaps was,
22 in part, you know, the final preparation of the

1 declaration. And then maybe two full days of, you
2 know, studying subsequent, making sure that, you
3 know, I submitted the declaration and then didn't
4 look at it for a bit, and the same with the exhibits
5 that were part of it. So I wanted to rereview
6 those.

7 Q. Okay. In preparing for your testimony
8 today, did you review any materials that were not
9 cited in your declaration?

10 A. No.

11 Q. Did you review Dr. Showalter's recent
12 deposition transcript from a couple weeks ago?

13 A. Yes, I have seen that.

14 Q. Okay. And that wasn't cited in your
15 declaration; right?

16 A. That's correct.

17 Q. Okay. So besides Dr. Showalter's
18 November --

19 A. I'm sorry, Ms. Danek. I'm trying to recall
20 now, there was a response about the breadth of the
21 claims, and I need to look and see if that was from
22 Dr. Showalter's original deposition or his response.

1 Q. So separate from Dr. Showalter's November
2 deposition transcript, you may have reviewed another
3 reference that was not cited in your declaration?

4 A. So the matter I'm referring to is
5 Exhibit 1105, so it is cited in the declaration.

6 Q. Okay. So other than Dr. Showalter's
7 November deposition transcript, you didn't review
8 any other materials that were not cited in your
9 declaration in preparation for today's deposition?

10 A. Not that I recall.

11 Q. Okay. Let's, I guess, pull up Exhibit 1106.

12 REMOTE TECHNICIAN: Stand by.

13 (Exhibit 1106, previously marked, ^ is
14 attached to the transcript ^ was retained by
15 counsel.)

16 REMOTE TECHNICIAN: 1106 on screen. Let
17 me -- hang on just -- there we go. Just click your
18 screen, sir.

19 BY MS. DANEK:

20 Q. So, Dr. Veal, do you see Exhibit 1106 in
21 front of you?

22 A. I do. Could you make it a little larger,

1 please? Thank you.

2 Q. And, Dr. Veal, you should be able to use
3 your cursor to navigate through the exhibit on the
4 screen.

5 A. I'm not seeing a response right now.

6 REMOTE TECHNICIAN: You should just be able
7 to click your screen. Do you have an announcement
8 saying that you can control my screen?

9 THE WITNESS: It's not responding to my
10 mouse.

11 REMOTE TECHNICIAN: Looks like Zoom changed
12 their thing. I've got you checked. And it says you
13 are now able to control.

14 MS. DANEK: Why don't we take a quick break
15 off the record so we make sure we get the right
16 technical details.

17 (A short break was had.)

18 BY MS. DANEK:

19 Q. Dr. Veal, do you have Exhibit 1106 in front
20 of you?

21 A. I do.

22 Q. Do you recognize Exhibit 1106?

1 A. I do.

2 Q. What is Exhibit 1106?

3 A. Exhibit 1106 is my reply declaration.

4 Q. And this exhibit accurately reflects the
5 analysis and opinions that you offered in support of
6 BeiGene's reply?

7 A. It does.

8 Q. And if you turn to the last page of the
9 exhibit, here below paragraph 265, is that your
10 signature?

11 A. It is.

12 Q. And before signing the document, you
13 reviewed the declaration to make sure that
14 everything was accurate and complete, subject to the
15 errors that you identified earlier?

16 A. I did.

17 Q. Okay. And other than those three
18 corrections that you provided earlier today, you
19 don't have any other corrections to the declaration?

20 A. There are none that I'm aware of.

21 Q. Now, in preparing this declaration, did you
22 draft the declaration yourself?

1 A. It was done in, you know, consultation with
2 my attorneys.

3 Q. When were you first contacted to work on
4 this matter?

5 A. It would have been in the early August time
6 frame.

7 Q. August of 2024?

8 A. That's correct.

9 Q. If we can turn and look at paragraph 5 of
10 the declaration. Are you there? Dr. Veal?

11 A. Yes.

12 Q. And you say here that you've reviewed the
13 documents referenced in the declaration, including
14 Dr. Showalter's opening and reply declarations?

15 A. Yes.

16 Q. Are all of the materials that you considered
17 in forming your opinion cited in your declaration?

18 A. Yes.

19 Q. So there's no references or other materials
20 that you looked at in the course of preparing your
21 declaration that you did not cite in your
22 declaration?

1 A. That's correct.

2 Q. And so your opinions aren't based on any
3 references that you haven't cited in your
4 declaration; is that fair?

5 A. Yes. All the opinions in my declaration are
6 based on documents that are cited in the
7 declaration.

8 Q. Okay. And so if you don't cite a document
9 in the declaration, then it didn't form a basis for
10 the opinions that you're offering; is that fair?

11 A. Yes, that's fair.

12 Q. And in drafting your declaration, you wanted
13 to make sure that your analysis was complete; is
14 that right?

15 A. Yes, to the best of my ability.

16 Q. And you also wanted to make sure that you
17 identified all of the references that you could find
18 that supported your opinions; is that fair?

19 A. Yes, that's fair.

20 Q. So how did you identify the documents that
21 you cited in your declaration? How did you go about
22 doing that?

1 MS. PATEL: Objection. Privilege.

2 Dr. Veal, I'm just gonna instruct you that
3 when you answer this question, please make sure that
4 you don't reveal any substantive conversations
5 you've had with your attorneys.

6 A. Could you repeat the question, please?

7 Q. Sure. How did you identify the documents
8 that you cited in your declaration?

9 A. They are documents that appeared relevant to
10 the case. You know, obviously the '803 patent, for
11 example, and then other materials that, you know,
12 provided, I think, results that informed on my
13 consideration of Dr. Eck's deposition and where I
14 thought there were parts of his declaration that I
15 did not agree with.

16 Q. In identifying references to cite in your
17 declaration, did you search and locate those
18 references or were they provided to you by counsel?

19 A. I think there was probably a mix.

20 Q. Okay. And you mentioned that you were first
21 contacted in August of 2024 about this case; is that
22 right?

1 A. I think that's correct.

2 Q. Who contacted you -- oh, sorry.

3 A. I was gonna say I believe our first meeting
4 was in mid August roughly, perhaps before that. I
5 could go back and look, but that's roughly the
6 correct time frame.

7 Q. Who contacted you?

8 A. So counsel did. So, you know, Priya and
9 Kathryn. I forget who sent the first email exactly.

10 Q. And prior to this case, did you have any
11 relationship with the law firm Weil Gotshal?

12 A. No.

13 Q. How about the law firm Williams and
14 Connolly?

15 A. Yes, I have done some work with them in the
16 past.

17 Q. And without revealing any conversations that
18 you've had with attorneys, what was the nature of
19 the work that you did with Williams and Connolly?

20 A. It involved the use of molecular modeling or
21 computational chemistry, and I'll use those terms
22 interchangeably just to go ahead and say, but the

1 use of molecular modeling or computational chemistry
2 in drug discovery matters or on drug discovery
3 projects.

4 Q. In the course of your work with Williams and
5 Connolly, were you acting as an expert consultant?
6 Was that the nature of your work?

7 A. Yes.

8 Q. And your expert consulting, was that related
9 to patent litigation?

10 A. Yes and no. In one case, it was. In one
11 case, it was related to possible or anticipated
12 patent litigation.

13 Q. Yeah. And, again, I'm not asking you for
14 any substance of any conversations that you've had.
15 I just want to understand your experience.

16 And in your work with Williams and Connolly,
17 have you ever prepared an expert report?

18 A. I have not.

19 Q. Prior to --

20 A. Sorry. Just to clarify there, I have never
21 prepared a formal declaration. I did prepare, you
22 know, an informal write-up of the analysis they

1 asked me to perform.

2 Q. So the contents I'm asking, have you ever
3 prepared a report of your analysis that was
4 exchanged with an opposing party, besides this
5 declaration?

6 A. No, not that I'm aware.

7 Q. Okay. Prior to this -- prior to August of
8 2024, what was your relationship, if any, with
9 BeiGene?

10 A. No relationship.

11 Q. And prior to August of 2024, did you have
12 any relationship or interactions with Pharmacyclics?

13 A. No.

14 Q. And then prior to August of 2024, did you
15 have any relationship or interactions with AbbVie?

16 A. I think, in 1991, I had a job offer from
17 AbbVie, or Abbott at the time.

18 Q. And since 1991, you haven't had any
19 interactions with AbbVie?

20 A. That's correct.

21 Q. I believe you started answering this
22 earlier, but just to be clear, how long did you

1 spend between August of 2024 and when you signed
2 your declaration on October 30, 2024 -- how long did
3 you spend preparing your declaration?

4 A. So much of the time I spent involved, you
5 know, actual modeling. So whether you consider that
6 preparing the declaration or not, I'm unclear. But
7 that was the -- you know, the majority of my initial
8 efforts. And then the preparation of the
9 declaration was in the October -- the actual writing
10 part of it was in the October time frame.

11 Q. Okay. And so in October, about how many
12 hours did you spend writing the declaration?

13 A. I would say at least three days. That's an
14 estimate.

15 Q. So three working days, so about 24 hours?

16 A. Yes.

17 Q. And you mentioned that there was a portion
18 of time in the course of working towards preparing
19 your declaration that you did modeling.

20 About how long did you spend modeling
21 compounds?

22 A. I would say, you know, total work time,

1 maybe 40 to 80 hours, something like that.

2 Q. And did you conduct any modeling of
3 compounds that you did not include in your
4 declaration?

5 A. Yes, there was some. So initially, as
6 you'll see in the declaration, the work that's
7 presented was all done using the Glide software,
8 which is one of the known or Schrödinger Glide
9 software package, which is one of the leading
10 packages. Initially, I was using the MOE or
11 Chemical Computing Group software package. That's
12 because that's -- you know, that's what I had access
13 to initially.

14 With Dr. Eck's declaration and seeing that
15 he used Glide, I switched to Glide to try and
16 better, you know, assess and compare my findings to
17 his. And so that was done. And then there are
18 compounds -- for example, I think one that I recall
19 is the -- in my declaration, I discuss -- in the
20 formula E scaffold to beta 3 patent, I discuss in
21 some detail E2, E3, and E4. However, I also looked
22 at the E1, E5, E6, E7, and E8, but that, you know,

1 didn't alter in any way my opinions in the
2 declaration, so they're not included in the
3 declaration.

4 Q. And do you recall if the compounds that you
5 modeled with the other E -- formula E scaffolds, did
6 they have different or similar docking
7 characteristics to E2, E3, and E4?

8 A. They had different characteristics to E2,
9 E3, and E4. They docked very much like ibrutinib,
10 and ibrutinib can basically be, you know, viewed as
11 the template for all of those compounds. And
12 obviously, in my declaration, ibrutinib is included.

13 Q. Okay. So the docking of the other formula
14 E scaffolds docked like ibrutinib and -- but that
15 modeling, you didn't include in your declaration.

16 A. That's correct.

17 Q. Okay. Other than the compounds having the
18 other formula E scaffolds, were there any additional
19 compounds that you modeled and didn't include in
20 your declaration?

21 A. Yes, there were probably some. I was doing
22 what I would call, sort of, test docking, if you

1 will, and particularly around the question of the
2 Z-prime group and the, you know, large, you know,
3 millions and billions of compounds or whatever it
4 included. And so I was trying to understand, you
5 know, could somebody, you know, on test model
6 evaluate those. And what I ended up doing was
7 focusing on the compounds that had the -- you know,
8 known in the art at the time that had the comparison
9 to zanubrutinib in terms of, you know, a 5, 6
10 bicyclic system where one ring was aromatic and one
11 ring was not.

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

14 So in the course of your analysis, you
15 conducted some modeling of compounds with various
16 Z-prime scaffolds across the potential -- strike
17 that.

18 In the course of your analysis, you
19 conducted some modeling of various Z-prime scaffolds
20 with different characteristics; is that fair?

21 A. So all of the modeling that led to the
22 opinions expressed in my declaration is included in

1 my declaration.

2 Q. That wasn't my question.

3 So my question was you indicated that you
4 had done some modeling of compounds with the Z-prime
5 group within the large number of compounds that are
6 included within the genus of the claims.

7 Is that what you testified?

8 MS. PATEL: Objection. Form.

9 A. I looked initially at, for example, I think
10 some of the scaffolds from, like, Ghose; and,
11 frankly, the modeling of them was challenging. It
12 took a lot of time. The idea of converting those
13 sorts of compounds into something that would satisfy
14 the specification was problematic. And given the
15 amount of time and just the huge number of things
16 that you would have to consider in terms of analogs,
17 I focused in on, you know, from that kind of draft
18 modeling to what was known in the art that would
19 have relevance to zanubrutinib, in particular.

20 Q. Okay. So the compounds that you -- that you
21 said -- I think you characterized them as test
22 compounds, you did not -- those do not form the

1 basis of any of your opinions; is that right?

2 A. That's correct.

3 Q. Okay. And you didn't disclose those; is
4 that right?

5 A. Yes, that's correct. I would consider, you
6 know, if you will, the equivalent of -- you know, a
7 draft document. And so, again, I want to emphasize
8 that everything that formed the basis of my opinion
9 in the declaration is included in the declaration.

10 Q. And the 40 or 50 hours that you spent
11 modeling compounds, a portion of it was spent
12 redoing modeling that you had done in an earlier
13 software package, in the Glide software package; is
14 that right?

15 A. Yes. There was a little bit of that. You
16 know, probably ten hours maybe. Five to ten hours.
17 I don't know.

18 Q. Okay. Let's go back to your declaration,
19 Exhibit 1106.

20 MS. DANEK: I think you're projecting the
21 wrong --

22 REMOTE TECHNICIAN: This is 1106, page 7.

1 MS. DANEK: I'm seeing a chat window.

2 REMOTE TECHNICIAN: Oh, my bad. Hang on
3 just a second.

4 Oh, here it is. There you go. My
5 apologies.

6 MS. DANEK: Okay.

7 BY MS. DANEK:

8 Q. So in paragraph 6, you start discussing your
9 qualifications?

10 A. Yes.

11 Q. And you indicate that you have a Ph.D. in --
12 this is in paragraph 8. You have a Ph.D. in
13 molecular biophysics?

14 A. That's correct.

15 Q. And you did your postdoc in computational
16 chemistry?

17 A. Yes. Glaxo.

18 Q. What is computational chemistry?

19 A. So computational chemistry is -- let's see.
20 How do I summarize it succinctly? It's the effort
21 to basically reproduce physical systems or
22 biophysical systems using computer software and then

1 to, you know, leverage that ability to try and do
2 things like design new molecules or, you know, in
3 particular, improve, you know, molecules. In this
4 case or in the case of pharmaceuticals, to, you
5 know, help advance the process of drug discovery.

6 Q. Okay. So computational chemistry is using,
7 sort of, known structural information to, sort of,
8 calculate and predict interactions between compounds
9 and targets?

10 MS. PATEL: Objection. Form.

11 A. So let me start by saying that first off,
12 computational chemistry has to make use of a lot of
13 approximations on the idea that if you consider a
14 biological system, you know, you have a protein and
15 if you're looking at, you know, in respect to
16 inhibitors, then you have the ligand or inhibitor.
17 You also have, in the biological system, water
18 molecules, solvent, counterion, and you have
19 associated proteins that are interacting with the
20 protein of interest. So it's a very complex system.

21 You know, computational chemistry, you know,
22 tends to simplify it often by, you know, focusing in

1 on the specific protein of interest and the ligand.
2 You or may not include solvent, depending on the
3 amount of effort and work that you're applying to
4 the target. And then you make approximations to try
5 and understand the interactions and ultimately, it's
6 a -- you know, a quantum mechanics phenomenon how a
7 ligand is interacting with its protein target.

8 You know, there's no way at this point even
9 today and certainly not at the time of the priority
10 date that you could, you know, recreate that in a
11 computer program or with software. So you apply all
12 these approximations. You know, you treat bonds as
13 springs and, you know, torsional angles as rotors,
14 that sort of thing. And you apply all those
15 approximations. And you try and understand how
16 ligands interact with a target. And there's, you
17 know, a low probability of success.

18 Modeling can suggest compounds. And really,
19 where it's most effective is where you have a known
20 scaffold and you're trying to optimize that
21 scaffold. So the medicinal chemist has already
22 identified, you know, an inhibitor through screening

1 efforts, and now, you know, he's trying to or she is
2 trying to, you know, optimize the inhibitor by
3 attaching substituents. He or she has identified,
4 you know, possible synthetic routes and possible
5 places of substitution.

6 Then the computational chemist will work
7 with the medicinal chemist to try and understand
8 how -- you know, which might be the best place to
9 substitute that sort of thing. Again, there's a --
10 you know, low probability of success for any
11 specific compound. You're trying to improve the
12 odds. And then ultimately, of course, you always go
13 back, and you test anything that's made -- after the
14 effort is made to -- when I say "test," you test in
15 a biological assay after the compound, the effort
16 has been made to synthesize the compound. And so
17 you learn from the results and then, you know, go to
18 the next step.

19 Q. Okay. So I think, you know, it will be
20 really helpful for today's deposition if you listen
21 carefully to my question and make sure you're
22 responding to the question I ask. That was a really

1 long -- a really long exposition, I think, that
2 wasn't quite responsive to my question. So I think
3 it would be useful to make sure that we're
4 communicating properly, that you're listening to the
5 question I'm asking, and you're responding to that
6 question. Is that okay?

7 A. Yes. Apologies. You asked me what a
8 computational chemist does, and it's a very broad
9 question.

10 Q. So what I -- so one of the things that you
11 mentioned is that -- the way that computational
12 chemistry is most effective is when there's a known
13 binding mode for a ligand to a target protein; is
14 that fair?

15 A. Yes, that's fair.

16 Q. Okay. And so in that instance where there's
17 a known binding mode for a ligand to a target
18 protein, then the application of modeling in
19 computational chemistry can be very valuable; is
20 that right?

21 MS. PATEL: Objection. Form.

22 A. The application of computational chemistry

1 can lead to suggestions about, you know, how to
2 improve that, you know, core scaffold that's binding
3 to the target.

4 I'm not sure what you mean by "very
5 valuable."

6 Q. Okay. That works.

7 So it -- they can help you identify how to
8 improve the core scaffold that's binding to the
9 target.

10 MS. PATEL: Objection. Form.

11 A. It can suggest, you know, derivatives of the
12 core scaffold that you could then try and synthesize
13 and then test in a biological assay.

14 Q. Okay.

15 A. The computational chemistry itself, you
16 know, does not, without the additional effort to
17 prepare the molecule and then test it in a
18 biological assay, computational chemistry is just
19 suggesting possible routes. And then there's the
20 subsequent -- multiple subsequent steps to
21 understand if there was, you know, an improvement in
22 the new ligand that was made.

1 Q. Okay. In paragraph 6 of your declaration,
2 you identify that you had worked on
3 interdisciplinary project teams where your role was
4 as the project team computational chemist; is that
5 right?

6 A. Yes, that's correct.

7 Q. So in the context of, for example, kinase
8 inhibitor, design or kinase inhibitor projects, it's
9 common to have a team of scientists working on those
10 projects?

11 MS. PATEL: Objection. Form.

12 A. I think there are different situations. So
13 there is the time where you have a program that's
14 just starting and you're trying to identify core
15 scaffolds or, you know, initial inhibitors. And
16 there it's, you know, often, particularly at the
17 time of priority date, you have a medicinal chemist
18 that is basically trying to understand what
19 molecules he or she might synthesize, and then that
20 could be coupled also with some sort of high
21 throughput screening of where the biologist, initial
22 biologist on the program is testing, for example,

1 corporate compound collection or is testing
2 compounds that the medicinal chemist may have
3 ordered in from vendors. And so in that situation,
4 you don't necessarily have other team members.

5 Once you've identified a lead scaffold and
6 you're sort of in the, you know, optimization
7 process, that's where, you know, typically I've come
8 on as a team member, if that makes sense.

9 Q. Okay. So once there's a compound that has a
10 known binding mode in looking for -- in a kinase
11 inhibitor project, then the team would include you
12 as a computational chemist and medicinal chemists
13 and potentially other team members; is that right?

14 MS. PATEL: Objection. Form.

15 A. I would say yes, that's correct. And for
16 kinase specifically, you know, that would be the
17 core scaffold that would interact with the hinge
18 region, which I think is understood from the
19 different declarations as, you know, the region that
20 forms the hydrogen bonds to the endogenous ligand
21 ATP to the adenine portion of ATP.

22 Q. Okay. And in the context of this case, it's

1 the Z-prime that forms the hydrogen bonds to the
2 hinge region of Btk; right?

3 MS. PATEL: Objection. Form.

4 A. So I -- I actually don't know what Z-prime
5 means specifically. I know it is in the claims --
6 in Claim 1. But in terms of the description, it's
7 really, you know, ibrutinib and maybe the formula E
8 structures and -- but to the extent you're saying
9 it's ibrutinib, it's the -- it would be the
10 pyrazolopyrimidine core of ibrutinib that would form
11 the hydrogen bonds to the hinge region.

12 Q. So that structure, the 5-6 fused
13 heterocyclic structure of ibrutinib is the structure
14 that forms the hydrogen bonds to the hinge; right?

15 A. The pyrazolopyrimidine of ibrutinib is what
16 forms the hydrogen bonds to the hinge region.

17 Q. And the pyrazolopyrimidine is a 5-6 fused
18 heterocyclic structure?

19 A. It is a biaryl where both rings are
20 heteroaryl structures so yes, it is a member of a
21 5-6 heterocyclic system or class.

22 Q. So you've mentioned you've worked on -- in

1 your declaration. You mentioned you've worked on a
2 number of kinase inhibitor projects and that you led
3 modeling efforts in connection with those.

4 When you were working on these kinase
5 inhibitor projects, did you do all of the modeling
6 yourself for those projects?

7 A. By and large, yes. I think I reference one
8 HER2, and in that case, I start off doing the
9 modeling, and then at the end of that, I was
10 supervising the, you know, junior computational
11 chemists, if you will, that were doing the modeling
12 on that.

13 Q. Okay.

14 A. Otherwise, yes. Otherwise, yes.

15 Q. Okay. So at some point in your role in
16 leading modeling efforts, you started supervising
17 others who were doing the modeling and you would
18 review those modeling results; is that fair?

19 A. That's fair.

20 Q. Okay. So in those instances, you weren't
21 the one manipulating and entering into the computer
22 program the structures and, you know, looking at the

1 parameters; is that right?

2 MS. PATEL: Objection. Form.

3 A. So you can see there six programs listed,
4 and I'm referring to -- well, whichever paragraph is
5 being shown on the screen. CDK2, P38, CDK4, VEGFR2,
6 HER2, PLK1. And there were other kinase programs I
7 worked on as well. HER2 is the only one where I was
8 not doing the day-to-day modeling, if you will. And
9 I started off doing that on HER2. So I would
10 characterize that the large majority of the kinase
11 modeling I've done, I was the person -- or that I
12 was involved with, I was the person doing the actual
13 modeling.

14 Q. Okay. In paragraph 12?

15 REMOTE TECHNICIAN: Counsel, Mr. Veal is
16 able to take mouse control now if he would like.

17 Just click your screen, sir.

18 THE WITNESS: Okay.

19 BY MS. DANEK:

20 Q. Page 7.

21 A. Yeah, sorry. It's not super responsive.

22 Q. Uh-huh.

1 A. Okay.

2 Q. So at paragraph 12, you start discussing
3 your career starting in 2009; is that right?

4 A. Yes.

5 Q. Okay. And in 2009, you became vice
6 president of research at Pamlico Pharmaceutical?

7 A. That's correct.

8 Q. And in your role as vice president of
9 research, did you perform modeling for any projects?

10 A. I did. Actually, you know, so after I left
11 Glaxo, so that was, I guess, in the 2003 time frame,
12 I went to a company Serenex, which was the one maybe
13 listed previous to this. So I went into biotech.
14 And at biotech, you wear many hats. And even as I
15 have moved up in terms of position, I have still
16 continued to have an active role in the
17 computational chemistry effort. And that's just the
18 nature of biotech where, you know, you may have, you
19 know, senior roles, if you will, presentations to
20 investors and the like, but you also have day-to-day
21 discipline roles.

22 And even to this day, in my current company,

1 858 Therapeutics, I still perform computational
2 chemistry. Our biology founders still does, you
3 know, assays in the lab. Our organic chemist
4 founder still actively is involved in preparing
5 synthetic schemes. So that's the nature of biotech.
6 You wear hats where you have senior cross-functional
7 roles but you still also have active roles with
8 regards to your specific discipline.

