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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BeiGene USA, Inc. and BeiGene, LTD.,

Petitioners,

v.

Pharmacyclics LLC

Patent Owner.

PGR2024-00009

U.S. PATENT NO. 11,672,803

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| <p>1 Deposition via Zoom of STEPHEN E.<br/>2 SPURGEON, M.D., a witness herein, called for<br/>3 examination by counsel for Petitioners in the<br/>4 above-entitled matter, pursuant to notice, the<br/>5 witness being duly sworn by MARY GRACE CASTLEBERRY, a<br/>6 Notary Public in and for the State of Maryland, taken<br/>7 at 8:29 a.m. PST, Friday, September 6, 2024, and the<br/>8 proceedings being taken down by Stenotype by MARY<br/>9 GRACE CASTLEBERRY, RPR, and transcribed under her<br/>10 direction.<br/>11<br/>12<br/>13<br/>14<br/>15<br/>16<br/>17<br/>18<br/>19<br/>20<br/>21<br/>22</p> | Page 2 | <p>1 APPEARANCE (Continued):<br/>2<br/>3 On behalf of the Patent Owner:<br/>4 BRENDA L. DANЕК, ESQ.<br/>5 Latham &amp; Watkins LLP<br/>6 330 North Wabash Avenue, Suite 2800<br/>7 Chicago, Illinois 60611<br/>8 (312) 876-7646<br/>9 brenda.danek@lw.com<br/>10<br/>11 ALSO PRESENT:<br/>12 ERIC VAVRASEK, Videographer<br/>13<br/>14<br/>15<br/>16<br/>17<br/>18<br/>19<br/>20<br/>21<br/>22</p>                                                                                                                                                                                                                                                                                                                                                     | Page 4 |
| <p>1 APPEARANCES:<br/>2<br/>3 On behalf of the Petitioners:<br/>4 PRIYATA Y. PATEL, ESQ.<br/>5 Weil, Gotshal &amp; Manges LLP<br/>6 2001 M Street N.W., Suite 600<br/>7 Washington, D.C. 20036<br/>8 (202) 682-7000<br/>9 priyata.patel@weil.com<br/>10 and<br/>11 KATHRYN LEICHT, ESQ.<br/>12 Weil, Gotshal &amp; Manges LLP<br/>13 767 5th Avenue<br/>14 New York, New York 10153<br/>15 (212) 310-8578<br/>16 kathryn.leicht@weil.com<br/>17<br/>18<br/>19<br/>20<br/>21<br/>22</p>                                                                                                                          | Page 3 | <p>1 C O N T E N T S<br/>2 WITNESS EXAMINATION BY COUNSEL FOR<br/>3 STEPHEN E. SPURGEON PETITIONERS<br/>4 By Ms. Patel 7<br/>5<br/>6<br/>7 Afternoon Session - Page 137<br/>8<br/>9 E X H I B I T S<br/>10 EXHIBIT NO. PAGE<br/>11 1 - Article entitled Pevonedistat, a<br/>12 Nedd8-activating enzyme inhibitor, in<br/>13 Combination with ibrutinib in patients with<br/>14 relapsed/refractory B-cell non-Hodkin lymphoma 58<br/>15 2 - Article entitled Hypertension treatment<br/>16 for patients receiving ibrutinib: A multicenter<br/>17 retrospective study 76<br/>18 1001 - U.S. Patent Number 11,672,803 87<br/>19 2014 - Declaration of Stephen E. Spurgeon, M.D.<br/>20 in Support of Patent Owner's Response 10<br/>21<br/>22 - - -</p> | Page 5 |