9 Q. And in addition to doing modeling -- some of
10 the modeling yourself, you also rely on junior team
11 members to perform modeling that you review; is that
12 right?

13 A. Not at Pamlico. And thinking out through my
14 career history, I think at Quantical
15 Pharmaceuticals, we had others that were doing
16 modeling -- or one other that was -- you know, not
17 even a dedicated modeler. That person was still a
18 medicinal chemist as well. So I've been the one
19 that does the dedicated computational chemistry.

20 Q. So in all of your projects since 2009, if
21 there was modeling to be done, you're the only
22 person who would do it?

1 A. I wouldn't say I'm the only person that does
2 it. I do the majority of it. And particularly for
3 complex tasks like trying to dock a molecule to a
4 protein target, I would handle that role.

5 Increasing these days, medicinal chemists -- and
6 even in 2011, medicinal chemists also may have some
7 molecular modeling expertise. And so they may be
8 doing some themselves. But I have retained an
9 active familiarity with computational chemistry and
10 modeling.

11 MS. DANEK: I think we've been going for a
12 little over an hour. Why don't we take a break.

13 (A short break was had.)

14 BY MS. DANEK:

15 Q. Dr. Veal, what will be displayed on the
16 screen shortly is a document entitled "James M.
17 Veal, Kinase Inhibitor Drugs, Chapter 16: Practical
18 Use of Computational Chemistry in Kinase Drug
19 Discovery." You should be able to manipulate this,
20 including zooming in how you prefer. But please
21 take a minute to look at this document, which will
22 be marked Veal Exhibit 1.

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

3 THE WITNESS: Am I able to zoom it myself?

4 REMOTE TECHNICIAN: Yes, just the plus and
5 minus up here.

6 THE WITNESS: Okay. Got it.

7 MS. PATEL: Can we get it dropped in the
8 chat, too, please? I don't see it available for
9 download for us.

10 REMOTE TECHNICIAN: Let me have mouse
11 control real quick for a second, Mr. Veal.
12 Mr. Veal, if you can let me have it for just a
13 second here.

14 THE WITNESS: Do I have to give it back to
15 you or not?

16 REMOTE TECHNICIAN: Okay. Now, go ahead and
17 click your screen again. You're good.

18 THE WITNESS: Okay.

19 BY MS. DANEK:

20 Q. Dr. Veal, do you see this document in front
21 of you?

22 A. I do.

1 Q. And do you recognize this document?

2 A. Yes. It's from a while ago.

3 Q. Is this a book chapter that you wrote and
4 published in 2009 on the practical use of
5 computational chemistry in kinase drug discovery?

6 A. It is.

7 MS. PATEL: Can we just still -- I'm not
8 seeing it on the chat for us to download.

9 MS. DANEK: I see it in the chat.

10 REMOTE TECHNICIAN: Yeah, I did send it to
11 everyone.

12 MS. PATEL: It is not showing up for me.

13 REMOTE TECHNICIAN: Mr. Veal, if you'll
14 allow me real quick --

15 THE WITNESS: Okay.

16 REMOTE TECHNICIAN: Okay. I just sent it
17 again.

18 MS. PATEL: I think -- like, I see -- the
19 only message I see is from Tiffany with the
20 real-time information. I think others on our side
21 are not able to see it either.

22 ///

1 BY MS. DANEK:

2 Q. Dr. Veal, do you see it in the chat?

3 A. I'm not looking in the chat. I see it on
4 the screen.

5 MS. PATEL: Can you take a quick look at the
6 chat, Dr. Veal, and let us know if you can see a
7 link to download the exhibit?

8 THE WITNESS: I'm not -- I'm looking for the
9 chat now.

10 MS. PATEL: The bottom of your screen.

11 THE WITNESS: Oh, okay. For some reason,
12 my -- all the stuff on the bottom of my screen has
13 gone away.

14 REMOTE TECHNICIAN: First of all, Counsel,
15 you want to go off the record?

16 MS. DANEK: Yeah, let's go off the record.

17 (A short break was had.)

18 MS. DANEK: Okay. Can we put up Veal
19 Exhibit 1 on the screen, please?

20 Q. Dr. Veal, can you see what's been marked as
21 Veal Exhibit 1 now?

22 A. Yes.

1 Q. Do you have control of it?

2 A. I do.

3 Q. Okay. And you indicated that you did
4 recognize this document.

5 A. Yes.

6 Q. Okay. This is a book chapter that you
7 wrote?

8 A. Yes.

9 Q. And published it in 2009?

10 A. Yes.

11 Q. Have you reviewed this recently?

12 A. I have not.

13 Q. But you expect that everything that you said
14 in -- or you made sure that everything that you
15 wrote in this chapter was accurate in order to
16 publish it?

17 A. To the best of my knowledge, yes.

18 Q. Okay. Okay. So if you can turn through the
19 front matter to the chapter?

20 A. Do you know what page that is on?

21 Q. I think it might be on page 14.

22 A. Okay.

1 Q. Oh, 15.

2 A. Okay. I think I'm there.

3 Q. And then I'll use the page numbers of the
4 printed page. So you can see this is page 403,
5 which is the front page of your chapter?

6 A. Yes.

7 Q. Okay. And if you stop here at page 405 --
8 I'm sorry -- 404, that top paragraph, in here, you
9 describe the goal of your chapter.

10 Do you see that?

11 A. Yes. Allow me to look at it for a moment.

12 Q. Uh-huh.

13 A. Okay.

14 Q. And in putting together this chapter, you
15 wanted to present to the field how computational
16 techniques apply in kinase inhibitor design; is that
17 right?

18 MS. PATEL: Objection. Form.

19 A. Yes, that's correct, looking at the
20 introduction.

21 Q. Okay. And in putting together the chapter,
22 you did some research and identified that "modeling"

1 and "docking" and "computational" and
2 "structure-based" and "structure activity" were
3 keywords that appeared hundreds of times in the
4 context of kinase inhibitors; is that right?

5 MS. PATEL: Objection. Form.

6 A. Yes.

7 Q. Okay. And so at least by 2009, there were
8 numerous examples of modeling and docking and
9 structure-based activity in the context of kinase
10 inhibitor design; is that right?

11 MS. PATEL: Objection. Form.

12 A. Yes. Computational chemistry was being used
13 and applied to kinase drug discovery.

14 Q. Okay. And, in fact, you identify that one
15 of the objectives was to focus on how these
16 techniques can be effectively integrated with other
17 team members of kinase inhibitor projects, including
18 medicinal chemists and screening biologists; is that
19 right?

20 A. Yes.

21 Q. And so the teams that you were talking to
22 for kinase inhibitor design included medicinal

1 chemists, screening biologists, and computational
2 chemists; is that right?

3 MS. PATEL: Objection. Form. Foundation.

4 A. Yes, that's correct. I --

5 Q. Okay.

6 A. -- I would have to review the chapter, but I
7 think it's referring to, you know, where a project
8 had launched on a specific target. And so you've
9 brought together a team of scientists.

10 Q. Okay. And if you turn to section 16.3.3,
11 which is at page 411 of the publication.

12 A. Yes.

13 Q. Okay. So here in section 16.3.3, it's
14 entitled -- you have a section entitled "Focused
15 Compound Collections, Library Design, and Novel
16 Scaffolds for Screening"; is that right?

17 A. Yes.

18 Q. Okay. And in this section, the third
19 sentence of that first paragraph under this section,
20 it reads, "First, the adenine moiety of ATP provides
21 a defined scaffold from which to derive a range of
22 core templates, which can then be incorporated into

1 two-dimensional descriptor-based searches."

2 Do you see that?

3 A. Yes.

4 Q. Okay. And you go on to say, "that the
5 protein kinase ATP-binding pocket provides a
6 well-defined pharmacophore target in terms of
7 hydrophobic cleft, designed for an aromatic ring
8 system, and an adjacent acceptor-donor-acceptor
9 hydrogen-bonding motif afforded by the hinge
10 region."

11 Do you see that?

12 A. Yes.

13 Q. Okay. And so part of the reason that you
14 say the ATP-binding pocket is a -- well-suited for a
15 range of templates is because the active site has
16 this hydrophobic cleft next to the
17 acceptor-donor-acceptor hydrogen-bonding motif of
18 the hinge; right?

19 MS. PATEL: Objection. Form.

20 A. Yes, that's correct.

21 Q. Okay. And, in fact, you show that in
22 figure 16.5 just below; right?

1 A. Yes.

2 Q. So on the left side of figure 16.5, you have
3 a depiction of the adenine of ATP hydrogen bonding
4 to the hinge region of a kinase; right?

5 MS. PATEL: Objection. Form.

6 A. Yes.

7 Q. And on the right side, you have what you
8 call "Representative substructures that can be used
9 in developing screening libraries"; is that right?

10 A. Yes.

11 Q. Okay. And you indicate that the
12 substructures "all have precedent as adenine
13 mimetics for protein kinases"; right?

14 A. Yes.

15 Q. And the substructures that you identify as
16 adenine mimetics include all the structures on the
17 right -- strike that.

18 Let me start over.

19 So all the structures on the right, you
20 identify as adenine mimetics for use in kinase
21 inhibitor design; right?

22 MS. PATEL: Objection. Form.

1 A. I think how these scaffolds would be used is
2 on the idea that -- well, two ways. One is where
3 you have an existing corporate compound collection.
4 There may be hundreds of thousands or millions of
5 compounds. And you're trying to get down to a set
6 to screen against say a new kinase target of
7 interest to something that's in the range to 20 to
8 40,000 compounds and so that when you perform the
9 biological assays and screening, you, you know, have
10 a chance of not having to screen so many compounds.
11 And so you would run scaffolds like this against
12 your corporate library and try and develop a focus
13 kinase set, if you will, that then, you know, once
14 you, you know, clone the kinase and develop the
15 assay, you would then test against.

16 Alternatively, you may want to bring in
17 additional compounds from external vendors, and
18 again, you know, you have millions of choices about
19 what compounds you might want to bring in from
20 vendors. So you might use scaffolds like these to
21 try and filter and bring in compounds from the
22 vendor to add to the corporate compound collection,

1 which, again, then you would use -- you know,
2 incorporate into the screening paradigm to see if
3 you can identify, you know, hits of interest that
4 then you would try and optimize using medicinal
5 chemistry as part of a project team effort.

6 Q. Okay. So let's go back to my question,
7 which was that the scaffolds that you identify on
8 the -- in the right part of figure 16.5 are
9 representative substructures that you note are
10 adenine mimetics in the context of kinase inhibitor
11 design; correct?

12 MS. PATEL: Objection. Form.

13 A. Yes. But to be clear, there is no guarantee
14 at all and actually, you know, a low probability
15 that any specific scaffold, unless it's, you know, a
16 direct -- you know, a mimetic to ATP would bind to a
17 specific kinase of interest. And so the way to use
18 these scaffolds is more to bias compound collections
19 for screening purposes with the hope that when you
20 test, you know, one -- you know, a compound that may
21 have been either culled from the corporate library
22 that already exists or brought in from a vendor with

1 the hope that once you test it, it would provide a
2 hit structure that then you could try and optimize.

3 Q. Okay. So what you told the field in 2009
4 was that these were substructures that had precedent
5 as adenine mimetics; correct?

6 MS. PATEL: Objection. Form.

7 Q. This is a yes or no answer.

8 A. Yes.

9 Q. Okay. And the substructures that you told
10 the field in 2009 were adenine mimetics included
11 structures that weren't fully aromatic; correct?

12 MS. PATEL: Objection. Form. Foundation.

13 A. Yes.

14 Q. Okay. And so in 2009, you would agree then
15 that adenine mimetics did not have to be fully
16 aromatic; correct?

17 MS. PATEL: Objection. Form.

18 A. Yes.

19 Q. And, in fact, the adenine mimetic
20 substructures that you identified also had a variety
21 of different hydrogen-bond participating functional
22 groups in them; is that right?

1 MS. PATEL: Objection. Form.

2 Q. Let me be more clear.

3 The hydrogen-bond interacting portions of
4 adenine as seen on the left are the exocyclic amine
5 and the nitrogen that form -- that is part of the
6 six-membered ring; is that right?

7 A. Correct.

8 Q. Okay. But the adenine mimetic structures
9 that you identify do not all have
10 hydrogen-bond-forming functional groups limited to
11 an exocyclic amine and a nitrogen as part of an
12 aromatic six-membered ring; correct?

13 MS. PATEL: Objection. Form.

14 A. I think the point here is that --

15 Q. The answer -- you can say your answer, but
16 my question is -- please focus on my question --
17 that the adenine mimetic structures that you
18 identify are not limited to those structures that
19 have an exocyclic amine and a nitrogen in a
20 six-membered aromatic group.

21 MS. PATEL: Objection.

22 Q. Is that right?

1 MS. PATEL: Objection. Form.

2 A. The point of showing these different
3 fragments is the concept of improving screening
4 library potential. And yes, while there's no
5 requirement necessarily to have the, you know, amino
6 pyrimidine moiety of ATP in these scaffolds, there's
7 also no guarantee that any one of these would bind
8 to a particular kinase of interest. And in fact,
9 there would be, you know, probably a low probability
10 that any one of them would bind to a specific kinase
11 of interest. And so without elaborating these
12 fragments via medicinal chemistry efforts and
13 performing the biological testing, you would not
14 know.

15 Q. Okay. So the adenine mimetic substructures
16 that you identified in 2009 included structures that
17 would form hydrogen bonds via an amide group;
18 correct?

19 MS. PATEL: Objection. Form. Foundation.

20 Q. If we look at the top right structure in
21 16.5, those -- that structure is presenting an amide
22 group as hydrogen bond for the formation of hydrogen

1 bonds to the hinge; correct?

2 A. I think if you look at the first sentence of
3 the legend where it says "Representative
4 substructures that can be used in developing
5 screening libraries," that is the point of these
6 fragments where you use these to either create a
7 focus library out of the existing compound
8 collection or you go out and run them against
9 external vendors and identify compounds that you
10 might want to bring in for screening.

11 Again, there's no guarantee of success with
12 any one of these fragments against a specific
13 kinase, and I would actually have to look back and
14 see, with respect to the one that you're
15 referencing, whether that -- whether there was
16 literature precedence or whether it was just an idea
17 of using that to bring in compounds for screening
18 purposes that then might, you know, enable a
19 medicinal chemist to start a program.

20 Q. Okay. Let me ask you a very specific
21 question.

22 If we look at the structure in the top

1 right, that is a saturated nonaromatic cyclic ring
2 with an amide substitution off of it; is that right?

3 A. Yes.

4 Q. Okay. And it's the amide substitution that
5 would have the potential to form hydrogen bonds to
6 the hinge of the kinase; correct?

7 MS. PATEL: Objection. Form. Foundation.

8 A. That would have the potential, but it would
9 require bringing in a specific compound that has
10 that feature for testing or for synthesis, and the
11 probability of success would be low for any specific
12 compound.

13 Q. Okay. But what you told the -- and what you
14 told the field was that the structures in 16.5,
15 including the one in the top right, which is a fully
16 saturated ring with an amide substitution, that they
17 have precedent as adenine mimetics; correct?

18 MS. PATEL: Objection. Form.

19 A. Yes.

20 Q. Okay. And in addition to the saturated ring
21 with the amide substitution as a precedented adenine
22 mimetic, you also included, for example, in the

1 lower left on the right-hand side, another saturated
2 ring with a nitrogen and a carbonyl substituent.

3 Do you see that?

4 A. Yes.

5 Q. Okay. And so this is another saturated ring
6 with a different hydrogen bond-forming potential of
7 functional groups than adenine; correct?

8 MS. PATEL: Objection. Form.

9 A. Again, I would say that these are fragments.
10 They would have to be incorporated into a larger
11 molecule. They would have to be, you know, either
12 synthesized or identified through an external vendor
13 or through a corporate compound collection. You
14 would hope that one of these might bind to a kinase
15 of interest. There would be a low probability of
16 success. And you certainly wouldn't know without
17 testing the molecule.

18 In other words, what the computational
19 chemistry is doing here is suggesting yes, you might
20 look at these sorts of fragments, again, to
21 prioritize what you screen in a corporate compound
22 collection or to prioritize what you purchase from

1 an external vendor but --

2 Q. Okay. Let me go back to my question.

3 A. -- the probability of success --

4 MS. PATEL: Let him answer the question,
5 please.

6 A. The probability of success would be low and,
7 you know, the question of what sort of potency you
8 would get, again, would it be interest? I think the
9 idea is that these are suggestions. They're in no
10 way predictions, and there's a low probability of
11 success -- you wouldn't know at all without
12 screening any of these fragments as part of a, you
13 know, a larger scaffold that they were incorporated
14 into.

15 Q. Okay. I understand you have a position
16 about all of the next steps. I am asking you about
17 a very particular question that's very focused. So
18 if you could please try to focus on the question I
19 am asking, and if your counsel wants additional
20 information, she can ask follow-up questions. But
21 please listen to the question that I am asking.
22 Okay?

1 A. Yes.

2 Q. Okay. Looking at the lower left structure
3 on the right-hand side of figure 16.5, that is a
4 saturated heterocyclic ring with different
5 functional groups that have the potential to form
6 hydrogen bonds than the functional groups present in
7 adenine; is that correct?

8 MS. PATEL: Objection. Form.

9 A. Yes.

10 Q. Okay.

11 A. And, again, I would say --

12 Q. If you have -- if your counsel has
13 additional questions, she can ask you, but you've
14 answered my question so I'm gonna move on.

15 MS. PATEL: Let him --

16 MS. DANEK: He finished.

17 MS. PATEL: No, no. He clearly wants to
18 finish his answer.

19 A. Again, I think it's really important to
20 emphasize the context of, you know, how these
21 fragments that you're pointing to would be used, and
22 it's the idea that they would be used to prioritize

1 a corporate compound collection or to find
2 additional molecules from an external collection.
3 They would have to be incorporated into a larger
4 molecule, if you will, given their small size.

5 There would be a low probability of success
6 for any one of these to bind to any particular
7 kinase and that you would have to, you know,
8 synthesize or optimize these scaffolds if you were
9 not purchasing them for screening, and you would
10 have to conduct all activity around screening. In
11 other words, the computational chemistry here
12 suggests these fragments to try and bring something
13 in, but in no way is it like, oh, well, this
14 predicts what's gonna happen, so ...

15 Q. Dr. Veal, I'm asking very specific
16 questions. I understand you have a position about
17 all of the additional testing and that there's no
18 guarantee. We've heard a lot. So understood. I've
19 heard that. But I am asking very specific
20 questions. So please listen to my questions and
21 respond to those. Okay?

22 A. I'm trying to provide the appropriate

1 context.

2 Q. I have heard you say it a lot already. So
3 now I'm asking my questions, and please focus on my
4 questions. Okay?

5 Now, in your description to the field in
6 2009 about representative substructures that could
7 be adenine mimetics, at the end of the figure
8 caption, you state "Note also that combining or
9 substituting the various mimetics allows for
10 targeting an additional backbone carbonyl group in
11 the hinge region that is well positioned for
12 hydrogen bonding."

13 Do you see that?

14 A. Yes.

15 Q. Okay. And so here you're identifying for
16 the field that additional combinations and
17 functional groups that have the capability of
18 forming hydrogen bonds to the hinge may also be
19 appropriate adenine mimetics; is that correct?

20 MS. PATEL: Objection. Form.

21 A. Yes.

22 Q. Okay. Okay. Let's scroll to page 413. Are

1 you at 413?

2 A. I thought so.

3 Q. Do you see at the top of the page, there's a
4 sentence there that says "Virtual screening, in
5 which a database is searched and evaluated, leading
6 to a specific screening set for a specific target is
7 now also routinely employed as a method to identify
8 hits or starting compounds of interest for a given
9 kinase."

10 Do you see that?

11 A. Yes.

12 Q. And you go on to say "The methodology used
13 may involve direct docking of compounds into a
14 kinase X-ray or model structure or the development
15 of a 3-D pharmacophore model that is then used to
16 search a database."

17 Is that right?

18 A. Yes.

19 Q. And so in 2009, a virtual screening using
20 X-ray crystallography data was a known technique for
21 assessing the potential for kinase inhibitor
22 binding?

1 MS. PATEL: Objection to form.

2 A. So I'm glad you --

3 MS. PATEL: Objection to form.

4 A. This is exactly -- I mean, I guess I wasn't
5 describing it clearly, but this is what I was trying
6 to describe. So you would use those fragments and
7 you would use those to, you know, develop a focus
8 screening step from an existing corporate compound
9 collection or you'd use virtual screening of an
10 external database to bring in specific existing
11 molecules that were known to screen against the
12 kinase. And so you're -- in both cases, you have
13 already existing molecules that you're either --
14 you're trying to improve your probability of success
15 by either reducing the amount of a corporate -- the
16 size -- you have to screen from a corporate compound
17 collection or, you know, bringing in a set of
18 molecules from an external vendor. So that's what's
19 meant by virtual screening here.

20 Q. Okay.

21 A. That's why I was trying to describe it above
22 is that you go out and you look at these existing

1 molecule sets, something that's already known, and
2 you bring them in and then you do the biological
3 assay and test them and hope that you get, you know,
4 some small fraction of hits out of the larger number
5 of compounds that you bring in.

6 Q. And part of that effort that you describe
7 was the use of virtual screening, which would be
8 docking of compounds of a larger library into a
9 structural information for a particular kinase; is
10 that right?

11 A. Right.

12 MS. PATEL: Objection to form.

13 Q. Yes. Okay. So now can we go --

14 A. No, I wanted to answer that question. So
15 you would -- the virtual screening would involve,
16 again, using perhaps one of those fragments that you
17 described above to identify compounds from your
18 corporate compound collection or from an external
19 vendor, known compounds that would then be brought
20 in and potentially docked for screening. And so
21 it's -- it's always the idea that you have, you
22 know, the known compound, and it's always the idea

1 that it's -- that these are then going to be
2 screened with the hopes of identifying hits and, you
3 know, the additional caveat is the probability that
4 any one is gonna be a hit is low.

5 Q. Okay. Let's turn to page 414. Here at the
6 top, you have Section 16.3.3.2 with the heading
7 "Novel Scaffold Identification"; right?

8 A. Yes.

9 Q. And you're informing the field in 2009 that
10 an increasing role for computational chemistry in
11 the realm of kinase drug discovery is to assist in
12 the design of novel scaffolds; correct?

13 A. Yes.

14 Q. And two sentences later, you say "One method
15 for addressing the challenge within the field is to
16 design and synthesize novel templates, including
17 so-called scaffold morphing or hopping, and as such
18 de novo design has arguably been used more in the
19 kinase target space than in any other protein
20 systems class."

21 Is that right?

22 A. Yes.

1 Q. So one of the ways that computational
2 chemistry was used in kinase inhibitor projects was
3 to design new scaffolds based on scaffold morphing
4 or scaffold hopping; is that correct?

5 MS. PATEL: Objection. Form.

6 A. Yes. But to be clear -- and I want to
7 again, you know, put the appropriate context here,
8 the idea of conceiving a novel template or scaffold
9 morphing has a low probability of success as is
10 indicated in my declaration in response to some of
11 the articles that Dr. Eck pointed me to. And it
12 requires subsequent synthesis and testing, and I
13 want to emphasize the low probability of success. I
14 think that's a key point. So there may be
15 suggestions and if you have, you know, a medicinal
16 chemist that's agreeable to synthesize the molecules
17 and then, you know, you test them, you may have some
18 success. But it's a very challenging and
19 time-consuming effort.

20 Q. Okay. And you told the field that in
21 particular, the idea of morphing or hopping
22 scaffolds that would bind within the ATP-binding

1 site was of particular -- had been used more for
2 kinases than any other protein target; is that
3 right?

4 MS. PATEL: Objection. Form.

5 A. The reason for saying that is because of the
6 available structural information or X-ray data that
7 were available for kinases.

8 Q. And in 2009 -- by 2009, there was actually a
9 significant amount of structural data available to
10 the field concerning the ATP binding, the structure
11 of the ATP-binding site; correct?

12 MS. PATEL: Objection. Form. Foundation.

13 A. I mean, "significant" is a -- is sort of a
14 qualifier. But yes, there were a fair number of
15 X-ray structures that were available for kinase
16 targets.

17 Q. Yeah.

18 And in particular, the ATP-binding site of
19 kinases was a well-conserved structure across
20 kinases; correct?

21 MS. PATEL: Objection. Form. Foundation.

22 A. I would take issue with that. What you have

1 is the -- you have a common protein fold where you
2 have an end-terminal region that then goes to the
3 hinge region, and that's why they call it the hinge.
4 And then it connects to a C-terminal region. So you
5 have that common protein fold, but you have, you
6 know, multiple amino acid differences that then can,
7 you know, determine whether one molecule will bind
8 against a specific kinase or not. And so there's a
9 conserved ATP-binding site, if you will, in terms of
10 protein fold, but the amino acids may be quite
11 different. And so, you know, each kinase is its own
12 entity, if you will, in that regard. And so whether
13 a specific compound will bind to a specific kinase,
14 again, requires, you know, testing.

15 Q. And by 2011, the crystal structure of Btk,
16 so the active site of Btk was available to the
17 field; correct?

18 MS. PATEL: Objection. Form. Foundation.

19 A. Yes. If you're referring to the Marcotte
20 structure, that's correct.

21 Q. We've been calling it Marcotte.

22 A. Sorry. Yeah.

1 Q. I'm not sure if you have a better
2 pronunciation history with that, but is that what
3 you're referring to, the Marcotte structure?

4 A. Yes.

5 Q. Yeah.

6 At the bottom of the page, you have a
7 section called "Hit Optimization."

8 Do you see that?

9 A. Yes.

10 Q. And in this section in that first paragraph,
11 you indicate that "The goal of the computational
12 chemist at this point is to develop plausible models
13 that can provide insight into binding modes, offer
14 strategies for optimization, and suggest routes to
15 pursue to improve selectivity if that is an issue."

16 Do you see that?

17 A. Yes. And then I'd also point to the
18 sentence that follows that --

19 Q. Okay.

20 A. -- where "The goal is not to provide the
21 designed candidate molecule," rather it's "to
22 facilitate the discovery project -- process that" --

1 which, of course, involves synthesis and testing and
2 "leads a project team to a candidate molecule." And
3 then I think the other thing is the idea that it
4 suggests -- and that's the -- I know we've had a
5 back and forth, but that's the point I'm trying to
6 make is that you have to put the modeling of the
7 computational chemistry in the appropriate context,
8 and that's that there's consistently a relatively
9 low probability of success, and so you're suggesting
10 things. You're trying to help out the medicinal
11 chemist. In this case, it's where you have a known
12 binder that's already been identified, and so, you
13 know, I think context is important here for how --
14 what's being described.

15 Q. So in the context of having a known binder,
16 computational chemistry has more information to
17 provide around how modifications to that known
18 binder might affect binding mode and activity?

19 A. Yes. This is --

20 MS. PATEL: Objection to form.

21 A. Yes. This is where I would say that the,
22 you know, significant majority of my work as a

1 computational chemist has been. It's the idea that
2 you're not conceiving of a core that binds to the
3 hinge region. You've already identified that
4 through some screening process. And we discussed
5 that above. But then now, the medicinal chemist is
6 trying to improve the potency. Say it's a low
7 micromolar initial hit that was identified through
8 the screening process, and they have identified
9 synthetic routes that they might pursue then to try
10 and improve the molecule, different positions they
11 might be able to substitute.

12 And so at that point, the computational
13 chemist will work with the medicinal chemist and
14 say, you know, out of the substitutions that you're
15 considering at this position, you know, these look
16 favorable. Working off this position might be
17 better than working off an adjacent one and sort of
18 that back and forth. And so you make suggestions,
19 which a medicinal chemist can consider prior to
20 synthesizing the molecule and then having it tested.

21 Q. Okay. And the reason that a computational
22 chemist can make suggestions about where productive

1 substitutions or modifications could be made is
2 because of the structural information that was
3 available about the known binding of the original
4 compound; correct?

5 MS. PATEL: Objection. Form.

6 A. Yes, that's correct.

7 Q. Okay. Okay. Let's scroll to 415. And at
8 the second sentence of the first full paragraph
9 there, you state, "The degree of effort needed" for
10 screening potential compounds "is largely dependent
11 on the X-ray data available."

12 Do you see that?

13 A. Yes.

14 Q. Okay. And so one of the determining factors
15 is the availability of X-ray data that reveals the
16 binding mode of a known compound to its target
17 protein; is that right?

18 MS. PATEL: Objection. Form.

19 A. Yes. I think what's being referred to here
20 is that particularly in that time frame, although
21 there was kinase data available or kinase X-ray data
22 available, it wasn't available for every target of

1 interest. And so in addition to the other efforts
2 that the computational chemist would need to make,
3 that would be heightened if there was no X-ray
4 available for this specific protein. And what they
5 would do then is to take, you know, X-ray structures
6 for other kinases where there was a known structure,
7 look at what the amino acids -- how they differ.
8 And as I mentioned, even though the protein fold of
9 an ATP-binding site is conserved, the actual amino
10 acids that compose it are quite different from one
11 kinase to the other. So the extra effort would be
12 in developing this homology model where you try and
13 basically create a virtual, you know, model of the
14 protein of interest. That's what's meant by the
15 homology model.

16 Q. Okay. And so the -- having access to X-ray
17 crystal structure of a bound ligand in a binding
18 mode that is the target of interest for your kinase
19 inhibitor project would be very valuable to
20 understanding how modifications to a new compound
21 would be interacting with the kinase.

22 MS. PATEL: Objection.

1 Q. Is that right?

2 MS. PATEL: Objection. Form.

3 A. Yes and no. So yes, it would be helpful. I
4 think one thing to consider, though, is that if you
5 have an X-ray structure for one ligand and you have
6 a ligand that is quite different, the protein is not
7 a static structure in any fashion. And actually,
8 you can see this here where I'm referencing this
9 DFG-out versus DFG-in. So to me, that specific
10 sentence, "The possibilities range from the need to
11 develop full homology models for the kinase of
12 interest, to developing a DFG-out model when a
13 DFG-in X-ray is available (or vice versa), to
14 developing a series of models that take into account
15 possible side chain rotomers of key residues,
16 (gatekeeper or catalytic lysine)."

17 And so the point of that sentence and it's
18 part of this paragraph you're pointing to is that
19 you may have a protein structure of one ligand but
20 if you're considering the binding of another ligand
21 and it is significantly different from the existing
22 ligand, you have to factor in a number of things,

1 such as -- you know, you could have major protein
2 rearrangement, such as this DFG. That's a loop on
3 the kinase that can rearrange, depending on the
4 ligand, to a specific side chain rotomers and such.
5 And there's also, you know, the whole question of,
6 you know, do water molecules rearrange?

7 Again, it's very complex is, I think, the
8 take-home point. And so you only draw so much from
9 an existing X-ray if the ligand that you're pursuing
10 has substantive differences from the existing
11 ligand.

12 Q. Okay. And then in table 16.1, which I
13 believe starts on the next page, you report a couple
14 dozen representative examples of inhibitors that
15 were identified using computational chemistry
16 techniques?

17 A. I'm scrolling through the table.

18 Q. You can look at the title of your table.

19 A. Yes. I'm reviewing the comments just --
20 obviously, I would have to go back and look at each
21 of these again, but it looks like in all cases, it's
22 a question of where you have a known scaffold that's

1 binding, and it's a situation or it's describing
2 where you're working with a medicinal chemist and
3 they have different positions they might substitute
4 to try and improve potency. It's that scenario,
5 again, rather than conceiving of a novel molecule.

6 Q. Okay. And then if you turn to page 418 --

7 A. And another point I would make, of course,
8 is that --

9 Q. There's not a pending question, Dr. Veal.

10 If you could turn to page 418, please.

11 MS. PATEL: He's finishing his answer. Let
12 him finish his answer, please. Don't interrupt him.

13 A. And then to add to my answer, the other
14 point is that, you know, all of these where it says
15 "improved potency," that implies the compound was
16 then synthesized and, of course, tested.

17 You said page 418?

18 Q. Yeah. So here, we have a section called
19 "Lead Optimization"?

20 A. Yes.

21 Q. And in the second full paragraph, you
22 identify that "High-throughput docking, or more

1 specifically restrained docking, is a particularly
2 useful computational technique to apply to the
3 process of lead optimization."

4 Do you see that?

5 A. I do.

6 Q. You also go on to say that "The objective of
7 the computational chemist should be to first help in
8 prioritizing which substitution positions are likely
9 to be most beneficial and then, in cases where
10 reagents are widely available, to prioritize a set
11 of analogs for synthesis"; is that right?

12 A. Yes. I mean, that's exactly what I've been
13 describing.

14 Q. Right.

15 A. And so I'm glad to see it here. Yes.

16 Q. Right.

17 So the computational chemist is essentially
18 acting as a filter to identify the most likely
19 binding cabinet -- candidates and discard the least
20 likely binding candidates?

21 MS. PATEL: Objection. Form. Foundation.

22 A. So what is done here is that, again, what is

1 implicit here and what's being described is where
2 you have a known inhibitor or a known scaffold
3 that's been identified. So known core or Z-prime,
4 if you will, that has been identified. You're going
5 to stick specifically to that Z-prime. And the
6 medicinal chemist has a lot of synthesis work to do
7 and is trying to understand, out of all the
8 compounds that he or she can make, you know, are
9 there ones that have a higher likelihood of success.
10 No guarantee at all. In fact, you know, it's likely
11 that most will not be successful.

12 So the medicinal chemist will have different
13 synthetic schemes that they think they can get to
14 work, and then they come to the computational
15 chemist, and the medicinal chemist says, "I think I
16 can do this chemistry, and there are these starting
17 materials available where I can take that starting
18 material and attach it to my known core. Could you
19 help prioritize or try and suggest which ones you
20 think may work?"

21 Q. Right.

22 A. At that point the computational chemist

1 becomes involved. The medicinal chemist may or may
2 not take those suggestions, and I've seen cases,
3 certainly, where they have not, but where they have,
4 then they'll go through the efforts to synthesize
5 the molecule, and then, you know, the molecule will
6 be transferred to the biologist for further
7 testing -- or for testing in biological assays.

8 Q. And you indicate here that this sort of
9 analysis of assessing binding to a target protein
10 can be conducted through a high throughput docking;
11 is that right?

12 A. Yes. High throughput is a relative term
13 so --

14 Q. Okay. And you mentioned that you could make
15 suggestions to -- the computational chemist would
16 have information about the structure and how a
17 particular compound -- a particular compound's
18 likely binding modes and make suggestions to the
19 medicinal chemist, but the medicinal chemist doesn't
20 necessarily always listen to the computational
21 chemist and may go ahead and synthesize compounds
22 that the computational chemist had identified would

1 maybe have a low likelihood of being a successful
2 inhibitor; is that right?

3 MS. PATEL: Objection. Form.

4 A. It would be along the lines of where they
5 have a chemistry that they feel is robust, for
6 example, and so they want to try out some analogs in
7 that regard.

8 Q. Okay. Despite the fact that the
9 computational chemist may have advised them in your
10 experience. That those chemistries would not be
11 necessarily successful?

12 MS. PATEL: Objection. Form.

13 A. I don't think it's despite. I think it's
14 that, you know, the idea that we know going in that,
15 you know, their low probabilities of success. So
16 one case, I've got a synthetic probability where I
17 can, you know, make this analog with certainty, but
18 it may not, you know, have as high a probability or
19 chance of success from a computational approach.

20 Conversely, there may be a compound where
21 the computational chemistry indicates that it looks
22 pretty good but the chemistry is tough. You know,

1 so how do you balance those knowing that, you know,
2 again, in both cases, that, you know, it's likely to
3 be overall a low probability of success.

4 Q. And you keep saying "low probability of
5 success." Is your definition of low probability of
6 success achieving improved properties over the
7 compound that you're trying to optimize?

8 MS. PATEL: Objection. Form.

9 A. Yes, I think that's correct. I think, you
10 know, generally, as a first, you know, as a first
11 step improving potency, but then there are other
12 questions about, well, even if I improve potency in
13 a biological test tube assay, have I also improved
14 potency or properties with regards to cell
15 permeability, which you need to have a readout in a
16 cell? I mean, you have all those issues as well.
17 Again, points to the complexity of the process and
18 the idea that you have to test, you know, really on
19 multiple fronts. First, in a biological in vitro
20 setting, an enzyme assay, and then in cellular
21 assays to see if you've made any substantial
22 improvement.

1 Q. Okay. And at the bottom of this paragraph
2 here on page 418, you say that the personal view --
3 you've passed it already -- yeah. "However, the
4 personal view" -- speaking of yourself -- "is that
5 docking or scoring energies should be used as a
6 filter to winnow down possible analogs of interest
7 to a number on the order of 20 percent of the
8 original possibilities and from that point both
9 binding energies and visual inspection, often in
10 conjunction with medicinal chemists, should be used
11 to guide selection of the final set of analogs to
12 pursue synthetically." And that was your view of
13 how kinase inhibitor optimization should proceed;
14 correct?

15 A. Let me make sure I provide the context of
16 what is being spoken to here. So this is where you
17 have a known scaffold, okay, and you want to attach
18 that scaffold at -- or you want to substitute that
19 scaffold at Point A. So, again, you have a known
20 Z-prime, if you will, that's already been identified
21 through screening processes by, you know, a
22 medicinal chemist ordering in molecules and them

1 being screened. So you have that core scaffold and
2 you're trying to substitute at a certain position.
3 Okay? And say that involves, you know, reacting
4 something that has a carboxylic acid with that core
5 position.

6 So there would be many, many, many
7 carboxylic acids that you could pursue. And so what
8 you do to try and help the medicinal chemist to say
9 that I think, if you take 20 percent of these many,
10 many, many carboxylic acids that are available,
11 which is still a large number of compounds
12 potentially, this would provide a representative set
13 where they could substitute at one position on a
14 molecule to try and improve potency. Okay? So
15 it's -- the context is important here. We're
16 talking about modifying a known hit structure at a
17 single position by reducing the number of compounds
18 or number of starting reagents that you would use to
19 modify that position.

20 Q. Right. And your personal view is that these
21 docking and these scoring energies would be used to
22 filter out compounds -- possible compounds to

1 identify the ones that would have a better chance of
2 success; right?

3 MS. PATEL: Objection. Form.

4 A. So you can see here that there are two
5 criteria. One is using the binding energies as you
6 describe. So that's, you know, one way of
7 suggesting what are the best compounds. The other
8 is visual inspection. And that's the idea that you
9 sit down and you spend the time to look through all
10 the possible possibilities on a computer screen and,
11 after spending that time, based on visual
12 inspection, and you're, you know, hopeful
13 understanding of the system, that you would come up
14 with a set that way.

15 So it's really a combination of what the
16 computer says is a binding energy or a score, but
17 then also putting in the time to do the visual
18 inspection.

19 Q. Right. So the two things together, the
20 visualization of how the compound is binding to the
21 target, as well as the calculation of how well that
22 compound is binding, both of those feed into the

1 computational chemist's ability to prioritize
2 structures on their likelihood of being successful
3 inhibitors; correct?

4 MS. PATEL: Objection to form.

5 A. Yes.

6 MS. PATEL: Dr. Veal, if you could just make
7 sure you pause so I can interpose --

8 THE WITNESS: I'm sorry.

9 A. Yes, I think that is correct. There's often
10 this idea that the computer spits out a number
11 and -- in terms of a binding energy, and that will
12 be the best guide. But in my experience, you make
13 use of the binding energy that's determined and, you
14 know, for the purpose of the declaration, that would
15 be the Glide score.

16 But then also you spend -- the computational
17 chemist spends what can be a significant amount of
18 time to perform visual inspection of all these
19 structures and -- as I've already indicated, but to
20 emphasize this is a case where, you know, you have a
21 known core template that you have bound in, and
22 you're looking at just the different modifications

1 off, you know, this or that position.

2 Q. Okay. So if we turn to the page 424, and
3 here you have a summary section?

4 A. Yes.

5 Q. And in the middle of this paragraph, you
6 state "There is now a substantial body of examples
7 where computational techniques have provided
8 significant contributions toward the development of
9 screening libraries and discovery of new scaffolds,
10 promising hits, and optimized leads that have
11 ultimately become drug candidates."

12 Is that right?

13 A. Yes.

14 Q. And "The wealth of protein structural data,
15 coupled with ever-improving computational power, has
16 made the past decade a particularly exciting one for
17 computational-based research applied to kinases."

18 Is that right?

19 A. Yes.

20 Q. And so by 2009, the application of the
21 kinase structural data with improving computational
22 power had made it a particularly exciting use of

1 understanding kinase inhibitor design; is that
2 right?

3 A. So I want to refer back to the sentence to
4 be specific about how the computational chemistry
5 was being used. And so to read, "There's now a
6 substantial body of examples where computational
7 techniques have provided significant contributions
8 towards the development of screening libraries and
9 discovery of new scaffolds, promising hits, and
10 optimized leads that have ultimately become drug
11 candidates."

12 And so if you parse that sentence, first,
13 it's the development of screening libraries and
14 discovery of new scaffolds. And so that is the case
15 where you take, you know, some sort of fragment, you
16 apply it against the corporate library with the idea
17 of reducing the number of compounds that you'd have
18 to screen in the corporate library, define a
19 promising hit, or you apply it to an external vendor
20 library to consider compounds for acquisition for
21 the discovery of, you know, promising hits. So
22 that's applying it to known compounds that are

1 either part of your compound collection or part of
2 an external vendor library.

3 And, again, after you bring those compounds
4 in, you pay the money to purchase them, you screen
5 them and test them and hope you identify something.
6 So that's part one.

7 And then the second part is the optimized
8 leads, which is what we've described, where now
9 there's already been identified a known inhibitor or
10 known core scaffold, a known Z-prime, if you will,
11 that's demonstrated binding, and you're now trying
12 to optimize it.

13 So there are those two prongs where it's,
14 first, you screen known existing compounds, and then
15 the second prong is where you have an identified hit
16 and you're trying to optimize it. So those are the
17 two prongs that are being described here where there
18 have been some examples of success.

19 Q. And you already -- and you also described in
20 this chapter the use of computational chemistry
21 to -- for novel scaffolds in the context of scaffold
22 hopping and scaffold morphing; correct?

1 MS. PATEL: Objection. Form.

2 Q. We looked at that earlier. Do you remember?

3 A. Yes. And I think what was referred to -- so
4 that's not referenced here. And I think that
5 perhaps what that, you know, again, is referring to
6 is the idea that, you know, you find these fragments
7 or, you know, from a screening library to test. And
8 so, you know, at the end of the day, it's the idea
9 of, you know, trying to test against known
10 compounds, to screen or to optimize known compounds
11 for higher potency, either via biochemical assay or
12 cellular assay, to improve the process.

13 And to be clear, all of this takes quite a
14 bit of work to do as well as a computational
15 chemist. And, again, the idea is to increase your
16 probability of success, although the probability
17 remains low.

18 Q. Okay. And just as a threshold question, you
19 agree that the field was aware of the concept of
20 scaffold hopping and scaffold morphing in
21 identifying structures for binding within the
22 ATP-active site of a kinase; correct?

1 MS. PATEL: Objection. Form. Foundation.

2 A. I mean, scaffold hopping or morphing is a
3 broad term, so I think it would be good to point to
4 specific examples, and we can discuss those.

5 Q. This is a thresh- -- you said it's a broad
6 term.

7 Was it a broad term that was known and used
8 in the field of kinase inhibitor design in 2011?

9 A. Yeah, I think it is. You know, it's -- it
10 can mean different things to different people, I
11 suppose.

12 Q. But it was -- it was at least a category of
13 approaches for kinase inhibitor structures that bind
14 to the ATP active site; correct?

15 MS. PATEL: Objection. Form. Foundation.

16 A. Again, I think you need to point to specific
17 examples to discuss. I mean, scaffold morphing can
18 mean a relatively small change or a large change.
19 And without knowing the specific context of an
20 example, it's -- you know, it's hard to discuss.

21 Q. But both examples would have been within the
22 knowledge of the field for kinase inhibitor design

1 in 2011.

2 MS. PATEL: Objection. Form. Foundation.

3 A. I mean, as an example, if you take ibrutinib
4 and then you scaffold morph to, you know, one of the
5 E1, E4, E5, E6, or E8 -- I think ibrutinib is E7 in
6 the '803 patent -- that's a scaffold morph in that
7 you change a carbon to a nitrogen or vice versa.

8 Q. Okay. I think we can take a break.

9 (A short break was had.)

10 (Exhibit 2 was marked for identification
11 and is attached to the transcript.)

12 BY MS. DANEK:

13 Q. Dr. Veal, did you speak with your counsel
14 during any of the breaks?

15 A. No, I have not.

16 Q. Okay. So I'm going to mark as Veal
17 Exhibit 2 a document entitled "Protein
18 Crystallography" -- or titled "Kinases" in the book
19 "Protein Crystallography in Protein [sic]
20 Discovery." The first author is Adams. The second
21 author is James Veal.

22 Can you take a look at this exhibit? You

1 should have control of it.

2 A. Yes.

3 Q. Do you recognize this exhibit?

4 A. I do.

5 Q. And is this a book chapter that you
6 co-authored?

7 A. It is.

8 Q. And it was published in 2004?

9 A. Yes.

10 Q. And in this, you write about the use of
11 protein crystallography in the context of kinase
12 drug discovery?

13 A. Yes, that's correct. The -- I wrote the --
14 or that chapter, I believe there were -- if I can
15 get to the authors, there were three of us. One who
16 was a medicinal chemist.

17 Q. I think it starts on page 16 of the PDF, if
18 that's helpful.

19 A. One moment, please.

20 Yes. So just for clarity, so Jerry Adams is
21 a medicinal chemist, I was a computational chemist,
22 and then Lisa Shewchuk was an X-ray

1 crystallographer.

2 Q. Okay. And so you co-authored this chapter
3 to describe the use of protein crystallography in
4 kinase drug discovery?

5 A. That's correct.

6 Q. Okay. And at the bottom of this first page
7 you state that "X-ray crystallography has proven to
8 be the central technology driving our understanding
9 of the structural features governing inhibitor
10 binding and providing direction in the search for
11 selective kinase inhibitors"; is that right?

12 A. Would you point to where that is, please?

13 Oh, at the very last sentence.

14 Q. The last sentence, yeah.

15 A. Yes, I see that sentence.

16 Q. Okay. And so in 2004, X-ray crystallography
17 had been the central technology driving the
18 understanding of how structural features govern how
19 inhibitors bind to their target kinases?

20 MS. PATEL: Objection. Form.

21 A. Yes. And I would add I think it's, you
22 know, the central technology to understand

1 regardless of target class. I mean, X-ray
2 crystallography is -- in terms of understanding
3 binding features, there's X-ray crystallography,
4 NMR spectroscopy, and now cryo-EM. Cryo-EM is
5 relatively new and so at the time, X-ray
6 crystallography was -- regardless of the protein
7 class, was, you know, a central technology to
8 understand binding interactions.

9 Q. Right.

10 So well before 2011, X-ray crystallography
11 was used to understand how particular structural
12 features drive binding of kinase inhibitors to
13 kinases?

14 MS. PATEL: Objection to form.

15 A. Yes.

16 Q. Okay. And then if you turn to page 48,
17 which would be the next page, you have a section
18 here that's entitled, "Structure and Function," and
19 then a subsection of the -- describing the "Tertiary
20 Function" of kinases; is that right?

21 A. Yes.

22 Q. Okay. And in describing the structure and

1 function of kinases, you state that there's been "A
2 great level of structural knowledge" that's
3 "accumulated for protein kinases over the past
4 decade"; is that right?

5 A. That's correct.

6 Q. So even by 2004, well before 2011, there was
7 a significant amount of structural information
8 concerning protein kinases and its -- and their
9 function; is that right?

10 MS. PATEL: Objection to form. Foundation.

11 A. Yes, that's correct.

12 Q. Okay. So if we turn then to page 56.

13 A. Okay.

14 Q. You have a section here called "Inhibitor
15 Design"?

16 A. Yes.

17 Q. And within that, you have a subsection
18 called "Binding in the ATP Cleft"?

19 A. Yes.

20 Q. And this ATP cleft, this is the active site
21 of a kinase?

22 A. That's correct.

1 Q. And you have a cartoon here that describes
2 sort of the structural geometries of the ATP active
3 site?

4 MS. PATEL: Objection. Form.

5 A. Yes, figure 2.2.

6 Q. Yes.

7 And figure 2.2 identifies that there's a
8 particular location within the active site called
9 the adenine pocket that is adjacent to these
10 hydrogen bond donors and acceptors for the hinge; is
11 that right?

12 A. Yes. Figure --

13 MS. PATEL: Objection.

14 A. Figure 2.2 shows multiple regions within the
15 kinase active site, one of which is the adenine
16 pocket. Then there's also a gatekeeper pocket and
17 then a lipophilic plug pocket and then a sugar
18 pocket, a surface site, and a triphosphate region.

19 Q. Okay. And in the description of discussing
20 how, you know, these pockets and regions within
21 the -- within the kinase, this is not specific to a
22 particular kinase. This applies to all kinases, the

1 understanding of how these structural features
2 appear in all kinases; correct?

3 MS. PATEL: Objection to form.

4 A. That's right.

5 MS. PATEL: Dr. Veal, if you could just
6 pause before you start answering your questions so I
7 can put in an objection, please.

8 THE WITNESS: Apologies.

9 A. So if you look at figure B on the right-hand
10 side, you can see roughly how ATP occupies the
11 adenine pocket, the sugar pocket, and then the
12 triphosphate region. Then there are additional
13 pockets that are not occupied by ATP, both behind
14 ATP and also to the front. And you see the hinge
15 region. And so you have hydrogen bonds with ATP to
16 specific amino acids in the hinge region. Note that
17 those are backbone atoms, so they're conserved.
18 They're independent of the residue.

19 However, even shown here, you see a
20 so-called gatekeeper residue, which is a
21 phenylalanine. That can be, you know, multiple
22 different sorts of residues in a given protein

1 kinase.

2 Q. Okay. And above that description or above
3 that figure in the context of inhibitor design, you
4 state, "The primary attractiveness of the ATP site
5 is that it affords a deep hydrophobic cleft for the
6 adenine of ATP that is common to all kinases and yet
7 highly varied in shape." And that "The commonality
8 of binding elements provides inhibitor design
9 features that can be applied to all kinases"; right?

10 A. Yes.

11 Q. Okay. And so the structural understandings
12 of kinases isn't limited to a specific kinase but
13 is -- this commonality of these binding elements
14 applies to all kinases; correct?

15 A. Well, there's a nuance there, important
16 context. And so you have common features. Then you
17 also have a high variability in shape and -- due to
18 the makeup of the different residues that form the
19 active site for ATP. So there's both the
20 commonality but also a high variability.

21 Q. Right.

22 So -- and those variabilities can be

1 exploited for, sort of, increasing the selectivity
2 of particular inhibitor design but the -- for
3 example, the adenine pocket is a common -- there's a
4 commonality of binding within the adenine pocket
5 that applies to all kinases; correct?

6 A. Yes. But it also means that for a given
7 ligand, if it is not targeting -- even within a
8 specific kinase, if it is not targeting the
9 identical regions of that kinase, you know, in a
10 significantly overlapped way due to the variability
11 of the kinase shape, that even within a specific
12 kinase, if it's utilizing features, such as hydrogen
13 bond at the hinge, that's no guarantee that, you
14 know, two ligands will, you know, have the same
15 binding properties and even if one or the other will
16 bind.

17 Q. Okay. Now above this section that we're
18 just looking at is scheme 2.2.

19 Do you see that?

20 A. I do.

21 Q. And in here, you report hydrogen bonding
22 patterns of inhibitors to the kinase backbone that

1 have been determined by X-ray crystallography;
2 correct?

3 A. Yes.

4 Q. And so here, there are eight compounds that
5 have -- that are kinase inhibitors whose structures
6 have been solved by X-ray crystallography, and you
7 denote with arrows the hydrogen bond donors and
8 acceptors in each of these compounds; correct?

9 A. Yes.

10 Q. Okay. And the kinase inhibitors that you
11 identify don't all have an adenine scaffold;
12 correct?

13 A. That's correct.

14 Q. And they include compounds that, in fact,
15 differ structurally from adenine; correct?

16 A. Yes.

17 Q. Okay. And they're not all fully aromatic in
18 their -- in the structures that interact with the
19 hinge; correct?

20 A. Yes, that's correct.

21 Q. And, in fact, compound 7, right, the
22 scaffold that interacts with the hinge is not a

1 fully aromatic scaffold; correct?

2 A. That's correct.

3 Q. And I believe compound 5 similarly is not a
4 fully aromatic scaffold that interacts with the
5 hinge?

6 A. I'm not sure about compound 5, whether the
7 flavone is considered aromatic or not.

8 Q. The compound -- compound 10 is not fully
9 aromatic as well?

10 A. That's correct.

11 Q. So in your collection of eight compounds,
12 there is at least three of the eight compounds have
13 scaffolds that are not fully aromatic in interacting
14 with the hinge; correct?

15 A. That's correct.

16 Q. And the functional groups that interact
17 with -- that form these hydrogen bonds with the
18 hinge are not limited to the same functional groups
19 in adenine that form hydrogen bonds with the hinge;
20 correct?

21 A. Yes, that's correct.

22 Q. Okay. So, for example, there are carbonyl

1 groups that form hydrogen bonds with the hinge in a
2 number of these compounds in scheme 2.2, but there's
3 not a carbonyl that forms hydrogen bonds to the
4 hinge in adenine; correct?

5 A. That's correct.

6 Q. And then similarly, there's hydroxy groups
7 that form hydrogen bonds to the hinge in this
8 collection of compounds, but there's no hydroxy
9 group that forms a hydrogen bond to the hinge in
10 adenine; correct?

11 A. That's correct.

12 Q. So at least by 2004, the field was aware
13 that different functional groups were capable of
14 forming hydrogen bonds to the hinge, not just the
15 functional groups that were present in adenine;
16 correct?

17 A. Yes.

18 Q. And additionally, by 2004, there were
19 structures, scaffolds known to hydrogen bond to the
20 hinge that were not fully aromatic; correct?

21 A. Yes.

22 Q. Okay. So if you want to turn to page 66?

1 And you have a section here called "Homology Models
2 and Surrogate Kinases."

3 Do you see that?

4 A. I do.

5 Q. And you start this section by saying "The
6 conservation of tertiary structure and mechanism,
7 which complicates the discovery of highly selective
8 kinase inhibitors, provides for a portability of
9 learning from one kinase to the next."

10 Do you see that?

11 A. I do.

12 Q. And so because the tertiary structure and
13 the mechanism of kinases is highly conserved,
14 structural understandings from one kinase is highly
15 portable to another kinase; is that right?

16 A. That would depend on the situation.

17 Q. But that's what you're telling the field
18 here in this paragraph; correct?

19 MS. PATEL: Objection. Form.

20 A. It says "The more closely two kinases are
21 related, the more likely the information can be
22 applied to the second kinase." And as an example,

1 an inhibitor that was known to bind to LcK might be
2 more likely to bind to Btk because they are receptor
3 tyrosine kinases that are closely related in
4 sequence. There is an inhibitor that binds to CDK2,
5 which is, you know, a serine/threonine kinase. It's
6 not a receptor tyrosine kinase. It's much less
7 likely that that would transfer over.

8 So it would be dependent on the specific
9 situation where you're comparing two kinases,
10 whether a ligand that was already known would be,
11 you know, likely to bind to another kinase. And, in
12 fact, you know, that's what you would, you know,
13 test biologically to see if that were the case,
14 so ...

15 Q. Okay. And so for -- a person of ordinary
16 skill in the art, then, wouldn't limit their
17 understanding of kinase structure and function
18 information to a particular kinase but would look to
19 at least closely related kinases to have additional
20 insight to the structure and function of their
21 target kinase?

22 A. Yes, I think a POSA would consider the

1 available data. That's correct.

2 Q. Okay. And the available data, certainly by
3 2011, included a large number -- an even larger
4 number than we've looked at in your publications
5 from 2009 in here and 2004, a large number of X-rays
6 crystal structures for a variety of kinases bound to
7 different ligands; correct?

8 A. Yes, but I --

9 MS. PATEL: Objection to form.

10 A. Yes, but I think you would have to, you
11 know, go and look at each one of those structures
12 that you were showing earlier, understand what the
13 potency is for the specific kinase that it bound to,
14 and that's not shown in that structure. And then,
15 you know, you would have to take that ligand, known
16 ligand, and screen it against your target kinase of
17 interest to see if, in fact, the -- you know, you
18 see any potency against your target kinase of
19 interest. And there would be no presumption of that
20 up front without, you know, first testing it. Yes,
21 so there's a context there.

22 Q. Okay. If you want to turn to page 68? And

1 you have here a section -- you just scrolled by it.
2 You have here a section called "Paradigms For Kinase
3 Drug Discovery"?

4 A. Yes.

5 Q. And you note here that "One gauge of the
6 impact of protein crystallography on kinase
7 inhibitor design is the increasing frequency of its
8 use. The majority of recent publications employ
9 molecular modeling and report the use of protein
10 kinase inhibitor structures in the design process."

11 Is that right?

12 A. Yes.

13 Q. So by 2004, the majority of reports on
14 kinase inhibitor projects were employing molecular
15 modeling?

16 MS. PATEL: Objection. Form.

17 A. Yes. And I think we discovered -- discussed
18 with my previous publication how it was being used.

19 Q. Okay. Do you want to turn to page 70? And
20 above that figure, the paragraph above that
21 figure -- actually, you might not have been to 70
22 yet.

1 A. Oh.

2 Q. Yeah, okay. This is 70. So in the last
3 paragraph on this page, you state "It is important
4 to note that in the three-to-five-year period prior
5 to crystallographic confirmation of these models,
6 they were used successfully by several research
7 groups to design new templates and to advance lead
8 optimization programs." So in 2004, there had been
9 successful reports of structural models for kinases
10 to design new templates and to advance lead
11 optimization compounds?

12 A. Yes.

13 Q. Okay. And that was in 2004, and the field
14 continued to use models and structural information
15 to design new templates and advance lead
16 optimization compounds?

17 MS. PATEL: Objection to form.

18 A. Right.

19 MS. PATEL: Foundation.

20 MS. DANEK: All right. I think we can take
21 this down.

22 A. The -- well, I was going to answer the

1 question.

2 Q. I believe you already did.

3 A. No, I didn't.

4 Q. Okay.

5 A. Can you return to the document, please?

6 REMOTE TECHNICIAN: Would you me to put that
7 back up?

8 THE WITNESS: Yes.

9 A. Would you repeat the question, please?

10 Q. You had testified that, in 2004, the field
11 used models and structural information to design new
12 templates, and I said, "And since 2004, the field
13 continued to use models and structural information
14 to design new templates and advance lead
15 optimization compounds.

16 MS. PATEL: Objection. Form. Foundation.

17 A. So the underlying context there is that
18 modeling may have been used to suggest possible
19 changes, but as I've stated before and will continue
20 to to provide the context, the probability of
21 success there is low, and then there's a subsequent
22 need for synthesis and testing. And so to the

1 extent that modeling could help in that regard,
2 there's still the issue of, you know, probability of
3 success, the effort to use the modeling, the effort
4 to synthesize the molecules, and the effort to test.
5 So I think it's important to have the entire
6 context.

7 Q. So is the answer that yes, the field did
8 continue to use models to identify new templates and
9 advanced lead optimization compounds?

10 MS. PATEL: Objection. Form. Foundation.

11 A. The answer is that molecular modeling and
12 computational chemistry would be incorporated into
13 the process of synthesizing or identifying which new
14 scaffolds might be synthesized with the hope, then,
15 that when they are tested, biological assays, that
16 they would have some activity.

17 Q. Okay.

18 MS. DANEK: We can take this down.

19 Let's put Exhibit 1106 back up and talk
20 about your declaration. Let's go to paragraph 42,
21 which is at page -- let me see -- page 24 of the
22 document. And, in particular, I'm interested in

1 footnote 3 that's off of paragraph 42. Yeah. You
2 can see we're there.

3 Q. Dr. Veal, in footnote 3, you state that a
4 POSA would have understood the disclosure in the
5 specification of biaryl refers to a ring system
6 containing two heteroaromatic rings, and this is how
7 you've used the term "biaryl" here?

8 Do you see that?

9 A. Yes.

10 Q. And you don't have any citation to any
11 reference in your footnote here; right?

12 A. That's correct.

13 Q. And the specification itself doesn't provide
14 a definition of biaryl, that you're aware of?

15 A. I believe the specification defined aryl and
16 said biaryl would be understood from that.

17 Q. Do you understand that the definition of
18 biaryl includes heteroaromatic rings?

19 Strike that. Let me ask it again.

20 Do you understand that the definition of
21 aryl in the specification includes heteroaromatic
22 rings?

1 MS. PATEL: Objection. Form. Foundation.

2 Q. Do we want to look at the patent
3 specification?

4 A. Yes, that would be good.

5 Q. Okay.

6 MS. DANEK: Let's pull up Exhibit 1001.

7 (Exhibit 1001, previously marked, ^ is
8 attached to the transcript ^ was retained by
9 counsel.)

10 Q. And as we're looking at that, is it your
11 understanding that aryl would include
12 heteroaromatic?

13 MS. PATEL: Objection. Form. Foundation.

14 A. I believe this is discussed in
15 Dr. Showalter's declaration, and we can refer to
16 that. I believe he pointed to confusing language in
17 the '803 patent.

18 Q. Uh-huh. So you're --

19 MS. DANEK: You have the wrong exhibit. I
20 need Exhibit 1001.

21 REMOTE TECHNICIAN: My apologies. Please
22 stand by.

1 On screen.

2 MS. DANEK: Okay. And if we can go to
3 page 71 of this.

4 REMOTE TECHNICIAN: Doctor, again, you can
5 click your screen and take control.

6 BY MS. DANEK:

7 Q. Do you see the definition of aryl at the top
8 of column 15?

9 A. Yes.

10 Q. And in the patent, it defines "aryl" as "an
11 aromatic ring wherein each of the atoms forming the
12 ring is a carbon atom."

13 A. Yes.

14 Q. And so the definition of aryl in the patent
15 excludes heteroatoms in the ring, doesn't it?

16 MS. PATEL: Objection. Form. Foundation.

17 A. What I'd like to say here is that
18 Dr. Showalter commented on this I think fairly
19 extensively in his declaration. I agree with his
20 comments. And he would be the expert here. I'm
21 happy to read from his inclusions, which I agree
22 with.

1 Q. Okay. Well, let's go back to your
2 declaration because I want to understand what you
3 put in your declaration.

4 So if we go back to Exhibit 1106, and in
5 this footnote, you say, without citing
6 Dr. Showalter, that "A POSA would have understood
7 that the disclosure of biaryl in the specification
8 refers to a ring system containing two
9 heteroaromatic rings," and that's how you've used
10 the term; is that right?

11 A. Would you go to paragraph 53, please?

12 Q. I think you can control -- you should have
13 control of the document if you want to scroll.

14 A. I don't have -- I do not have control.

15 So this is a reference, I believe, to
16 Dr. Showalter's comments on biaryl core and the
17 conclusions around that, given the confusion in the
18 '803 patent, and so I agree with those comments.
19 He's the expert there and would refer to these if
20 you want to look at these.

21 Q. Okay. So I just -- just to be clear then,
22 in your footnote 3 with paragraph 42, you don't cite

1 any supporting reference for how biaryl was
2 understood in the field; correct?

3 It's back at page 20 of the declaration.
4 24 of the PDF.

5 A. Again, I agree with Dr. Showalter's comments
6 about what is made -- what is referred to by a
7 biaryl core and reference those, I believe, in
8 paragraph 53 and specifically, in example 11 -- or
9 Exhibit 1105, paragraphs 41 and 42 is where he
10 discussed that. So --

11 Q. Okay. So you're not -- sorry.

12 A. If you would like to go there, you know, we
13 can look at that.

14 Q. No. I want to look at what your opinions
15 and what your analysis is.

16 So you're not offering -- you're not
17 offering an opinion about what biaryl would mean to
18 a person of ordinary skill in the art. You're
19 relying on Dr. Showalter's assessment of what biaryl
20 would mean to a person of ordinary skill in the art?

21 A. What I am saying is that the references to
22 biaryl in the '803 patent were confusing.

1 Dr. Showalter made a detailed reference to that.
2 And, again, I would point to Exhibit 1105,
3 paragraphs 41 and 42. I have read that and concur
4 or agree with his conclusions.

5 Q. Okay. So you haven't done your own analysis
6 to try to identify any references in the art that
7 describe what a person of ordinary skill in the art
8 would understand biaryl to mean; is that right?

9 A. I've read Dr. Showalter's comments around
10 biaryl, given the confusion in the '803 patent.

11 Q. Uh-huh.

12 A. Exhibit 1105, paragraphs 41 and 42. And I
13 agree with his assessment.

14 Q. Okay. So other than reading Dr. Showalter's
15 analysis of how a person of ordinary skill in the
16 art would understand biaryl, you've not done any
17 other assessment of how a person of ordinary skill
18 in the art would understand biaryl.

19 A. I'll repeat the answer I just gave, which is
20 that there was confusion around -- in the
21 '803 patent around the use of biaryl. Dr. Showalter
22 provided a detailed analysis, which was within his

1 expertise. I've read that, and I concur with his
2 conclusion.

3 Q. Okay. So Dr. Showalter did the analysis.
4 And you read it and you agreed with that analysis;
5 is that correct?

6 A. Yes.

7 Q. Okay. And other than doing that, reading
8 Dr. Showalter's analysis and agreeing with it, you
9 didn't do any other --

10 COURT REPORTER: Looks like we lost the
11 tech.

12 MS. DANEK: Let's -- okay. Maybe we should
13 go off the record while we wait for him to
14 reconnect.

15 (A short break was had.)

16 BY MS. DANEK:

17 Q. Dr. Veal, did you speak with your counsel
18 during the break?

19 A. No, I did not.

20 Q. Okay. So we were talking about -- and if we
21 can pull up 1106.

22 We were talking about your description of

1 biaryl in your declaration. And you had indicated
2 that Dr. Showalter did an analysis that you read and
3 agreed with; is that right?

4 MS. PATEL: Objection. Form.

5 A. Yes. So I looked at the '803 patent, and
6 there was confusion. I looked at the analysis that
7 Dr. Showalter performed and agreed with that
8 analysis.

9 Q. Okay. And you agree that there's no
10 definition of biaryl in the specification; correct?

11 MS. PATEL: Objection. Form. Foundation.

12 A. Again, Dr. Showalter provided his comments
13 on what he understood to mean as the definition of
14 biaryl, and I agreed with those comments.

15 Q. And neither Dr. Showalter nor you identify a
16 definition for biaryl from the specification;
17 correct?

18 MS. PATEL: Objection. Form. Foundation.

19 A. Again, I would defer to Dr. Showalter's
20 summary -- summary on this aspect.

21 Q. Okay. I'm asking you a very straightforward
22 question.

1 Are you aware, yes or no, of a definition of
2 biaryl in the specification?

3 MS. PATEL: Objection. Foundation.

4 A. There is a -- I believe a reference to
5 biaryl in regards to formula E. Dr. Showalter
6 provides an analysis on that. Reading his analysis,
7 I agree with his analysis.

8 Q. So this isn't -- I understand. You've said
9 that a bazillion times. I am asking you a very
10 specific question, and please let me know if you
11 don't understand it.

12 Are you aware of a definition of biaryl in
13 the '803 patent specification?

14 MS. PATEL: Objection. Foundation.

15 A. My answer is the same I just gave.

16 Q. I don't understand.

17 Are you aware or not?

18 Sitting here today, do you think that there
19 is a definition of biaryl in the patent
20 specification?

21 MS. PATEL: Counsel, please watch your tone.

22 Objection. Foundation.

1 A. In the '803 patent, there is a reference in
2 formula E to biaryl. Dr. Showalter reviewed that
3 and made an analysis on what was meant by biaryl. I
4 read his analysis, and I agree with his comments.

5 Q. Okay. And if you didn't cite a definition
6 of biaryl from the specification, does that indicate
7 that you're not relying on any definition of biaryl
8 from the specification?

9 MS. PATEL: Objection. Form. Foundation.

10 A. Again, there is a reference in formula E to
11 biaryl. Dr. Showalter analyzed that reference and
12 how he interpreted it. I read his analysis, and
13 concur with it.

14 Q. Okay. Listen to my question, please, and
15 answer it specifically. I understand what you're
16 saying about Dr. Showalter's analysis. I am not
17 asking about Dr. Showalter's analysis. I am asking
18 about what you understand. Okay?

19 Do you understand that? Dr. Veal?

20 A. Yes.

21 Q. Okay.

22 A. And again --

1 Q. I just asked if you understood that I'm
2 asking about what you know. Okay?

3 The answer is yes?

4 A. I saw the reference to biaryl with respect
5 to formula E. It's confusing. I looked at
6 Dr. Showalter's analysis of what is meant by biaryl.
7 That made sense to me, and I agree with his
8 analysis.

9 Q. Okay. Can you point me to anywhere in the
10 specification that defines biaryl?

11 MS. PATEL: Counsel, do you want to put the
12 patent up?

13 A. Yes. I was gonna say if you want to bring
14 up the --

15 Q. I don't control this. He controls this.
16 The patent is one of the exhibits that's listed
17 there.

18 REMOTE TECHNICIAN: And, Doctor, you can
19 click your screen and take control.

20 THE WITNESS: I'm not sure how to do a
21 control F to find the reference to biaryl.

22 Actually, I don't know if I have control at

1 this point.

2 REMOTE TECHNICIAN: Should be the standard
3 control F.

4 A. I'm trying to do a control F and not getting
5 a response.

6 Q. Okay. Let me ask you a different question.

7 You have referenced a couple of times that
8 there is a mention of biaryl in connection with
9 formula E; is that right?

10 A. That's correct.

11 Q. Sitting here today, is that your only
12 understanding of where biaryl is used in the
13 specification?

14 MS. PATEL: Objection. Form.

15 A. I would like to look through the patent
16 here, and I'm unable to do a control F. So if
17 somebody else is able to do it, that would be great.

18 Q. Dr. Veal, let's do it this way. Let's look
19 at paragraph 43, footnote 3. This should be a very
20 straightforward question that I'm asking you, and
21 you seem to have a very difficult time understanding
22 exactly what I'm asking. And I am simply asking

1 whether or not you relied on any definition of
2 biaryl in the specification.

3 This has been going on for way too long. I
4 cannot understand what you don't understand. You
5 have not identified what you do not understand about
6 my question.

7 MS. PATEL: Objection. Form.

8 Counsel, please continue to watch your tone.
9 He is providing answers to your question. You may
10 not like --

11 MS. DANEK: He is deliberately not providing
12 answers to my question. So I want to know --

13 (Unreportable crosstalk.)

14 MS. DANEK: Stop talking. Stop talking.

15 BY MS. DANEK:

16 Q. Do you know if the patent specification --
17 and if you don't know, you can just say no.

18 Do you know if the patent specification
19 provides a definition of biaryl?

20 MS. PATEL: Objection. Foundation.

21 A. I believe I have answered the question to
22 the best of my ability. So there is a reference as

1 I'm aware to biaryl with regards to formula E.

2 Q. Okay. And so that's the only reference to
3 biaryl that you're aware of?

4 That's the only one you've mentioned.
5 You're not aware of any other reference to biaryl in
6 the specification; is that correct?

7 MS. PATEL: Objection. Foundation.

8 A. That is why I would like to look at --
9 excuse me.

10 Q. I am asking, sitting here today, if you are
11 aware of it. You can do your investigation later.
12 I am not interested in that. I am interested in
13 what you're aware of right now.

14 MS. PATEL: Objection. Foundation.

15 Q. The only -- so let's do it this way. Let's
16 do it this way.

17 The only reference that you've mentioned of
18 biaryl in the specification is in connection with
19 the description in formula E; is that correct?

20 A. I would like to look at the '803 patent and
21 search for that right now, please.

22 MS. DANEK: Brian, is there a way to control

1 F in the exhibit? He seems to not be able to do it.

2 REMOTE TECHNICIAN: Yeah. I've been able to
3 bring that up. What word would you like, Doctor?

4 THE WITNESS: Biaryl.

5 REMOTE TECHNICIAN: Spell that, please.

6 THE WITNESS: B-i-a-r-y-l.

7 MS. DANEK: No, b-i-a --

8 THE WITNESS: -- r-y-l.

9 MS. DANEK: Okay.

10 BY MS. DANEK:

11 Q. There's one instance of biaryl in the
12 specification, according to the find function.

13 Do you see that?

14 A. Yes, I believe that was the one I was
15 referring to.

16 Q. Right. And so there's no definition of
17 biaryl in the patent specification.

18 Do you agree with that?

19 MS. PATEL: Objection. Form.

20 A. So following from the word "biaryl" here, in
21 some embodiments, the sentence, you see the formula
22 E structures. From that, Dr. Showalter provided an

1 analysis on what he concluded biaryl to mean. I've
2 read that analysis and I agree with it.

3 Q. Okay. So you agree with me that biaryl
4 appears once in the patent specification; correct?

5 A. Yes.

6 Q. And the place where it appears is in a
7 description of some embodiments of formula E; is
8 that correct?

9 A. And from that, Dr. Showalter provided --

10 Q. Dr. Veal, listen to my question. It is a
11 yes-or-no question.

12 MS. PATEL: Counsel.

13 Q. The --

14 MS. PATEL: He was answering your question.

15 MS. DANEK: He was not.

16 Q. The context of my question is that the
17 single place that biaryl appears in the
18 specification is in the sentence in the description
19 of formula E that says "In some embodiments, the
20 portion of formula E is a substituent fused by aryl
21 moiety"; is that correct?

22 A. I answered that that was the case --

1 Q. Okay.

2 A. -- and that Dr. Showalter --

3 Q. That's all I needed to know. Thank you very
4 much.

5 MS. PATEL: Counsel, let him finish his
6 answer.

7 MS. DANEK: He has said that 75 times.

8 MS. PATEL: You don't know what he's going
9 to say.

10 MS. DANEK: I know exactly what he's going
11 to say.

12 MS. PATEL: And he can provide whatever
13 context he wants for every single answer he provides
14 to your questions. Are you going to assume that
15 context applies with every answer he provides you?

16 MS. DANEK: It has. It has. So I'm gonna
17 move on from this.

18 MS. PATEL: Okay. You instructed him at the
19 beginning of this deposition, he can clarify or
20 provide context to any of his answers at any time.

21 MS. DANEK: Priya, I am done with your
22 lecturing. Please let us continue with this

1 deposition.

2 MS. PATEL: Okay. Well, please continue to
3 watch your tone as you continue the deposition.

4 MS. DANEK: All right.

5 A. I was unable to provide an answer in that
6 regard to the last question.

7 BY MS. DANEK:

8 Q. I'm gonna move on. I believe you indicated
9 how you're gonna answer all of these questions.

10 Okay. In paragraph 44, if we go back to
11 1106, you are describing portions of Dr. Eck's
12 assessment of the description of the specification.
13 And in the middle of the paragraph, you indicate
14 that, as Dr. Eck admitted, a POSA would know that
15 even compounds that have each of the features of a
16 phenoxyphenyl hinge binding substituent and hinge
17 binding substituent, that each of those features may
18 not irreversibly inhibit Btk because other
19 characteristics of the compound, such as
20 electrostatics, complementarity, and Van der Waals
21 interactions, would impact the ability to covalently
22 bind to Btk.

1 Do you see that there?

2 A. I do.

3 Q. And modeling software takes into account and
4 calculates electrostatics and Van der Waals
5 interactions; isn't that right?

6 MS. PATEL: Objection. Form and foundation.

7 A. Yes, that's correct.

8 Q. Okay. So when a person of skill in the art
9 would model a compound into a target structure, the
10 modeling software would provide an assessment of
11 electrostatics and Van der Waals interactions;
12 correct?

13 MS. PATEL: Objection. Form. Foundation.

14 A. It would provide an assessment, but as I've
15 indicated earlier, the ability of modeling software
16 to accurately predict the binding would be limited
17 at best.

18 Q. Okay. And as part of your analysis, you
19 also -- you also reviewed a Pan paper from 2007.

20 Do you recall that?

21 A. Yes, that's correct.

22 Q. Okay.

1 MS. DANEK: Let's pull up Exhibit 1060.

2 (Exhibit 1060, previously marked, ^ is
3 attached to the transcript ^ was retained by
4 counsel.)

5 REMOTE TECHNICIAN: Stand by.

6 On screen.

7 MS. DANEK: Okay.

8 BY MS. DANEK:

9 Q. On your screen is Exhibit 1060, a reference
10 with the first author Pan. Is this the reference
11 that you remember analyzing in your -- in the course
12 of your -- in preparing your declaration?

13 A. Yes.

14 Q. Okay. And if we look at the bottom of
15 page 1. Okay, stop scrolling. In that paragraph,
16 underneath the figure on the right, Pan describes
17 that they identified compound 1 as having a high
18 potency towards Btk; is that right?

19 A. Yes, I see that.

20 Q. And the potency towards Btk, they prepared a
21 homology model to assess how this compound 1 would
22 bind within Btk; correct?

1 A. Yes.

2 Q. Okay. And so let's take a look at that
3 homology model, which is figure 1, which is on the
4 second page. Right? So this compound 1 has the
5 same phenoxyphenyl group as ibrutinib; correct?

6 A. Yes.

7 Q. And it has an adenine mimic scaffold like
8 ibrutinib has?

9 MS. PATEL: Objection. Form.

10 A. Yes.

11 Q. And then there's a heterocyclic structure
12 that is off of the scaffold in the opposite
13 orientation from the phenoxyphenyl group; correct?

14 A. Carbocyclic structure.

15 Q. Carbocyclic -- yeah, it's carbocyclic
16 structure. And Pan modeled the binding of
17 compound 1 with these features, the phenoxyphenyl
18 and an adenine mimic scaffold, into a structure of
19 Btk -- into a model of Btk; correct?

20 A. Yes.

21 Q. And in this model, Pan identified that the
22 phenoxyphenyl feature binds within the hydrophobic

1 back pocket of Btk; correct?

2 A. That's how it is modeled, that's correct.

3 Q. And, in fact, that this -- a similar
4 compound to this is what was reported in the
5 Marcotte reference; right? The crystal structure in
6 Marcotte; is that right?

7 MS. PATEL: Objection. Foundation.

8 A. That's correct.

9 Q. Okay. And Marcotte confirms that the
10 phenoxyphenyl group attached to the adenine mimic
11 scaffold binds within the hydrophobic back pocket of
12 Btk; correct?

13 MS. PATEL: Objection. Form. Foundation.

14 A. Yes.

15 Q. Okay. And Pan models the adenine mimic
16 scaffold as making particular hydrogen bonds to the
17 hinge region of Btk; correct?

18 MS. PATEL: Objection. Form.

19 A. Yes. I mean the pyrazolopyrimidine core
20 that you're looking at here is essentially one
21 carbon atom change from how adenine binds in the
22 binding site. So you would overlap that directly

1 onto adenine given the very close correspondence.

2 Q. Right. And, in fact, then Marcotte, in its
3 crystal structure of this similar compound, confirms
4 that the adenine mimic scaffold makes hydrogen bonds
5 to the hinge region of Btk; correct?

6 A. Yes.

7 Q. And then the cyclo alkyl group that is
8 appended from the scaffold on the opposite
9 orientation from the phenoxyphenyl group is oriented
10 towards the cysteine in the Btk active site;
11 correct?

12 A. Yes.

13 Q. And Marcotte later, in solving the crystal
14 structure of this similar compound, confirmed that
15 the -- that the cyclo group off of the scaffold was
16 oriented towards the cysteine group of Btk; correct?

17 A. Yes, it's binding in the same place as the
18 ribose of ATP.

19 Q. Right. And if we look at -- so Pan, looking
20 at this model, states at the bottom of page 1 -- if
21 we can just scroll up a little bit there -- the
22 bottom of page 1, he says "Based on sequence

1 alignments of the 491 kinases, there are only 10
2 kinases with a cysteine in this position near the
3 active site." And Btk is one of them; correct?

4 A. Yes.

5 Q. And then he says that -- sorry -- based on
6 this cysteine, they synthesized a series of
7 irreversible inhibitors that would covalently
8 bond -- intended to covalently bond with that
9 cysteine?

10 A. Yes.

11 Q. Okay. And the reason he describes targeting
12 the cysteine is sort of it coordinates with the
13 model where that cyclo alkyl group is oriented
14 towards the cysteine; right? He puts a warhead off
15 of a structure, off of that -- in that position
16 where that cyclo alkyl group is; correct?

17 A. That's correct.

18 Q. Okay. And that warhead, that is a structure
19 that was known in the art to be reactive to the
20 thiol groups on cysteines; correct?

21 A. That's correct.

22 Q. And if we turn to table 3, here Pan reports

1 a series of different linker warhead structures that
2 were added to the adenine mimic and the
3 phenoxyphenyl group of compound 1; is that right?

4 A. Yes.

5 Q. And the different linker and warheads that
6 were added to the adenine mimic and phenoxyphenyl
7 resulted in compounds that all had nanomolar IC50
8 inhibition of Btk; right?

9 A. Not all of them do.

10 Q. One is 20 nanomolar. The rest are all in
11 the single or lower digit nanomolar?

12 A. Yes.

13 Q. Okay. But all of these are potent
14 inhibitors of irreversible inhibitors of Btk;
15 correct?

16 A. They're potent inhibitors. I'd have to look
17 through each one to see whether it was confirmed
18 that they bind irreversibly.

19 Q. Yeah, so let's --

20 A. I think one point that you always have to
21 make is that, just because you see a binding
22 affinity, that doesn't necessarily mean it's

1 irreversibly modifying the cysteine. You would have
2 to confirm that by additional methods, either X-ray
3 crystallography or some sort of mass-spec-based
4 approach or a washout experiment.

5 Q. Yeah. So if you take a look at the top of
6 page 2, in the top paragraph -- right there. You
7 see the second sentence where it says, "We confirmed
8 the irreversibility of these compounds using two
9 methods"?

10 A. Is that all the compounds?

11 Q. Yeah.

12 A. Okay.

13 Q. And it says that they did -- "after
14 recombinant Btk was pre-treated with the compounds"
15 from table 3; right?

16 You can see the reference to the table 3
17 compounds in the previous sentence?

18 A. Yes.

19 Q. So after the "Btk was pre-treated with the
20 compounds, its activity was not recovered by
21 multiple washings"; right?

22 And that's an indication of irreversible

1 inhibition?

2 A. Yeah. So they have demonstrated for this
3 specific Z-prime scaffold, if you will, the ability
4 to generate irreversible binding.

5 Q. Right.

6 So the -- if you go back then, let's take a
7 look at table 3. They report, you know, a dozen --
8 a dozen different linker warhead structures of
9 compounds that were demonstrated to be irreversible
10 inhibitors of Btk; right?

11 A. Yes.

12 Q. And all of them are potent inhibitors of
13 Btk; right?

14 A. Yes.

15 Q. And the linker warheads that they chose have
16 different orientations. Some of them are -- have
17 the warhead at a meta position and at a para
18 position. But despite that change in orientation,
19 the linker warheads were all shown to be potent,
20 irreversible inhibitors; correct?

21 A. So they cover a certain span of space that
22 is, you know, I think quite specific to the Z-prime

1 group used, which, of course, is the, you know,
2 pyrazolopyrimidine, which is, you know, one-atom
3 change from adenine. And so the concept that this
4 somehow generally indicates that you can move a
5 Michael acceptor wherever you want and have binding,
6 I want to make sure that there's no indication that
7 I agree with that because I don't.

8 I think in the context here where you have,
9 you know, a very specific substitution, i.e., you
10 know, the substitution that's mimicking the
11 carbocycle that we were talking about earlier, you
12 have some flexibility to still obtain irreversible
13 inhibition. Once you go outside that, there's no
14 guarantee at all that you'll be able to irreversibly
15 inhibit Btk just because you have a Michael acceptor
16 present.

17 Q. Okay. And so what Pan is teaching you is
18 that when he changes the linker warhead orientation
19 and size, that potent covalent inhibition is --
20 these compounds still are potent covalent
21 inhibitors.

22 MS. PATEL: Objection.

1 Q. Right?

2 MS. PATEL: Objection. Form.

3 A. What Pan is teaching, in my opinion, is that
4 you have a ligand that's a very close mimetic to
5 adenosine. In other words, the core or the Z-prime
6 is one atom different from adenine. And the
7 substitution off the core is identical to the ribose
8 substitution of, you know, what you see with
9 adenosine. And within that context, there is some
10 flexibility for where the Michael acceptor is
11 located.

12 Q. Okay.

13 A. However, once you expand beyond that with,
14 you know, much more novel scaffolds, there's no
15 certainty at all that because you have a Michael
16 acceptor present, you will be able to generate
17 irreversible inhibition as determined by an
18 experiment, like a washout or mass spec experiment.

19 Q. Okay. And the type of experiment to confirm
20 irreversible inhibition, these -- the washout
21 experiment or the mass spec experiment, those were
22 known ways to assess irreversible inhibition as of

1 2011; correct?

2 A. Yes. They required, you know, a fair amount
3 of effort both the washout and a mass spec approach.
4 It's significantly more effort than the effort
5 already required just to determine the IC50.

6 Q. And the IC50 assays were well-known and,
7 sort of, in standard use as of 2011 to assess
8 potency for kinase inhibitors?

9 A. In my experience -- and, again, I'm not a
10 biology expert. But generally, when a new kinase
11 program would start, there would be a good amount of
12 time put into preparing the protein and then
13 understanding, you know, how you perform the assay,
14 you know, what substrate you might use to get a
15 readout on and that sort of thing. And you would
16 have to establish that assay and maintain it and
17 then, of course, run it regularly whenever you had a
18 new compound to test.

19 Q. But once a kinase project was not at its
20 beginnings, once they've already identified, for
21 example, a lead compound, measuring IC50 values for
22 additional compounds would have been done using the

1 same methods that had already been established for
2 the program to date?

3 A. Yes. You would continue to use the same
4 screening assay and do the weekly work to perform
5 that assay. Again, that would not inform on
6 irreversible inhibition. Just inhibition of, you
7 know, whatever biological readout you're looking at.

8 Q. Okay.

9 MS. DANEK: Let's pull up Exhibit 2001.

10 (Exhibit 2001, previously marked, was
11 retained by counsel.)

12 A. And I would add just to finish that, you
13 know, beyond that are the cell-based assays where
14 you have to, you know, each week, split cells, grow
15 the cells, and do all of that and then screen in the
16 cellular assays to see if you have any cellular
17 potency.

18 Q. Yeah.

19 And those sorts of cellular assays were
20 also, sort of, standardly part of a kinase inhibitor
21 project to assess the potency of the compounds in
22 the project; correct?

1 A. They would be part of the regular flow
2 scheme.

3 Q. Yep.

4 All right. Let's take a look at
5 Exhibit 2001.

6 REMOTE TECHNICIAN: On screen.

7 Q. So, Dr. Veal, this is the Marcotte reference
8 that we've talked about a couple of times. And you
9 indicated that this was one of the references that
10 you considered in forming your opinions in this
11 case.

12 A. Yes.

13 Q. Okay. And if we take a look at figure 2 --
14 I think it's figure 2. Yeah.

15 MS. DANEK: Not this one. This one is
16 figure 1. Okay.

17 Q. Okay. So this is figure 2 here on page 3 of
18 Exhibit 2001. And this reports the X-ray crystal
19 data for the compound having an adenine mimic
20 scaffold attached to the phenoxyphenyl back pocket
21 binder and then a cycloalkyl linker group in the
22 opposite orientation from the phenoxyphenyl; is that

1 right?

2 A. Yes.

3 Q. Okay. And in this crystal structure data of
4 this compound binding to Btk, part of what the --
5 part of what the authors report is the location of
6 the Cys481 relative to where the compound is
7 binding; right?

8 A. Yes.

9 Q. So in, for example, figure 2D you see a
10 notation of C481 in the lower right; is that right?

11 A. Yes.

12 Q. And C481 is a reference to cysteine 481 of
13 Btk?

14 A. That's correct.

15 Q. And the yellow coloration around C481, is
16 that an indication of the thiol group of the
17 cysteine amino acid?

18 A. It's a little hard for me to tell if it's
19 the entire cysteine or just the thiol.

20 Q. Okay. And if you -- the cysteine group
21 there, Marcotte reports that as adopting two
22 different positions; right?

1 A. Yes, two side chain rotomers.

2 Q. Right.

3 So that indicates that that cysteine is a
4 rotomer, it can rotate; right?

5 A. Yes.

6 Q. Okay. And that the linker, the linker
7 structure, right, the linker structure, the
8 cyclopentyl, for example, that is also made up of
9 flexible bonds?

10 A. For a cyclic structure, there's reduced
11 flexibility compared to a -- you know, a noncyclic
12 structure.

13 Q. Right.

14 And the warhead structure that is appended
15 to the linker, that is also a rotatable bond; right?

16 A. It's an amide bond, so it has two possible
17 confirmations, generally speaking.

18 Q. Okay. And then also the information here
19 about the cysteine -- the structure of where the
20 cysteine is indicates that it's exposed more on the
21 solvent portion of the kinase; is that right?

22 A. Yes. It's toward the front, what I would

1 describe as the solvent interphase.

2 Q. Right.

3 So there's no, for example, other portions
4 of the kinase that are, like, blocking access to the
5 cysteine of Btk.

6 MS. PATEL: Objection. Form.

7 A. It's not shown here, but there are other
8 amino acids in the vicinity, so I think it would
9 require detailed analysis to understand, you know,
10 whether there were certain regions that were, you
11 know, sterically hindered from the C481 occupying.

12 Q. Okay. But you agree with me that Marcotte
13 describes and presents that the C481 is on the
14 solvent-exposed surface of Btk.

15 MS. PATEL: Objection. Foundation.

16 A. Can you point to where it's discussed around
17 the side chain rotation?

18 Q. I think you already agreed with that.

19 A. No, I didn't necessarily already agree with
20 that. I would accept that there are two possible
21 confirmations for the cysteine based on the
22 preferred side chain rotomers. And so that

1 provides, you know, some additional flexibility, if
2 you will, for targeting with a Michael acceptor. I
3 think, however, you have to, you know, keep in mind
4 that what we're talking about here is a chemical
5 reaction, not just a binding interaction, which is
6 quite different and requires a good deal of
7 specificity in terms of orientation. And so you may
8 have a situation as is shown by Pan where, in the
9 context of, you know, the pyrazolopyrimidine, the
10 close adenine mimetic and then the substitution
11 that's directly analogous to the ribose substitution
12 of adenosine, that you can have, you know, multiple
13 positions for the covalent modifier to make the
14 interaction of the cysteine.

15 However, once you go beyond that, i.e., with
16 a novel scaffold idea that just because you're
17 somehow in range of the cysteine means that you're
18 gonna covalently modify it is -- I think is
19 incorrect because, again, there are detailed
20 chemistry matters in terms of a covalent interaction
21 about bringing the Michael acceptor warhead proximal
22 in the correct orientation to the cysteine. So

1 there's, you know, there's quite a bit of complexity
2 there. And there's no guarantee at all that just
3 because you have a Michael acceptor on the molecule
4 and that you have, you know, two side chain rotomers
5 for the cysteine, somehow that guarantees you're
6 gonna form a covalent bond.

7 Q. So let's take a look at page 7 of the PDF.
8 And at the top of the right-hand column, it says
9 that --

10 A. Am I at page 7? Sorry.

11 Q. This is page 7. Yeah. No, you're gonna
12 move past it. There at the top there.

13 It says, "Furthermore, Cys481 in the active
14 site of" the kinase domain Btk "could also be
15 exploited to gain kinase selectivity in which a
16 small molecule may be irreversibly bound to this
17 cysteine via covalent bond."

18 Do you see that?

19 A. Sorry. Could you point --

20 Q. Yeah. It's the last sentence of the top
21 paragraph of the right column.

22 A. Yes, I see that.

1 Q. Right. So what Marcotte is actually
2 identifying is that that cysteine is available to be
3 exploited for irreversible -- by an irreversible
4 bond through a warhead interaction; correct?

5 MS. PATEL: Objection. Form.

6 A. Yes, Marcotte is indicating that there's the
7 potential to target the cysteine.

8 Q. And that's what Pan had already shown as
9 well, that a number of different compounds with
10 varying linker warhead structures were able to
11 irreversibly bind to Btk; right?

12 A. What Pan had showed was that, in the case
13 where you have a very close adenosine mimetic, where
14 you have a single atom change from the adenine of
15 adenosine, and you position or substitute off the
16 ligand in the same way that you substitute off of --
17 you substitute the ribose off of adenine in
18 adenosine or ATP, that that allows you to identify
19 covalent inhibitors.

20 Q. And in Pan, he made and presented a series
21 of compounds with different linker warhead
22 structures that covalently bound Btk; right?

1 A. Again, what was done was to substitute off
2 of the pyrazolopyrimidine, you know, the direct
3 isostere, if you will, of adenine, with, you know, a
4 moiety similar to the ribose. And then you had some
5 flexibility for forming covalent modification as
6 determined by the, you know, washout and mass spec
7 experiments.

8 Q. Okay. So if we go back to your declaration,
9 1106, I believe you mentioned something along this.
10 If we turn to page -- well, paragraph 56, which is
11 at -- it starts on page 32 of the PDF. Yep, there
12 you are. And it spills over to the next page.

13 So in the -- in the portion of paragraph 56
14 that's on the next page, you state "Indeed,
15 proximity to Cys481 alone does not ensure that the
16 two will form a covalent bond because a very
17 specific geometry is required for the linker warhead
18 to approach and covalently bind to Cys48." Well,
19 you say 48 there. Do you mean 481?

20 A. Yeah, it should be Cys481.

21 Q. Okay. And the support that you have for
22 that sentence that a specific geometry is required

1 to approach and covalently bind to the cysteine of
2 Btk are two references, 1157 and 1158.

3 A. Yes.

4 Q. Okay. So let's take a look at that.

5 MS. DANEK: So let's pull up 1157.

6 (Exhibit 1157, previously marked, was
7 retained by counsel.)

8 Q. And there's no other reference that you cite
9 as your support for your opinion that a specific
10 geometry would be required for the linker warhead to
11 approach and covalently bind to Cys481; right? This
12 is the only support that you've identified?

13 A. Those are the two publications I came
14 across.

15 Q. Okay. So let's pull both of them up because
16 they're kind of in tandem, just to confirm. So we
17 have 1157. Let's start there.

18 And this is an article from Krenske that
19 was -- let's see. When was it published?

20 Do you recall or do you recognize this
21 reference from Krenske as the support for your
22 position that a specific geometry was required?

1 Let's see, I think it was published in 2011. Yep.

2 A. Yes.

3 Q. Okay. And then if you look at 1158.

4 (Exhibit 1158, previously marked, was
5 retained by counsel.)

6 Q. This is the supporting information for that
7 same reference; right?

8 A. Okay.

9 Q. I mean, do you agree? Is that right?

10 A. Yes.

11 Q. Okay. So it's this one reference and its
12 supporting information is the support for your
13 opinion that a specific geometry is required for
14 forming a covalent bond to Cys481; right?

15 A. This is one reference that I thought, you
16 know, provided a nice description of the covalent
17 modification. I wouldn't say in any way at all.
18 It's the only reference.

19 Q. Well, it's the only reference you cited;
20 right?

21 A. But there's a broader understanding in
22 organic chemistry -- and I'm not an organic

1 chemist -- but that, you know, how a cysteine will
2 react with a Michael acceptor --

3 Q. Okay. Oh, I'm sorry.

4 A. -- via, like, an SN2 reaction; right?

5 So ...

6 Q. Okay. But you didn't cite any other
7 reference for any particular broader understanding.
8 These are the references you cited for the support
9 for that opinion; right?

10 A. That's correct. I mean, there's an element
11 that a medicinal chemist or organic chemistry POSA
12 would understand that.

13 Q. Okay. Well, let's take a look at what this
14 reference does describe. So if we take a look at
15 1157, and it says the title of it is "Transition
16 States and Energetics of Nucleophilic Additions of
17 Thiols to Substituted Alpha Beta Unsaturated
18 Ketones: Substituent Effects Involve Enone
19 Stabilization, Product Branching, and Solvation."

20 Do you see that?

21 A. I do.

22 Q. Okay. And in the abstract, it describes the

1 reaction of a methylthiol; right? An MESH?

2 A. Correct.

3 Q. So that's not a cysteine residue. That's a
4 free thiol group?

5 A. Yes, that's correct. I think these sorts of
6 approaches are often done, as you can imagine,
7 irreversible inhibition is of significant interest
8 to the pharmaceutical industry starting then and
9 continuing. So people will often use model systems
10 that they can then apply, you know, quantum
11 mechanics where there's a limited in terms of the
12 size of the system that you can use to evaluate. So
13 that was what was done here.

14 Q. Right. And so what it is reporting on is
15 this methylthiol and then the reaction with an alpha
16 beta unsaturated ketone; right? And there's an
17 indication of a particular R group off of the end of
18 that carbon-carbon double bond of the unsaturate
19 ketone; right?

20 A. Yes.

21 Q. Okay. And so there's a proposed reaction of
22 the methylthiol reacting with the warhead of the

1 alpha beta unsaturated ketone and then forming a
2 covalent bond between the sulfur group of the thiol
3 and the end carbon of the -- what was the
4 carbon-carbon double bond; right?

5 A. Correct.

6 Q. And the reference to an R group means that
7 there's gonna be variation in a particular
8 substituent off the end of the warhead; right?

9 A. Yes.

10 Q. Okay. And so when you look at the
11 description of what they were exploring in, like,
12 for example, let's take a look at chart 1. They
13 were looking at different warheads that had
14 different substituents in figure 1, different
15 substituents?

16 A. Where is chart 1? Sorry.

17 Q. If you go to the top of the previous page,
18 do you see the figure 1 and chart 1?

19 A. Yes.

20 Q. They have chart 1 of particular irreversible
21 inhibitors, and then figure 1 are the reactions that
22 they were measuring the transition state and

1 energetics of; right?

2 A. Yes.

3 Q. Okay. So they're looking at how the
4 energetics of the reaction changed as the warhead
5 had different substituents off the end carbon;
6 right?

7 A. Yes.

8 Q. Okay. And there's no discussion here about
9 the precise geometry of the -- of how the warhead
10 and the thiol approach one another; right? This is
11 a solution reaction. There's no limitation on how
12 the thiol and the warhead approach one another;
13 right?

14 A. That's what you're looking at here in
15 figure 3. So this is the specific geometries of the
16 interaction. And I think this is likely the point
17 of including this reference because you can see the
18 distances and the specific orientations that are
19 required and what are preferred orientations and how
20 there's a limit there. And so this is, you know,
21 actually was the intention is a reference to show
22 that how they determine what specific -- the

1 specific transition structures were as determined by
2 quantum mechanic methods. And, again, they're
3 limited in the size of the system that they could
4 use because it's applying quantum mechanics. But
5 here's -- you know, figure 3 is of interest.

6 Q. Okay. But what they're actually looking at
7 is the effect on the reaction when you change the
8 warhead structure; right?

9 A. In my declaration, I was referring to the
10 concept that there are specific geometries involved.
11 And those specific geometries are what are
12 highlighted in figure 3. So this is the -- you
13 know, substance which I was referencing to.

14 Q. Right. And even with all of these
15 geometries, these reactions still form, these
16 covalent bonds still form; right?

17 A. Yes. I think that's a point, if you can
18 achieve the specific geometry. The point of my
19 declaration and in showing here is that, normally,
20 when a ligand binds that's reversible, you have
21 multiple interactions, such as Van der Waals
22 interactions, and there are less, in terms of

1 orientational requirements, for some of those
2 interactions. Think of like Van der Waals
3 interactions or if you're displacing solvent from a
4 lipophilic site.

5 However, once you go into the realm of
6 forming a covalent reaction, the geometries become
7 more specific, and that adds an additional hurdle to
8 achieve. So, again, if you have a situation where
9 you're looking at a new ligand that's not a close
10 mimetic of ATP and you, you know, are hoping to form
11 a covalent interaction, there's a lot of work there,
12 and there's no guarantee at all that just because
13 you attach a Michael acceptor, that it will work.

14 Q. And you didn't identify any compound in
15 which the Michael acceptor on the inhibitor failed
16 to form a covalent bond with cysteine 418; right?

17 A. The inhibitor. I'm sorry. I'm not sure
18 what you --

19 Q. I'm gonna ask that again. So you didn't
20 identify any compound, any inhibitor that -- where
21 the Michael acceptor on the warhead -- so I'm sorry.
22 Any inhibitor within the scope of the claims, you

1 didn't identify any compound where the inhibitor
2 failed to form a covalent bond to cysteine 481?

3 A. I'm still not sure what you mean by that
4 question.

5 Q. So your only -- the citation that you have
6 here for a precise geometry required is -- let's
7 take this piece by piece.

8 So this reference, you agree with me, is not
9 describing warhead Btk cysteine covalent bond
10 formation; right?

11 A. Right. What this references is describing
12 is that you have to achieve a precise geometry to
13 form a covalent interaction that is -- and by
14 corollary, is a higher threshold than just a binding
15 interaction. So it's an additional hurdle that you
16 have to achieve.

17 Q. And, actually, it doesn't say anything about
18 a precise geometry that's needed. It just reports
19 what the geometry of these covalent-bond-forming
20 reactions were modeled to be; right?

21 A. Right. What it's showing here are
22 transition -- you know, transition state structures.

1 So this is the, you know, geometry that was observed
2 by quantum mechanics as being needed to be achieved.

3 Q. Right.

4 And all of them end up forming the covalent
5 bond between the thiol and the warhead; right?

6 A. Yes. In this model system, that's correct.

7 Q. Yep.

8 And the difference that is presented is a
9 difference as you change the warhead; right?

10 A. Again, the point of this publication --

11 Q. I -- let's answer my question.

12 The difference that they're reporting on is
13 the effect of changing the warhead structure; right?

14 A. What is germane here is how I was
15 referencing this exhibit or publication. And the
16 way I referenced it was with respect to the concept
17 that a precise geometry must be obtained to achieve
18 covalent interaction, and that is an additional
19 hurdle beyond just binding, you know, in the case of
20 a reversible ligand. So that was the context that I
21 was referencing this publication, and this figure 3
22 is highlighting that.

1 Q. Okay. And nothing in the publication says
2 that these -- that these different warheads were
3 unable to achieve covalent bond formation between
4 the warhead and the thiol group; right?

5 A. Yes. This is a model system.

6 Q. Right.

7 And in the description of what the authors
8 say that they are exploring, if you look under
9 scheme 2 on the second page of the reference --

10 MS. DANEK: I think it's up one more or a
11 couple more pages.

12 So here under scheme 2, that paragraph, "The
13 emerging importance"?

14 A. Yes.

15 Q. Okay. And in that paragraph, the authors
16 say, "Here, we examine the effects of substituents
17 on the Michael acceptor"; right?

18 If you scroll down in that paragraph.

19 A. They do say that. But, again, I think
20 you're not appropriately appreciating why I made
21 reference to this publication. And, again, if you
22 turn back to my exhibit, the reason I made reference

1 to this publication was to make the point that a
2 precise geometry is required for the vinyl chromide,
3 which is one of the examples shown to form a
4 covalent interaction with a thiol, which a cysteine
5 is -- contains.

6 And the reason for referencing this was to
7 provide that figure 3 that's shown, showing the
8 precise nature of the transition state that has to
9 be achieved to form the reaction.

10 So I take your point that they look at
11 other -- other, you know, Michael acceptors where
12 the vinyl group is substituted. But the intent in
13 terms of my reference to this publication was really
14 to highlight the precise nature of the geometry
15 which you'll see across all of these Michael
16 acceptors applies. And so it makes the point again
17 that when you have a ligand bound to a kinase and
18 you're hoping to get irreversible inhibition,
19 there's no guarantee at all that just because you
20 have a Michael acceptor, particularly if it's, you
21 know, well removed from the adenine ribose of ATP,
22 you'll be able to form that interaction.

1 Q. And in fact -- oh, I'm sorry.

2 A. And you'll have to be able to, you know, do
3 the appropriate testing and that sort of thing as
4 well. And so that's why I made reference to this
5 publication.

6 Q. Well, you actually didn't cite this figure,
7 did you? You just cited the reference in total;
8 right?

9 A. Yeah. I thought it would be -- sorry. I
10 should pause. I thought it would be clear from my
11 publication or my declaration and the reference to
12 the geometry of the orientation, you know, why I
13 cited this publication.

14 Q. Okay. But, in fact, even looking at this
15 figure, the methyl thiol group is actually oriented
16 in at least two, if not more, orientations in
17 forming the transition state with the -- with the
18 warhead, isn't it?

19 A. What's shown here is I think the preferred
20 transition state. And so the one on the top left
21 would be the one that is relevant where you have a
22 vinyl -- just a simple vinyl group. And so it's

1 TS-1.

2 Q. Right.

3 And when you -- but it shows as you change
4 the warhead, as you say, there are different
5 orientations of the thiol -- the methylthiol group
6 to the warhead structure.

7 A. That's right. And --

8 Q. Okay.

9 A. -- if you look at TS-1, the third one over,
10 that's where you consider potentially the effect of
11 solvent. So that would make the argument, the idea
12 that you can somehow model and predict these even
13 more complicated.

14 Q. Right.

15 And so there are even -- as you say for
16 TS-1, there -- the ability to form a covalent bond
17 with the vinyl warhead, there are depicted two
18 different geometries and two different bond
19 distances for that transition state; right?

20 A. One is where you have -- you know, you're
21 considering the effect of solvent. One is where
22 it's gas-phased, so there's a difference there. I

1 think, again -- you know, I would make the point
2 that when you're trying to predict whether something
3 can form a covalent interaction, it's very
4 challenging. And yes, you have some flexibility;
5 however, at the end of the day, you have to have
6 this, you know, proper approach to the molecule.

7 I mean, when both Dr. Eck and I modeled
8 ligands binding to Btk, we converted the cysteine to
9 an alanine. And the reason for doing that is that
10 you can see that in these transition states, you
11 have this approach of two and a half angstroms.
12 Normally, you can't achieve that unless you're
13 performing a covalent interaction. And so when
14 you're modeling compounds, you don't form a covalent
15 interaction. You're just trying to see oh, is it in
16 the right range?

17 And so, again, that goes to lack of
18 predictability around modeling whether you're able
19 to form a covalent interaction and certainly, you
20 have to follow up anything you synthesize with
21 detailed testing to confirm it.

22 Q. Okay.

1 MS. DANEK: I think we can take this down.

2 MS. PATEL: Counsel, is this a good time to
3 take a break?

4 MS. DANEK: Oh, sure.

5 (A short break was had.)

6 BY MS. DANEK:

7 Q. Dr. Veal, let's take a look at your
8 declaration. So if you can pull up 1106. And let's
9 go to page 29 of the PDF.

10 So in paragraph 51, you assess the
11 specification surrounding the description of
12 structures that will bind to the Btk active site;
13 right?

14 MS. PATEL: Objection. Form.

15 A. Yes. Which part of the paragraph are you
16 referring to?

17 Q. Just orienting you to the discussion.

18 And you agree -- and maybe if we also --
19 let's make sure we get the patent. It's probably
20 useful to look at that. So that's Exhibit 1001.
21 You should have that as a separate tab up there.

22 REMOTE TECHNICIAN: Just click on the tab,

1 Doctor.

2 Q. Okay. And so in -- if you scroll up from
3 there, we were looking at this earlier. So in
4 Exhibit 1001, and we're gonna look at formula E.

5 Right. And the description here is that
6 the -- for formula E at the top of column 62 that
7 we're looking at here, that this orb "is a moiety
8 that binds to the active site of a kinase"; right?

9 A. Yes.

10 Q. And as we were discussing earlier, the
11 active site of the kinase is -- was understood to
12 include binding to the hinge region through those
13 hydrogen bonds; right?

14 A. Yes. That's part --

15 MS. PATEL: Objection. Form.

16 A. Yes. The active site of the kinase contains
17 or involved the hinge region.

18 Q. Okay. And then below that is the
19 description of particular examples of the scaffold
20 that could bind to the active site. So if we scroll
21 down a little bit in here, it says -- starting
22 around line 44 of column 62, it says, "In some

1 embodiments," the orb "is a substituted fused biaryl
2 moiety selected from," and then it lists eight
3 example scaffolds; right?

4 A. Yes.

5 Q. And the -- the description is that these are
6 some embodiments of the structure that would bind to
7 the Btk active site; right?

8 MS. PATEL: Objection. Form.

9 A. Yes. That's how the text reads.

10 Q. Okay. And let's just take a quick look at
11 the definition of heterocycle. So if you turn to
12 column 15, I think might be on page 71 of the PDF.
13 So you're at page 93 of the PDF.

14 Okay. And at the bottom of column 15,
15 there's a definition of heterocycle; right?

16 So you can see it starts at the bottom of
17 column 15 and wraps up to the top of column 16. It
18 says, "The term 'heterocycle' refers to
19 heteroaromatic and heteroalicyclic groups containing
20 one to four heteroatoms each selected from oxygen,
21 sulfur, and nitrogen." And then there's some more
22 details; right?

1 A. Yes.

2 Q. Do you see that?

3 A. Yes.

4 Q. And so heterocyclic as used in the patent
5 includes structures that are both heteroaromatic and
6 heterosaturated rings; right?

7 A. Yes.

8 Q. Okay. And that's the definition that you
9 applied in forming your opinions regarding the
10 claims in this patent; right?

11 MS. PATEL: Objection. Foundation.

12 A. Yeah. I'm not sure what you mean by that
13 question.

14 Q. So you understand that the claims here
15 employ the term "heterocyclic"; right?

16 A. Yes, with reference to a Z-prime.

17 Q. Right.

18 And in forming your opinions around Z-prime
19 and the heterocycles of Z-prime, you applied this
20 definition of what a heterocycle is; right?

21 A. I think it is confusing in that -- sorry.

22 Q. Maybe it would be more straightforward if we

1 go to -- we go to paragraph 162 of your declaration,
2 which is at PDF page 110.

3 A. You said page 110?

4 Q. Uh-huh.

5 And you see here that you say that "Dr. Eck
6 applies certain claim constructions for the
7 following terms as defined in the specification."
8 And included in that is heterocyclic and
9 heterocycle, and you say that you've used these
10 definitions from the specification in your analysis;
11 is that right?

12 A. Yes.

13 Q. Okay. So the definition that you've used
14 for heterocycle and heterocyclic is the definition
15 that we just looked at from the patent specification
16 at Columns 15 to 16; right?

17 A. Yes.

18 Q. Okay. And so you understand that
19 heterocycle includes both heteroaromatic, as well as
20 saturated heterocyclic structures; right?

21 A. Yes, based on the definition.

22 Q. Right.

1 Okay. So let's take -- let's go back to the
2 patent and take a look at formula E and the sum
3 embodiments that are exemplified for formula E. So
4 that is at, I believe, page 93 of the specification.
5 94.

6 Okay. So here, we have at the bottom of
7 column 62 to the top of column 63, we have the
8 example embodiments of the Z-prime scaffold; right?

9 A. So these three embodiments -- Z-prime is, as
10 I'm aware, are not referenced in the specification.
11 Z-prime in Claim 1 refers to the heterocyclic group.
12 And then in subsequent claims, these formula E
13 structures are shown.

14 Q. Right.

15 So these are the examples of the portion of
16 the compound that binds to the Btk active site;
17 right?

18 A. Yes.

19 Q. And each of these example structures are
20 heterocyclic structures; right?

21 A. Yes.

22 Q. And each of the structures is a fused

1 heterocyclic ring system; right?

2 A. That is correct. And I would say, beyond
3 that, they are also heteroaromatic.

4 Q. Sure. And each of these example structures
5 is a 5-6 fused heterocyclic ring structure; right?

6 A. Both rings are heteroaryl, and yes, it's a
7 fused structure.

8 Q. And given the definition in the patent,
9 they're 5-6 heterocyclic fused ring structures;
10 right?

11 MS. PATEL: Objection. Form.

12 A. Given the definition, they are fully
13 heteroaryl, a subset of the heterocyclic definition.

14 Q. Okay. And each of these example structure
15 scaffolds has between two and four nitrogen
16 heteroatoms?

17 A. Yes.

18 Q. And each of the example scaffolds has at
19 least one nitrogen heteroatom in each of the rings
20 of the ring system; right?

21 A. Yes.

22 Q. Okay. Let's go to your declaration at

1 paragraph 71, which is at page 44 of the PDF. Okay.
2 I think -- so looking at this table, you agree with
3 me that ibrutinib has a hydrogen bond acceptor that
4 forms a hydrogen bond with the Met477 of Btk;
5 correct?

6 A. Yes.

7 Q. And zanubrutinib has a hydrogen bond
8 acceptor that forms a hydrogen bond with Met477 of
9 Btk?

10 A. Correct. The carbonyl oxygen that's, you
11 know, not part of the ring structure forms the
12 hydrogen bond to Met477.

13 Q. Okay. And ibrutinib has a hydrogen bond
14 donor that forms a hydrogen bond with Glu475 of Btk;
15 right?

16 A. Yes. The NH2 is part of an amide group.
17 It's distinct from the amino pyrimidine of ibrutinib
18 that forms the hydrogen bond to Glu475. Again,
19 knowledge of that is the post priority date.

20 Q. And zanubrutinib forms -- has a hydrogen
21 bond donor that forms a hydrogen bond with Glu475;
22 right?

1 A. I thought that was what you were just
2 asking. I'm sorry. Yes, the NH₂ amide of the
3 carbonyl forms a hydrogen bond to the carbonyl of
4 Glu475.

5 Q. Okay. So --

6 A. And, again, that wasn't known until post
7 priority date.

8 Q. I'm gonna ask you about paragraph 80.

9 A. What page?

10 Q. 49.

11 And in paragraph 80, you're identifying what
12 you see as differences between ibrutinib and
13 zanubrutinib, and this is one of the differences
14 that you discuss as you see between the two
15 compounds; is that right?

16 A. Yes.

17 MS. PATEL: Objection to form.

18 A. Yes. One of the many differences.

19 Q. Okay. And in here, you say that "The
20 six-membered fuse ring of zanubrutinib projects into
21 a region of Btk that may be used to generate
22 selectivity for one kinase versus another and can

1 significantly affect binding properties."

2 Do you see that?

3 A. Yes.

4 Q. Okay. And you don't have any citation for
5 that sentence. So is that -- so you don't -- you
6 didn't cite any support for zanubrutinib projecting
7 into this region of Btk?

8 A. That's not correct exactly. So it says
9 "Although this pocket is not emphasized and
10 Ghose 472" -- let me see if I can find it here -- it
11 is shown in the figure, in the declaration.

12 Q. So the figure that you're talking about is
13 the one in Dr. Eck's declaration?

14 A. It's -- if you'll give me one moment here.

15 Q. Yeah. Could you let us know what exhibit
16 you're looking at?

17 A. I'm looking at my declaration on my split
18 screen. So it's -- if you go to page 34, I'm trying
19 to go to -- okay. So Exhibit 2010. So the pocket
20 that's being referred to is here, and so it's shown,
21 you know, in this declaration. And when I say it
22 wasn't really referencing Ghose, it's showing the

1 structure. It's Ghose 2010? Let me confirm that.

2 Q. No, this is Dr. Eck's expert declaration.

3 A. Give me one moment again.

4 So I'll have to look and see the specific
5 reference that Dr. Eck took it from, but he shows it
6 here, and it wasn't emphasized in Ghose but it was
7 being called out. And I think actually, in the
8 publication of mine you pointed out earlier, it was
9 called out.

10 And so this is the region where ibrutinib
11 projects into that you can see it -- just from the
12 schematic, is clear where direct adenine mimetics
13 like ibrutinib would bind to. So the fact that
14 zanubrutinib is projecting into this region, and
15 I'll go now back to where we were before. So here
16 it is again. Should have gone there in the first
17 place. So it's this region specifically. And,
18 again, one of the things that, you know, is now
19 appreciated is that the long axis view, the biaryl
20 ring systems are quite opposed to each other when
21 you compare ibrutinib to zanubrutinib. You can see
22 this in this structure where there's the -- if you

1 draw, you know, an axis along the -- or a long axis
2 along the biaryl ring, it's roughly parallel to the
3 page for Imbruvica or ibrutinib, and it's turned
4 nearly 90 degrees for zanubrutinib. And as a
5 result, the nonaromatic ring projects into an area
6 that's not at all occupied by ibrutinib.

7 And so you wouldn't have any understanding
8 from, you know, ibrutinib specifically or, you know,
9 that what would be the effect of that. And to my
10 mind as well, because it's nonaromatic where you
11 have additional pucker in the ring in, what can
12 often be a narrow binding clip, that additional
13 uncertainty about how that would be tolerated. So,
14 again, this is one of many areas of difference
15 between zanubrutinib and ibrutinib.

16 Q. And Dr. Eck did a comparison between the
17 binding interactions of zanubrutinib and ibrutinib
18 in something that was called a LigPlot+ plot.

19 Do you recall that?

20 A. I do.

21 Q. And are you familiar with LigPlot+ plots?

22 A. Yes. I'm not that much of a fan in that, if

1 you look at a structure or overlap like this, I
2 think you can highlight much better -- I mean, what
3 LigPlot tries to do is basically take, you know,
4 what is a three-dimensional view and kind of smash
5 it down. And, you know, I generally don't make use
6 of LigPlot because it doesn't highlight, you know,
7 what are key differences between molecules.

8 Q. And one of the things, though, that LigPlot
9 does show is residues of the proteins and their
10 proximity to the bound structure; right?

11 MS. PATEL: Objection. Form. Foundation.

12 A. Yes, that's correct.

13 Q. And it allows for comparison of, you know,
14 what residues different bound structures are
15 interacting with as -- you know, as those
16 structures -- bound structures are different and
17 those interactions are different to the -- let me
18 start over.

19 So the LigPlot+ allows for a comparison of
20 the residues of the protein that interact with
21 different bound compounds; is that fair?

22 A. That's correct.

1 Q. And you didn't provide any analysis of -- or
2 disagreement with the LigPlot+ that Dr. Eck
3 generated in his declaration; right?

4 MS. PATEL: Objection. Form.

5 A. I attempted to summarize the differences in
6 this structure or this comparison, which I think is,
7 to my mind, more indicative of how different
8 zanubrutinib is from ibrutinib.

9 Q. And this structure that you put here in
10 paragraph 74 of your declaration, this was something
11 that you devised for your declaration here. This
12 isn't a standard annotation of compounds that's
13 known and used in the field; right?

14 A. It's a schematic that was included to
15 basically kind of visualize the differences that I'm
16 describing here. So, for example, the first of
17 differences, ibrutinib has a pyrimidine ring deep in
18 the kinase binding site near the hinge region. It's
19 an aromatic ring system. Whereas zanubrutinib lacks
20 any, you know, analogous ring system.

21 Q. Right. So I see that you have identified a
22 number of differences, and I don't need to go

1 through all of the ones that you detailed in your
2 declaration. I'm asking very specific questions
3 about what you've included. So just to be clear,
4 the annotation that you've included in your figure
5 at paragraph 73 is one that you devised for these
6 purposes. It's not annotations that are known or
7 standard in the field for describing comparisons
8 between two compounds?

9 MS. PATEL: Objection. Form.

10 A. It was intended to be a visual
11 representation of the, you know, key differences.
12 You know, paragraph 75 through paragraph 80, between
13 ibrutinib and zanubrutinib.

14 Q. Okay. So -- oh, I'm sorry. Do you have
15 more?

16 A. No. Other than to say that they're really
17 major differences, so ...

18 Q. Okay. And so the suggestion in paragraph 80
19 that zanubrutinib projects into this region of Btk
20 that may be used to generate selectivity, you
21 actually don't identify any residue of Btk that
22 zanubrutinib -- this portion of zanubrutinib

1 interacts with Btk that ibrutinib doesn't; right?

2 MS. PATEL: Objection. Form.

3 A. I would have to look at Dr. Eck's structure,
4 whether he included it or not. But as an example,
5 there are key residues on the roof of the binding
6 site as shown as zanubrutinib approaches that
7 ibrutinib does not.

8 Q. Okay. So --

9 A. They're not called out specifically here,
10 but the fact that you're projecting into that
11 pocket, well removed from where ibrutinib is, I
12 think strongly supports there will be key different
13 interactions. And so it's the residue, which is, I
14 believe, a leucine. It's not called out
15 specifically. I would have to look back at the
16 actual, you know, structure to identify that
17 specifically.

18 Q. Let's take a look --

19 A. There will be major interactions that are
20 not present with ibrutinib.

21 Q. Okay. Well, let's actually take a look,
22 then, at the LigPlot which, as you noted, does

1 describe the interactions -- the comparative
2 interactions between two bound structures to a
3 protein. So if we take a look at Dr. Eck's
4 declaration, so that's Exhibit 2010.

5 (Exhibit 2010, previously marked, was
6 retained by counsel.)

7 MS. DANEK: I think we need to open it.

8 REMOTE TECHNICIAN: Stand by. I'll pull
9 that up.

10 On screen.

11 MS. DANEK: If we turn to page -- I think it
12 might be page 71 of the PDF.

13 BY MS. DANEK:

14 Q. Are you able to navigate to that?

15 A. I'm getting there.

16 Q. I'm not seeing -- oh, okay. Okay. And this
17 is the -- here at paragraph 96 of Dr. Eck's
18 declaration, this is the LigPlot+ that we were
19 talking about earlier that is an automatic
20 generation by software that compares interactions
21 between two bound compounds to a protein target;
22 right?

1 A. Yes.

2 Q. And so you suggest that the six-membered
3 ring of zanubrutinib may be interacting with Btk at
4 a different -- in this different location than
5 ibrutinib interacts with Btk; right?

6 A. Yes.

7 Q. And -- but the LigPlot actually doesn't show
8 that there's any difference in interactions between
9 that portion of zanubrutinib and Btk than ibrutinib
10 and Btk; right?

11 If you look in the center -- the center
12 portion where the bound compound is, where the
13 six-membered ring is of zanubrutinib, it is not
14 interacting with any residues that aren't also
15 interacting with ibrutinib; right?

16 A. I am confident that they're different
17 interactions, just by the fact that you're still
18 well deep within the binding site. And as you can
19 look from -- you know, even perhaps see from the
20 2D-plot here, although it's a little bit more
21 difficult than when you look at the direct overlap,
22 you're occupying space that is different from

1 adenine, so you're still -- I'm sorry -- different
2 from ibrutinib. So you're still deep within the
3 kinase binding site, and you have, you know, the
4 ring system of ibrutinib that's mapping into an area
5 of -- that's distinct from ibrutinib. So it will
6 have distinct interactions.

7 And again, this is sort of a smashed-down,
8 2D-view of what is going on rather than, you know, a
9 more detailed description.

10 Q. Yeah.

11 And this -- you agree with me that the
12 LigPlot+ just takes the interactions as available
13 from the structural data and identifies the residues
14 that the compounds are interacting with; right?

15 A. Yes. And I think one thing you can see just
16 even from looking at this LigPlot is, you know, how
17 the ring system of zanubrutinib is oriented entirely
18 different from how that of ibrutinib is. And, of
19 course, if you brought on ATP here, you would see
20 that ibrutinib directly overlaps the adenine of ATP
21 where again, the 6-5 ring system of zanubrutinib
22 does not. You also see that, you know, it's

1 actually the Z-prime in terms of the ring nitrogen
2 of ibrutinib that's making the hydrogen bond in the
3 case to the NH of methionine 477.

4 In the case of zanubrutinib, the Z-prime is
5 not making a hydrogen bond -- the Z-prime ring, the
6 core ring is not making a hydrogen bond actually to
7 the hinge region. It's the amide that's substituted
8 off of the zanubrutinib structure.

9 Additionally, you have, you know, this third
10 hydrogen bond or potential hydrogen bond with the
11 zanubrutinib ring system and the, you know, modeling
12 and X-ray is long. That's a hydrogen bond donor.
13 That actually, you know, overlaps onto a hydrogen
14 bond acceptor of ibrutinib. And certainly, if
15 somebody was trying to conceive of the zanubrutinib
16 structure, they would have, you know, real concern
17 about if you have a long-range hydrogen bond that's
18 now replacing that of a, you know, hydrogen bond
19 acceptor. In the case of ibrutinib, would that be
20 favorable and consider taking that hydrogen bond out
21 of solvent. So even here, I think --

22 Q. Dr. Veal, you -- I understand that you have

1 identified a lot of differences that you've seen
2 between ibrutinib and zanubrutinib. It's in your
3 declaration. I understand that that -- you have
4 provided those opinions. We don't have to go
5 through every single one of them here.

6 I asked you a very simple question about
7 what LigPlot+ shows. I think you answered it. I
8 think we can move on. If your counsel has
9 additional questions, she can ask you them. But in
10 response to my very specific question providing a
11 litany of things that are -- take pages in your
12 declaration is just really not helpful.

13 A. Well, I wish to reply or to answer the
14 question because implicit in your question here is
15 that they're binding or they're the same, and
16 they're not. And so you're making this argument
17 that LigPlot in this 2D-compressed view is somehow
18 implying that they're the same. And they're not.
19 So as a result, I'm replying by providing a summary
20 of the differences since, you know, you -- the
21 intent or you've indicated you don't want to cover
22 the differences as I summarize them.

1 Q. The LigPlot which takes the actual crystal
2 data of the ibrutinib and zanubrutinib compounds
3 bound to Btk does not identify any different
4 residues of Btk that are interacted with
5 zanubrutinib at the six-membered ring than ibrutinib
6 in the six-membered ring; is that correct?

7 MS. PATEL: Objection. Form.

8 A. And I'm making the argument again that based
9 on the post-priority crystal structure that the ring
10 system of zanubrutinib, the six-membered ring
11 specifically is making different interactions, and
12 we would have to go to the X-ray structure. And I
13 would be glad to, you know, highlight those
14 differences versus ibrutinib.

15 Q. And the LigPlot which is an unbiased
16 assessment of the crystal structure data did not
17 produce any signal that the six-membered ring of
18 zanubrutinib was making a different contact with a
19 different Btk residue than ibrutinib; right?

20 MS. PATEL: Objection. Form.

21 A. I can't speak to the differences here. I'd
22 be happy to provide the unbiased view of looking at

1 the actual crystal structure, pointing out specific
2 distances between zanubrutinib and the six-membered
3 ring and residues on the protein -- of the Btk
4 protein to show you the difference.

5 Q. And if we go back to your declaration at
6 paragraph 80, you simply say that "The six-membered
7 fused ring of zanubrutinib projects into a region of
8 Btk that may be used to generate selectivity for one
9 kinase versus another and can significantly affect
10 binding properties."

11 That's what you say; right?

12 A. Yes.

13 Q. And you don't identify and you didn't do the
14 analysis that you say might be done to identify any
15 actual interactions between the six-membered ring of
16 zanubrutinib and Btk; correct?

17 MS. PATEL: Objection. Form.

18 Q. Dr. Veal, I'm not asking you to do the
19 analysis. I'm asking if you did that analysis and
20 included it in your declaration, which it is not in
21 paragraph 80; correct?

22 A. So this structure highlights the region

1 that's different. I think you can see that you're
2 still well within the kinase binding site as
3 compared to --

4 MS. PATEL: Let's just be clear on what
5 we're looking at. Can we just make sure the record
6 is clear what everyone is --

7 MS. DANEK: I would like the record to be
8 clear that you're going to be responding to my
9 question. Okay?

10 BY MS. DANEK:

11 Q. My question was in paragraph 80, you did not
12 identify any different interactions between
13 zanubrutinib six-membered ring and Btk that are not
14 present in ibrutinib; correct?

15 MS. PATEL: Objection. Form.

16 A. There are no specific interactions
17 identified. However --

18 Q. No. I -- that's all I needed to know. I do
19 not want you to do the analysis.

20 MS. PATEL: Hold on. Let him finish. You
21 asked a question.

22 MS. DANEK: I asked him a question.

1 (Unreportable crosstalk.)

2 BY MS. DANEK:

3 Q. I don't not want you to spout off for pages
4 again all of the differences that you think you
5 could do. This was not an analysis that you
6 included in paragraph 80.

7 MS. PATEL: He's pointing you to where he is
8 providing this analysis in his declaration. Are you
9 saying that he cannot do that right now? That he
10 cannot, during his deposition, answer your question
11 and point you to where in his declaration he
12 provides the analysis?

13 MS. DANEK: He answered my question. I'm
14 gonna move on.

15 Actually, let's take a break.

16 MS. PATEL: Make sure the record is clear
17 that you're not letting him do that.

18 (A short break was had.)

19 BY MS. DANEK:

20 Q. All right. So, Dr. Veal, in your
21 declaration, you performed and reported on at least
22 a portion of the modeling that you conducted as part

1 of your analysis; right?

2 A. Yes.

3 Q. Okay. And I think that it starts at
4 paragraph 92 of your declaration, which is at
5 page 57 of the PDF.

6 Maybe more specifically, it might be
7 later -- yeah, so it's actually at paragraph 105 at
8 page 67.

9 Right. And so this is the section that you
10 describe the modeling that you conducted or at least
11 some of the modeling that you conducted?

12 A. Yes.

13 Q. Okay. And in particular, you modeled
14 ibrutinib and zanubrutinib; correct?

15 A. Yes.

16 Q. And then you modeled certain compounds from
17 Exhibit 2010, as reported in -- starting in
18 paragraph 110?

19 Right?

20 A. Yes.

21 Q. So you modeled ibrutinib and zanubrutinib
22 and then you modeled compounds 7 and 8 from

1 Exhibit 2010?

2 A. Yes.

3 Q. And then as denoted in paragraph 112, you
4 modeled three compounds from exhibit -- from the
5 '446 patent, which is Exhibit 2024.

6 MS. PATEL: Objection. Form.

7 Q. And we can pull that up, but you didn't
8 include an exhibit number for the '446 in your
9 declaration. I just want to make sure that the --
10 that we all have the same understanding.

11 A. Yes.

12 Q. Okay. So you -- just let's make sure we
13 have the right group. You docked ibrutinib,
14 zanubrutinib, two compounds from exhibit -- from
15 Zhang 2020, which is Exhibit 2063. Again, you
16 didn't include that cite in your declaration so,
17 again, I want to make sure we're --

18 MS. PATEL: What are we looking -- sorry.
19 I'm confused. What paragraph are we on here?

20 MS. DANEK: Paragraph 110, 111, and 112.

21 MS. PATEL: The ones that start out "Dr. Eck
22 modeled"?

1 MS. DANEK: Right.

2 MS. PATEL: Okay.

3 MS. DANEK: These are modeling that he --

4 MS. PATEL: Okay.

5 MS. DANEK: Well, that Dr. Veal also did.

6 Right?

7 MS. PATEL: Where does it -- okay.

8 MS. DANEK: Well, let him answer the
9 questions, Priya. I think we understand -- we can
10 understand what he did --

11 MS. PATEL: I understand -- I'm just making
12 sure I'm looking at the right thing.

13 A. I'm sorry. What's the question?

14 BY MS. DANEK:

15 Q. So you modeled ibrutinib, zanubrutinib,
16 compound 7 and 8 from Exhibit 2063, which is
17 Zhang 2020, and compounds 20, 30, and 122 from
18 Exhibit 2024, which is the '446 patent; right?

19 MS. PATEL: Objection. Form. Foundation.

20 A. Yes.

21 Q. Okay. And based on the modeling, the
22 modeling that you did, you agree that the modeling

1 is consistent with the activity of the compounds
2 ibrutinib, zanubrutinib, compounds 7, 8, 10, and 11
3 from Zhang 2020, and compound 20 from the
4 '446 patent; right?

5 MS. PATEL: Objection. Form. Foundation.

6 A. Yes, we need to -- I mean, need to step
7 through each one of those compounds one at a time.

8 Q. Well, we can take a look at your footnote 6
9 if that's helpful. So that's at page 76 of the
10 declaration.

11 A. I think what I'm saying is that --

12 Q. One at a time?

13 A. Yes, please.

14 Q. Okay. Sure. Okay. So you agree that
15 the -- well, let's ask it this way. The modeling of
16 ibrutinib into Marcotte indicated that ibrutinib
17 would be a Btk inhibitor; correct?

18 MS. PATEL: Objection. Form. Foundation.

19 A. Could you repeat that question, please?

20 Q. Modeling of ibrutinib into Marcotte
21 indicates that ibrutinib would be a good -- or would
22 be a Btk inhibitor; right?

1 MS. PATEL: Same objection.

2 A. So when I modeled all of these compounds,
3 you return a Glide score, and so that's an
4 indication that you can use perhaps to compare to
5 other compounds. However, as indicated in my
6 declaration, that often didn't correspond with
7 actual IC50s when they were tested. And so I
8 modeled ibrutinib and saw a docking pose and
9 obtained a score. In terms of saying it's active or
10 not, you don't know that until you make and test the
11 compound.

12 Q. But the docking score that you achieved for
13 ibrutinib was consistent with a compound that would
14 inhibit Btk -- would bind to Btk?

15 MS. PATEL: Objection to form.

16 A. So, again, you dock ibrutinib and you get a
17 Glide score, which in and of itself, you know,
18 you're not sure exactly how to interpret. Generally
19 what you're trying to do is compare to other
20 compounds. And so ibrutinib scored reasonably well.
21 That's fair enough to say. So knowing that
22 ibrutinib had been tested and -- synthesized and

1 tested, you know, and found to be active, that
2 provided, if you will, a correlation point to
3 understand, you know, how the Glide scoring was
4 representing active compounds.

5 However, again, there were other examples,
6 multiple examples where I got a Glide score as good
7 as ibrutinib that were also tested and found to be
8 inactive. So, you know, it goes to the
9 predictability of modeling.

10 Q. Right. Let's talk through those -- let's
11 break that out a little bit. Okay? Again, through
12 this section, it would be really useful for you to
13 listen to the question I'm asking and respond to the
14 question that I'm asking and not provide context
15 that's not required by the question that I'm asking.
16 Okay? Or responses that are not relevant to the
17 question that I'm asking. I just would appreciate
18 your attention to the question that I'm asking in
19 this section. Okay?

20 A. Apologies. I thought that response was
21 quite relevant to the question you were asking.

22 Q. So as we go through these next questions, I

1 would appreciate if you would listen to my question
2 and answer the question I'm asking. Okay?

3 A. Yes.

4 Q. Okay. Okay. So in 2011, a person of
5 ordinary skill in the art would have known from the
6 specification that ibrutinib was a potent Btk --
7 irreversible Btk inhibitor; correct?

8 MS. PATEL: Objection. Form.

9 A. Yes, that's correct.

10 Q. Okay. And when you modeled -- as you noted,
11 when you modeled ibrutinib into the Btk structure
12 from Marcotte, it provided, as you said, I believe,
13 a reasonably good docking score; is that right?

14 A. It provided a docking score that then, based
15 on the known activity of ibrutinib, serves as sort
16 of a guidepost to try and understand how other
17 compounds, you know, might also look. Again, it
18 turned out not to be predictive, but you don't see,
19 in and of itself, that the modeling says this
20 compound is gonna be active or not.

21 Q. Okay. And in footnote 6, which is at
22 paragraph 119 of your declaration, you identify

1 other compounds that you modeled that whose modeling
2 was consistent with their reported activities;
3 right?

4 A. That's correct.

5 Q. And you amended your declaration at the
6 start of this deposition to include compound 7 from
7 Zhang in the list of compounds that should be
8 included in this footnote; right?

9 A. That's correct.

10 Q. So compound 7, compound 8, compound 10, and
11 compound 11 from Zhang, you concluded that the
12 modeling was consistent with the activity; is that
13 right?

14 MS. PATEL: Objection. Form.

15 A. Yes, that's correct.

16 Q. Okay. And you also conclude that
17 compound 20 from the '446 patent, its modeling was
18 consistent with its activity; right?

19 A. Yes, the compounds you're referring to are
20 the subset where, you know, the Glide scoring seemed
21 to align with the IC50s. Obviously, as indicated,
22 there were multiple other compounds where that was

1 not the case.

2 Q. Right. So one of the compounds where the
3 modeling did align with the IC50 was compound 20 of
4 the '446; right?

5 A. Yes, that's correct.

6 Q. And an additional compound that you
7 identified in your declaration, compound 2 of the
8 WO'185 reference; right?

9 A. Yes, that's correct.

10 Q. Yeah, that the -- the docking score for
11 compound 2 of the WO'185 reference was consistent
12 with its reported activity; right?

13 A. Yes. However, compound 9 from the WO'185
14 patent, which scored actually better than
15 zanubrutinib, if you refer specifically to the table
16 in paragraph 116, that compound was inactive, and so
17 compound 2 of '185 seemed to match. Compound 9 of
18 '185 didn't match at all. And, again, pointing to
19 the lack of predictability around the modeling for,
20 you know, those sorts of structures.

21 Q. And the two compounds that you identify, as
22 you started to say here, the two compounds that

1 you've identified where you think that the modeling
2 of the compounds does not align with the reported
3 activity are the two in the table at paragraph 118,
4 compound 81 from Exhibit 1108 and compound 9 from
5 Exhibit 1109; right?

6 A. Yes. Those are two examples, correct.

7 Q. And those are the two examples where you say
8 the modeling doesn't align with the reported
9 activity; right?

10 A. Right. I think there's a little bit of
11 caution there because, again, you're trying to
12 understand what the scale is. And so, you know, for
13 example, as zanubrutinib scored with a 9.3 on the
14 Glide score, compound 30 scored with an 8.5 and
15 compound 122 scored with an 8.3. So there's a
16 difference, but is that meaningful? You know, and,
17 again, Dr. Eck, in his original declaration,
18 reported the wrong score for ibrutinib, where
19 initially he had it at minus 8.8.

20 And so there's, again, the gradations here
21 are, you know, difficult to assess. And the idea
22 that somehow you're gonna predict what's active and

1 what's inactive by modeling in this regard is
2 challenging. Compound 7, for example, and from
3 the -- we need to go back to that footnote.

4 Q. So, Dr. Veal, you've answered my question.
5 This is sort of an example where you're spending
6 time providing, you know, sort of recitation of
7 things that are in your declaration that I'm not
8 asking questions about. So if you could please
9 focus on the question I'm asking, I'd appreciate it.

10 MS. PATEL: Counsel, he is answering your
11 questions, and he's providing context for his
12 answers. He is allowed to do that. Please don't
13 cut him off in providing his answers.

14 MS. DANEK: All right. Let me ask my
15 questions. Okay?

16 Q. So you indicated that Dr. Eck reported the
17 wrong score for ibrutinib, but scores for the same
18 compound are reflective of the parameters that are
19 set for a particular docking session; right?

20 MS. PATEL: Objection. Foundation.

21 A. I mean, to be clear, Dr. Eck, he modeled
22 ibrutinib in two different docking runs. In the one

1 case, he modeled the incorrect structure. So it
2 wasn't ibrutinib, and it had a score of minus 8.8.
3 Then he used that as a reference. He did not
4 report, initially, the correct score for ibrutinib
5 when he modeled it, you know, with the correct
6 structure, and that was a score of a negative 11.0.
7 So it moved it, you know, into the, you know, the
8 best category.

9 And so then everything else you were looking
10 at was like -- that he looked at was sort of
11 benchmarking relative to ibrutinib. And so when it
12 was negative 8.8, the wrong structure, that's one
13 thing. When it was negative 11.0, so a negative
14 2.2 score which you've already seen from this table,
15 I can point to it here -- you know, the range of
16 differences is, you know, in that range. And so
17 when you model the wrong structure and you have a
18 score of minus 8.8, you report that, and then you go
19 to the correct structure and it changes 2.2 units
20 to --

21 Q. Did you rerun that? Did you do -- did you,
22 in Dr. Eck's native file, did you rerun the

1 ibrutinib structure in the particular run where he
2 had the incorrect ibrutinib or the ibrutinib-like
3 analog with the added hydrogens? Did you run the
4 score in that modeling -- set of modeling
5 parameters?

6 A. There would be no --

7 MS. PATEL: Please refrain from interrupting
8 the witness when he's providing an answer.

9 A. I did not, and there would be no reason to
10 model, you know an incorrect structure, at least to
11 my mind.

12 Q. My question was, did you run -- did you
13 model ibrutinib where Dr. Eck had modeled the
14 ibrutinib analog that had the hydrogens? Did you
15 model ibrutinib in that modeling session?

16 A. When you say "had the hydrogens," so he had
17 one structure, the incorrect structure, where the
18 vinyl group was, you know, no longer a vinyl group,
19 it was an ethyl group. That is the score he
20 reported. I did not model that structure because
21 it's the incorrect structure.

22 Q. I'm not asking you if you modeled the

1 hydrogenated ibrutinib. I'm asking if you modeled,
2 in Dr. Eck's modeling session, if you added the
3 vinyl to the ibrutinib, did you see how it changed
4 the docking score in that modeling run?

5 A. So my score for ibrutinib is shown in this
6 table in paragraph 116. That's the correct
7 structure for ibrutinib. That's the structure of
8 ibrutinib that I modeled. When I compare the
9 docking pose that I achieved with modeling this
10 correct structure for ibrutinib, it matches the
11 docking structure that Dr. Eck had obtained when he
12 modeled the correct structure of ibrutinib.
13 However, he reported the score for the incorrect
14 structure, and it was a difference of negative 2
15 point -- or of 2.2 units difference, where the
16 correct structure, when he modeled it, was a
17 negative 11.0. It was a relatively good alignment,
18 and I attribute that to docking parameters.

19 However, again, you know, he reported this
20 different score, and so now you're comparing it and
21 trying to understand what to make of this difference
22 that you see. And as you can see from this table,

1 again, paragraph 116, the gradation between an
2 active and inactive structure can be quite limited.
3 And, in fact, inactive structures score better than
4 zanubrutinib did. It just points out again to the
5 challenge of using, you know, modeling to assume
6 somehow you can predict binding without testing the
7 structure and making -- doing the biological testing
8 of the compound. Much less, again, you don't speak
9 to whether there's covalent modification.

10 Q. Okay. And in your analysis, what you've
11 identified is just the two compounds in paragraph 18
12 where modeling does not align with the reported IC50
13 values; is that right?

14 MS. PATEL: Objection. Form.

15 A. So the compounds I modeled, again, you have
16 some sort of continuum. You don't know where to
17 draw the cutoff between what an active and inactive
18 compound is. And so compound 30 at a minus 8.5
19 versus zanubrutinib at a negative 9.3, you know, do
20 you call compound 30 for modeling active or
21 inactive? I'm not sure. If I'm comparing those two
22 in the absence of IC50s, I don't -- you know, of

1 known testing data, I don't know what to make of
2 that difference. And that's the same -- you know,
3 you can see compound 22 is down another notch. But
4 again, in the absence of, you know, already knowing
5 the biological data, how do you understand, you
6 know, what is a significant difference?

7 And I come back to the point that, you know,
8 when Dr. Eck modeled the wrong structure of
9 ibrutinib, his range, his difference was 2.2 just in
10 doing that incorrect structure, which again, you
11 know, if you compare this difference, how -- you
12 know, it goes to the idea that modeling may suggest,
13 you know, compounds to try, but it's not predictive.
14 And what you need to do then is to synthesize the
15 molecules and test them.

16 Q. Okay. So I want to talk about the compounds
17 that you say do not align -- where the docking
18 scores do not align with the reported IC50 values.
19 And that is in paragraph 118. You have a table;
20 right?

21 A. Yes.

22 Q. Okay. And so these are the two compounds

1 that you go through and say the docking scores "do
2 not align with the reported IC50 values"; right?

3 A. Yes. These two are called out specifically
4 because of the degree of difference.

5 Q. Okay. And you did not synthesize and test
6 either of the two compounds that you identify in
7 paragraph 118 to confirm that the reported IC50
8 values are correct; right?

9 A. That's fair to say.

10 Q. Okay. So you don't know whether or not the
11 patent applications that you took this data from
12 accurately reported the IC50 values for these two
13 compounds; right?

14 A. I don't know if any of the biological data
15 that is reported -- obviously, I didn't test any of
16 the compounds. And so, you know, there's the
17 assumption that -- you know, when you file a patent
18 application or when you make a -- you know, the
19 publications can be peer-reviewed, obviously,
20 there's, you know, an onus on the inventors or
21 authors to be accurate in their data reporting. And
22 so for any of the biological data that's, you know,

1 reported, whether it's Pan or these patent
2 applications, you know, yeah, certainly, you're
3 trusting in the veracity of the patent application
4 data or the publication data.

5 Q. Okay. But, again, you do not have any
6 knowledge about whether or not these reported data
7 are accurate for the compounds that you list in
8 paragraph 118; right?

9 A. Nor any of the other data that is listed.

10 Q. Right.

11 And, in fact, both of the references that
12 you cite in paragraph 118 are references that
13 postdate the -- 2011; right?

14 They would not have been available to a
15 person of ordinary skill?

16 A. I think the point of including these
17 compounds is that they make the point that -- you
18 know, the question is whether modeling is accurate
19 or not or it can be predictive. And so even though
20 they were postdate, that's correct.

21 But it is -- you know, the purpose of
22 assessing them was to evaluate whether, you know, a

1 known -- whether modeling can be predictive or not,
2 and that's why they were done.

3 Q. Right.

4 So you don't have -- so, again, my question
5 is just the two references that you cite in
6 paragraph 118 are both references that a person of
7 ordinary skill in the art would not have had in
8 2011; correct?

9 MS. PATEL: Objection. Form.

10 Q. Dr. Veal?

11 A. That is correct. But it doesn't affect at
12 all the, you know, relevance of the modeling or
13 performing the exercise to show whether modeling can
14 be predictive or not. That was the point of
15 modeling those compounds. And, in fact, what was
16 observed is that it's not predictive.

17 Q. Well, what you observed is that the modeling
18 that you did didn't align with the reported IC50
19 values; right?

20 A. That's right. And just to put a point on
21 it, if you look at figure -- I guess
22 Exhibit 1156.001. So paragraph 128, and then the

1 figure, Exhibit 1156.001, you can see the modeling
2 of the Glide docking poses that were obtained for
3 ibrutinib -- I'm sorry -- zanubrutinib versus the
4 compound 81, I believe, or -- yeah, compound 81 from
5 the '289 patent, how closely they overlap in the
6 modeling and yet the difference in activity was
7 profound.

8 Q. The difference in reported activity; right?

9 A. Yes. In all cases, I am relying -- you
10 know, for all the data that's shown -- biological
11 data that's shown in my declaration, I'm relying on
12 the veracity of either the authors of the
13 publication or the inventors of the patent.

14 Q. Okay. And then in paragraph 139, you start
15 and do some additional modeling on other scaffolds;
16 right?

17 A. Yes.

18 Q. Okay. And in particular, you identify in a
19 table at paragraph 141, the docking scores for the
20 compounds that you modeled with various Z-prime
21 scaffolds; right?

22 A. Yes. That table includes, you know, from

1 the formula E, the structures E2, E3, and E4. And
2 then the '820 patent, from the one scaffold. And
3 then two PDB structures, 2QD9 and 5TR6. And what I
4 attempted to do for all of those was to attach the
5 substituents, in particular, the phenoxyphenyl and
6 the linker warhead or Michael acceptor group to see
7 if I could obtain, you know, reasonable docking
8 poses with those.

9 Q. Okay. And in -- for each of these, the
10 compounds that you made with these scaffolds, for
11 each of them, you concluded that a person of
12 ordinary skill would have thought that those
13 compounds would not bind to Btk; right?

14 MS. PATEL: Objection. Form.

15 A. Yeah. So there's an element there, in part,
16 on -- drawing on Dr. Eck's conclusions with respect
17 to compound 122. And that's specific to the
18 structures E2, E3, and E4 where he makes his
19 argument in going from -- so this is the
20 '446 patent. Going from compound 20, which is
21 active, to compound 122, which is inactive, that
22 removing the nitrogen and in the case of -- removing

1 the nitrogen from the position -- the 4 position in
2 the ibrutinib scaffold, which makes the
3 hydrogen-bonded hinge region, that causes a loss of
4 activity. And so he attributes the lack of potency
5 to compound 122 to that.

6 So structures E2, E3, and E4, you can see
7 their docking scores, again, in this range where
8 you're trying to interpret them. They also lack the
9 nitrogen at that 4 position that ibrutinib has.
10 Obviously, inventors included them in the patent --
11 or not obviously, but inventors included them in the
12 patent with the understanding -- I imagine that they
13 thought they would be active, given they included
14 them in the patent.

15 However, if you go by Dr. Eck's conclusion
16 and you compare the docking score for compound 122,
17 the docking scores here for E2, E3, and E4, you
18 would conclude that these are inactive even though
19 they are included in the formula E specification.

20 Q. And for compound 122, Dr. Eck identified
21 that it doesn't make the hydrogen bond. And, in
22 fact, compound 122 is also missing the primary amine

1 substituent that is present in ibrutinib and
2 suggested in the scaffolds for E2 and E3; right?

3 A. That is correct, but compound 20 in the
4 '446 patent, which is active, also lacks that amino
5 group. And so in going from compound 20 to
6 compound 122, the difference is that you move the
7 nitrogen over one position, which is why I believe
8 he makes that conclusion as regards to the loss of
9 activity. And so at least in the compound 20,
10 compound 30, compound 122 of the '446 patent, for
11 compound 20, that amino group is not required, and
12 it's not present, I should say. And so there was a
13 single change in going from compound 20 to
14 compound 122 with regards to the Z-prime scaffolds
15 just moving the nitrogen -- structures E2, E3, and
16 E4, it's not that it's moved, it's removed. So it's
17 even a more significant change. Again, the
18 inventors of the '803 patent, you know, felt that
19 these structures should be included, and so I think
20 it points again --

21 Q. And you didn't -- I'm sorry.

22 You didn't make any other -- you just made a

1 single compound with scaffolds E2 and E3 and E4?

2 A. What I did was I used the -- the Markush
3 structures of E2, E3, and E4 where they, you know,
4 indicate the substitution points, and I matched them
5 to the, you know, substitutions of ibrutinib which,
6 to my mind, is the guidance in the patent app or the
7 patent.

8 Q. Okay. And based on the modeling that you
9 did for those compounds as reported in paragraph 141
10 of your declaration, you conclude that a person of
11 ordinary skill in the art would understand that
12 those compounds would be inactive as Btk inhibitors;
13 right?

14 A. I think what I concluded was that based on
15 Dr. Eck's assertion that removing the nitrogen or
16 moving it would cause inactivity based on what he
17 saw in going from compound 20 to compound 122, these
18 compounds have the same change. And then also
19 comparing the Glide scores that were observed as
20 well, that combination, Dr. Eck's conclusion and
21 rationale in the Glide scores seen here, that's the
22 reason for making that interpretation.

1 And so, again, it's -- you know, in a sense,
2 it's a conundrum because the inventors included
3 these structures, but the modeling suggests that
4 they are inactive, and so it makes a point that, you
5 know, you'd have to make them and test them.

6 Q. And the -- in looking at paragraph 146 where
7 you're discussing the compound you made with the E2
8 scaffold?

9 A. Yes.

10 Q. You state that the "Modeling suggests that
11 the structure E2 is inactive ... because it does not
12 form any hydrogen bonds to the Btk hinge region";
13 right?

14 A. And, again, that was clarified that the "it"
15 refers to the core scaffold. And you can see in
16 this structure, the core scaffold lacks the nitrogen
17 at the 4 position that is present in ibrutinib.

18 Q. And you didn't test -- you didn't test the
19 compound to see whether or not the structure is
20 inactive?

21 A. Are you asking me if I had the compound
22 prepared and tested?

1 Q. Yes.

2 A. Well, no.

3 Q. Okay. And similarly, for structure E3, you
4 conclude that the modeling suggests that this
5 structure E3 is inactive; right?

6 A. Yes. Again, using the combination of
7 Dr. Eck's conclusions where he very -- you know, he
8 states that you -- you know, looking at -- so now
9 looking at paragraph 147, so you see the Markush
10 structure. So Dr. Eck states for compounds 122, the
11 lack of nitrogen at the 4 position of what would be
12 ibrutinib causes a -- you know, that would be the
13 explanation for the loss of binding.

14 So I'm, you know, in a sense accepting
15 Dr. Eck's rationale there. That's, you know, what
16 he stated. These scaffolds also lacked the nitrogen
17 there. Their docking scores E2 and E3 were down.
18 E4 is terrible because, you know, I made -- I -- I
19 modeled it as the, you know, nonaromatic version
20 even though I don't agree that's what was intended.
21 And it, you know -- you know, didn't bind anywhere
22 near the hinge region.

1 Q. Right. So using your modeling, a person of
2 ordinary skill would have concluded that the
3 structure that you made with E4 would not be --
4 would be inactive; right?

5 MS. PATEL: Objection. Form.

6 A. Yes. But, again, the inventors chose to
7 include that, you know, Markush structure in the
8 patent application. So as I said, there's a
9 conundrum that, you know, indicates that you need to
10 synthesize and test the molecule.

11 Q. And then you indicated earlier that even
12 though you didn't include it in your declaration,
13 you did model compounds with the scaffolds E1, E5,
14 E6, and E8 and concluded that the modeling did
15 reflect compounds that would bind to Btk; right?

16 A. And that's correct. And if you look at the
17 formula E structures, they all have the nitrogen
18 that ibrutinib has. And so E7 is the ibrutinib core
19 specifically. So at the 4 position they have that
20 nitrogen. And so that gave rise to a favorable
21 docking score. Again, you would have to test those
22 molecules and -- synthesize and test those

1 molecules. But they scored roughly equivalent to
2 ibrutinib in terms of the Glide scores.

3 Q. Right. And so that would indicate that
4 the -- that a person of ordinary skill in the art
5 would understand from the Glide scores that the
6 compounds would be inhibitors of Btk?

7 MS. PATEL: Objection. Form.

8 A. To be clear, you never understand from the
9 Glide scores whether a compound is an inhibitor of
10 Btk or not. It's not until you synthesize and test
11 the molecule that you learn that. And moreover, in
12 terms of covalent modification, it's not until you
13 do the additional assays to confirm covalent -- you
14 know, confirm covalent modification. Or demonstrate
15 covalent modification.

16 What the modeling does is suggest compounds
17 that you might make, and then you have to go through
18 the effort to synthesize and test them. And as you
19 can see from E1-E8, these Markush structures were
20 all included in the '803 patent, but three of the
21 eight, modeling would question whether they should
22 be there. And that's based on Dr. Eck's conclusions

1 coupled with the Glide scores.

2 Q. You also then did modeling of -- starting at
3 paragraph 153, you did modeling of a compound having
4 the scaffold from the '820 patent?

5 A. Yes, that's correct.

6 Q. And based on that modeling, you concluded
7 that this compound would not be active in inhibiting
8 Btk?

9 MS. PATEL: Objection. Form.

10 A. So what was done with this compound, so the
11 structure that's shown in Exhibit 2023, what I
12 attempted to do was -- okay, so evaluate compounds
13 that have a 6-5 ring system where one of the ring
14 systems is nonaromatic. And so then it becomes a
15 question of -- it's a complicated effort, actually.
16 You have to first, you know, assess the structure
17 and say, well, how do I think this might interact
18 with the hinge region. You know, so that's your
19 Z-prime core. What is your Z-prime core? How do I
20 assess my interaction with the hinge region? And
21 then how do I consider, you know, how you might put
22 on the groups that would be the phenoxyphenyl to

1 target the back-binding site and then the linker
2 warhead.

3 And so you have to make all the
4 considerations there. And this is -- you know, so
5 that takes effort actually. It takes a good bit of
6 effort when you're modeling these. And, you know,
7 you make your best calls. And so in the case of
8 this compound specifically, the '820 patent formula,
9 I guess it's formula I, looking at the application,
10 I concluded that the pyrazole was likely the hinge
11 binder because pyrazoles were known at the time to
12 be hinge binders. You know, looking at the
13 substitution pattern, that seemed consistent with
14 that, although you can't be sure.

15 So then I tried to make modifications, you
16 know, a good faith effort, if you will. Well, could
17 I take this and somehow conceive of an irreversible
18 inhibitor or at least something that would bind and
19 put the linker warhead proximal to the cysteine.
20 Again, for modeling you can never determine if it
21 would be a covalent modifier. And so I tried that.
22 And it didn't go well. And --

1 Q. It not going well, you concluded that it
2 would not be -- it would not bind and inhibit Btk?

3 MS. PATEL: Objection. Form.

4 A. It had a low Glide score so -- and in the
5 docking pose, which is shown here, one of the best
6 ones, I didn't observe any bind to the hinge region.
7 So after all that work, it's like, okay, this is
8 what I got. And so let's go on to the next one.
9 Again, this is like conceiving just one structure
10 and how you might modify it at different positions.
11 And so it's, you know, a good bit of modeling
12 effort.

13 Q. Okay. And you did similar -- similar
14 efforts in the scaffolds in -- from the PDB 2QD9,
15 starting at paragraph 155, and PDB 5TR6 and 5TT7,
16 starting at paragraph 158?

17 A. Yes. And so for --

18 Q. That was a yes-no. You did a similar --
19 that was just a yes or no. You did a similar
20 exercise of using those scaffolds to build a
21 compound to model?

22 A. That's correct.

1 Q. Okay. And then, as you report in
2 paragraph 141, the compounds that you docked and
3 modeled from those -- with those scaffolds also had
4 poor Glide scores?

5 A. Yes. I mean, the concept here was that, you
6 know, there's this idea that from scaffolds that had
7 a 6-5 ring system that were known in the art with
8 one of the rings being nonaromatic, could you
9 somehow rapidly conceive of compounds that would,
10 you know, show a binding to Btk when docked that
11 would be suggestive of, you know, productive
12 interactions.

13 And so these were the scaffolds that were
14 known, tried to, you know, make the good faith
15 effort to modify them. Actually, for '820, I used
16 both with the amino group and without. And after
17 all the work, you get these docking poses that, you
18 know, don't look that favorable. And so it's sort
19 of, okay, there's nothing that's in the literature
20 or in the art that provides guidance, you know,
21 rated guidance on how to modify a scaffold to, you
22 know, satisfy the requirements of having a

1 phenoxyphenyl and the linker warhead in the correct
2 place.

3 So it's a challenging effort. It takes
4 quite a bit of modeling and time. I always say, at
5 the end, you'd still be back to the point of where,
6 even if you found something, you could conceive of
7 something that you liked, it would be back to the
8 medicinal chemist to discuss synthesis. He or she
9 would decide whether it could be made, and then you
10 would require the testing part of it.

11 Q. Right. And the modeling, as you said, that
12 you did for these two compounds that you report with
13 the scaffolds from Exhibit 2055 and 2046, you said
14 had poor binding poses and poor Glide scores; right?

15 A. Yes. Saying that, they actually match up to
16 structure E4. So to the extent that structure E4 is
17 viewed as a -- you know, because of its inclusion in
18 the formula E, they match that docking score. So
19 perhaps that's the way to say it.

20 I didn't observe hydrogen bonding when I
21 docked them to the hinge region, and also in terms
22 of interaction in regards to linker warhead, that

1 was also, I think, less than satisfactory. However,
2 the Glide scores do match up to what you see for
3 structure E4.

4 MS. DANEK: Okay. Let's take a break.

5 (A short break was had.)

6 BY MS. DANEK:

7 Q. Okay. Dr. Veal, let's take a look at
8 paragraph starting at -- the section starting at
9 paragraph 244 of your declaration, which is on
10 page 148 of the PDF.

11 Okay. And in particular, I want to take a
12 look at paragraph 247. And this is a section of
13 your paragraph related to the quantity of
14 experimentation as related to enablement; is that
15 right?

16 A. Yes.

17 Q. Okay. And in paragraph 247, you identify
18 that the structural limitations encompass both known
19 and unknown Z-prime scaffold, and evaluating the
20 full scope of the compound satisfying the structural
21 limitations would require evaluating known and
22 unknown structures; right?

1 A. It says it would have required extensive
2 efforts, and then -- yes.

3 Q. Yep. And then at the bottom of that
4 paragraph, you say "Specifically, modeling 4 million
5 potential candidates would have taken over seven
6 years assuming each one could be modeled and
7 evaluated in a single minute."

8 Is that right?

9 A. Yes.

10 Q. And that modeling billions would have taken
11 far longer; right?

12 A. That's correct.

13 Q. So is your assessment of the amount of
14 experimentation that's required based on an
15 assumption that a person of ordinary skill in the
16 art would have to make each and every compound
17 within the scope of the genus at a single time?

18 MS. PATEL: Objection. Foundation. Form.

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

21 Q. So you've identified how long it would take
22 to model 4 million potential candidates; right?

1 A. Yes.

2 Q. Is it your understanding that a person of
3 ordinary skill in the art, in order for the claim to
4 have been enabled, must be able to model all of the
5 compounds at once?

6 MS. PATEL: Objection. Foundation.

7 A. Again, when you say "model all the compounds
8 at once," I'm not quite sure what you mean there.

9 Q. Right. So -- well, why don't you tell me
10 why you included a calculation of how long it would
11 take to model 4 million potential candidates?

12 A. So with respect to that, why it would take,
13 you know, a substantial amount of time is that I
14 think maybe there was this notion that, you know,
15 you just tell the computer to go do it and then you
16 get back these results. And that's not the
17 situation at all.

18 You know, the -- Claim 1, as it stands
19 currently, where it basically indicates any
20 heterocyclic group, the, you know, number compounds
21 that that involves is enormous. It's somewhere from
22 4 million to a billion has been discussed in the

1 other declarations.

2 But from a computational point of view, to
3 go in and, you know, take scaffolds, look at all the
4 different positions of substitution, try and
5 understand how to substitute, you know, what to put
6 where, it's more than just using the computer. It's
7 also using personal work. And I think the idea that
8 you could do it in a minute is a very generous
9 estimate. I don't think that, you know, with a
10 skilled computational chemist trying to tackle
11 something like this, that it wouldn't be much longer
12 than a minute.

13 But having said that -- so that's the basis
14 of it. It's the idea that there's a lot of work on
15 the computer front to construct these compounds, you
16 know, to generate the Z-prime scaffold and construct
17 the modifications, and then do the part where you,
18 you know, prepare the ligand for Glide docking,
19 actually do the Glide docking, and then sit down and
20 analyze the poses and, you know, decide which ones,
21 you know, potentially look reasonable and which ones
22 don't.

1 Q. Okay. And so when you say there's a lot of
2 work to construct the compounds to generate the
3 Z-prime scaffolds, so are you envisioning that a
4 POSA would need to generate every single possible
5 Z-prime scaffold to evaluate in the experimentation
6 that you're describing in this paragraph?

7 MS. PATEL: Objection. Form.

8 A. Yes. That's where you would start is with
9 that assumption.

10 Q. Okay. Okay. And that was how you
11 approached understanding how to assess the quantity
12 of experimentation.

13 MS. PATEL: Objection. Form. Foundation.

14 A. Yes. I think that is correct. It's the
15 idea that when you have a lot of scaffolds -- and
16 I'd have to look back at what the Haas
17 declaration -- Dr. Showalter -- sorry -- declaration
18 to, you know, get that specific number of scaffolds.
19 But then where it blows up is all the different --
20 you know, the common or toil explosion, if you
21 will -- you know, all the different positions you
22 could, you know, put -- put substitutions on. And

1 so he did those calculations, which I concur with,
2 and I am saying that from a modeling perspective, to
3 look at all the different scaffolds and then to look
4 at all the possible substitution would be an
5 enormous effort.

6 Q. Okay. I --

7 MS. DANEK: If we can just take a quick
8 five-minute break, I think we may be able to wrap
9 this up.

10 MS. PATEL: Okay.

11 (A short break was had.)

12 MS. DANEK: Dr. Veal, I don't have any
13 further questions. Thanks for your time today.

14 A. Thank you.

15 MS. PATEL: I have a few questions.

16 Can we pull up Veal Exhibit 1, please.

17 REMOTE TECHNICIAN: Exhibit 1 on screen.

18 EXAMINATION

19 BY MS. PATEL:

20 Q. Dr. Veal, do you have control over this?

21 A. Yes.

22 Q. Okay. Do you see what's marked as Veal

1 Exhibit 1 in front of you?

2 A. I do.

3 Q. All right. Did opposing counsel ask you
4 questions about this exhibit?

5 A. They did.

6 Q. Okay. Can you turn to PDF page 23 or
7 page 411 of the document.

8 A. Sorry. Give me a sec.

9 Okay.

10 Q. I think one page down the other way. There
11 you go.

12 Can you -- what's the title of this section
13 16.3.3?

14 A. "Focused Compound Collections, Library
15 Design, and Novel Scaffolds for Screening."

16 Q. Okay. And can you scroll to figure 16.5
17 depicting the representative substructures that
18 opposing counsel asked you about?

19 A. Yes.

20 Q. Okay. Would modeling allow you to predict
21 whether any of these substructures would actually
22 bind the target or not?

1 A. No, it would not. It would be used for the
2 purpose of identifying compounds, again, from
3 internal corporate collection, you know, reducing,
4 you know, hundreds of thousands or millions of
5 compounds in a corporate collection down to 10 to
6 20,000 or to identify compounds from external
7 vendors to acquire and bring in for testing. And
8 only then after you tested the compounds would you
9 hope that some percentage -- likely, you know, a
10 small percentage would show activity against a
11 kinase of interest.

12 Q. Okay. When you testified earlier regarding
13 how modeling these representative substructures
14 would have a low probability of success, what did
15 you mean by "low probability of success"?

16 A. What I mean is that generally speaking, for
17 any given scaffold versus any given kinase, the
18 likelihood of success is low. And by that, you
19 know, the probabilities that it will have a hit --
20 you know, and certainly, if the cutoff is something
21 like one micromolar, it's even lower and so you, you
22 know, use this as a way to try and enrich for

1 compounds that might have -- be a hit. But, you
2 know, in no way do you assume that, you know, the --
3 you know, any high percentage of compounds you
4 acquire in would be active.

5 And again, you know, the underlying premise
6 is that you're using these to acquire known existing
7 compounds or to filter -- well, to acquire known
8 existing compounds from external collection or to
9 filter a corporate collection of known existing
10 compounds that then will be screened and tested in a
11 biological assay.

12 MS. PATEL: No further questions. Thank
13 you.

14 MS. DANEK: I have a question.

15 FURTHER EXAMINATION

16 BY MS. DANEK:

17 Q. And so those -- that process that you're
18 talking about of using these substructures to screen
19 the compound library for what should be tested, that
20 is in the context of a drug discovery program
21 looking to identify a potential lead candidate?

22 MS. PATEL: Objection. Form.

1 A. A lead candidate has, I think in the
2 pharmaceutical industry, a -- you know, an advanced
3 designation. These would be used to try and
4 identify, you know, initial hit structures, things
5 that show potentially some activity that then, you
6 know, could be optimized by a medicinal chemist
7 through the process of synthesis and testing.

8 Q. So that exercise of screening libraries of
9 compounds for a potential hit compound, that would
10 occur at a point before there's a lead compound
11 that's been identified; right?

12 A. Yes. That would be one approach where, you
13 know, for a specific target, you use this, again, to
14 go up against your corporate database or external
15 vendors and identify, you know, existing compounds
16 that you would like to screen.

17 Q. Okay.

18 MS. DANEK: I don't have any other
19 questions.

20 MS. PATEL: Okay. No further questions.

21 (Off the record at 5:33 p.m.)
22

1 CERTIFICATE OF COURT REPORTER - NOTARY PUBLIC

2
3 I, TIFFANY M. PIETRZYK, Certified Shorthand
4 Reporter No. 084-004371, CSR, RPR, CRR, and a Notary
5 Public within and for the State of Illinois, do
6 hereby certify:

7
8 That JAMES M. VEAL, Ph.D., the witness whose
9 deposition is hereinbefore set forth, was duly sworn
10 by me before the commencement of such deposition and
11 that such deposition was taken before me and is a
12 true record of the testimony given by such witness.

13
14 I further certify that the adverse parties,
15 BeiGene USA, Inc., and BeiGene, LTD., were
16 represented by counsel at the deposition.

17
18 I further certify that the deposition of
19 JAMES M. VEAL, Ph.D. occurred virtually, via Zoom
20 videoconference, on Friday November 22, 2024,
21 commencing at 10:01 a.m. CST to 5:33 p.m. CST.

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 and affixed my notarial seal this 25th day of
10 November, 2024.

11

12 My commission expires: February 28th, 2028

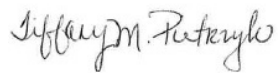
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18 NOTARY PUBLIC IN AND FOR THE

19 STATE OF ILLINOIS

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Conducted on November 22, 2024

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