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| <p>1 PROCEEDINGS</p> <p>2 THE VIDEOGRAPHER: We are now on the</p> <p>3 record in the matter of BeiGene USA, Inc. and BeiGene</p> <p>4 Limited versus Pharmacyclics LLC. Today's date is</p> <p>5 September 6, 2024. The time on the video monitor is</p> <p>6 8:29 a.m. Pacific Standard Time. This is the video</p> <p>7 recorded deposition of Dr. Stephen Spurgeon being</p> <p>8 taken remotely via Zoom videoconference.</p> <p>9 I am the camera operator. My name is Eric</p> <p>10 Vavrsek in association with Trustpoint.One. The</p> <p>11 court reporter is Mary Grace Castleberry also in</p> <p>12 association with Trustpoint.One.</p> <p>13 Will all attorneys please identify</p> <p>14 themselves and the parties that they represent</p> <p>15 beginning with the party noticing this proceeding.</p> <p>16 MS. PATEL: Good morning. This is Priyata</p> <p>17 Y. Patel for BeiGene, the petitioner. With me today</p> <p>18 is Kathryn Leicht also for petitioner. Both of us</p> <p>19 are from the law firm Weil, Gotshal.</p> <p>20 MS. DANEK: Brenda Danek from Latham &amp;</p> <p>21 Watkins representing Pharmacyclics and the witness.</p> <p>22 THE VIDEOGRAPHER: Thank you, Counsel.</p> | Page 6 | <p>1 A. No.</p> <p>2 Q. Have you ever testified at trial?</p> <p>3 A. No.</p> <p>4 Q. Okay. So since this is your first go</p> <p>5 around, let's go over just a couple of ground rules</p> <p>6 before we get into the questions.</p> <p>7 So there's a court reporter here today</p> <p>8 who's writing down everything that we say, so it's</p> <p>9 important that you provide verbal responses to the</p> <p>10 questions that I ask you. So, for example, you</p> <p>11 shouldn't, you know, nod your head yes or no in</p> <p>12 response to a question. You should provide an oral</p> <p>13 response.</p> <p>14 Do you understand that?</p> <p>15 A. Yes.</p> <p>16 Q. Okay. And if you don't understand a</p> <p>17 question that I ask you, let me know and I'll clarify</p> <p>18 or rephrase. If you don't ask me to clarify, if you</p> <p>19 don't ask me to rephrase, then I'm going to assume</p> <p>20 you understand my question.</p> <p>21 Do you understand that?</p> <p>22 A. Yes.</p> |
| <p>1 Will the court reporter now please administer the</p> <p>2 oath and then we may proceed.</p> <p>3 Whereupon,</p> <p>4 STEPHEN E. SPURGEON,</p> <p>5 was called as a witness by counsel for Petitioner,</p> <p>6 and having been duly sworn by the Notary Public, was</p> <p>7 examined and testified as follows:</p> <p>8 EXAMINATION BY COUNSEL FOR PETITIONER</p> <p>9 BY MS. PATEL:</p> <p>10 Q. Good morning. Please state your full name</p> <p>11 for the record.</p> <p>12 A. Stephen Edward Forbes Spurgeon.</p> <p>13 Q. Dr. Spurgeon, do you understand that</p> <p>14 you're here today for a deposition in PGR2024-00009</p> <p>15 between BeiGene Pharmacyclics concerning U.S. Patent</p> <p>16 Number 11,672,803?</p> <p>17 A. Yes.</p> <p>18 Q. And it's correct that you submitted an</p> <p>19 expert declaration on behalf of Pharmacyclics in this</p> <p>20 proceeding?</p> <p>21 A. Yes.</p> <p>22 Q. Have you ever been deposed before?</p>                                                                                                                                                                                                                                               | Page 7 | <p>1 Q. I'm going to try and take breaks every</p> <p>2 hour or so. If you feel the need to take a break,</p> <p>3 let me know, you know, we can wrap earlier maybe.</p> <p>4 One thing that I ask, though, is if there is a</p> <p>5 question pending that you haven't answered, that you</p> <p>6 answer that question before we take a break.</p> <p>7 Do you understand that?</p> <p>8 A. Yes.</p> <p>9 Q. Okay. Do you understand that you are</p> <p>10 under oath today?</p> <p>11 A. Yes.</p> <p>12 Q. Is there any reason you can't provide</p> <p>13 accurate and truthful testimony today?</p> <p>14 A. No.</p> <p>15 Q. So you were retained by Pharmacyclics to</p> <p>16 provide testimony in this case as it pertains to the</p> <p>17 '803 patent, correct?</p> <p>18 A. Yes.</p> <p>19 Q. When did you first learn about this case?</p> <p>20 A. I don't know the exact date. I was</p> <p>21 probably contacted about a year ago.</p> <p>22 Q. Okay.</p>                                   |



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| <p>Page 10</p> <p>1 MS. PATEL: So let's pull up tab 1 and<br/>2 mark it as Spurgeon Exhibit 1.<br/>3 THE VIDEOGRAPHER: One moment, Counsel.<br/>4 MS. DANEK: And Counsel, is this a new<br/>5 exhibit? This isn't one of the already marked<br/>6 exhibits?<br/>7 MS. PATEL: So this is going to be his<br/>8 declaration.<br/>9 BY MS. PATEL:<br/>10 Q. So I understand you have a hard copy of<br/>11 that in front of you, Dr. Spurgeon?<br/>12 A. I do, yes.<br/>13 MS. DANEK: Well -- and Priya, it already<br/>14 has an exhibit number? Do we not want to use the<br/>15 exhibit number that it has?<br/>16 MS. PATEL: That's fine. We can use the<br/>17 exhibit number it has.<br/>18 MS. DANEK: So this would be Exhibit 2014?<br/>19 MS. PATEL: Correct.<br/>20 (Spurgeon Exhibit No. 2014 was<br/>21 identified for the record.)<br/>22 BY MS. PATEL:</p>                                                    | <p>Page 12</p> <p>1 Something has -- I mean, I can hear you.<br/>2 MS. PATEL: Okay. Could we go off the<br/>3 record for a moment --<br/>4 THE VIDEOGRAPHER: Sure.<br/>5 MS. PATEL: -- so we can figure out the<br/>6 technical difficulties?<br/>7 THE VIDEOGRAPHER: Sure. Sure. Going off<br/>8 the record at 8:37 a.m.<br/>9 (Recess.)<br/>10 THE VIDEOGRAPHER: We're back on the<br/>11 record at 8:52 a.m.<br/>12 THE WITNESS: Ms. Patel, I wanted to<br/>13 clarify something you asked on a question.<br/>14 BY MS. PATEL:<br/>15 Q. Sure. Go ahead.<br/>16 A. So to clarify on the deposition, I have<br/>17 never given a deposition related to cases like this,<br/>18 patent cases. I gave one very brief deposition in an<br/>19 employment -- wrongful termination suit related to<br/>20 someone who was terminated for a medical condition.<br/>21 I think previously I just stated no, which is<br/>22 incorrect.</p> |
| <p>Page 11</p> <p>1 Q. Dr. Spurgeon, do you see that document up<br/>2 on the screen, Exhibit 2014?<br/>3 A. I do, yes.<br/>4 Q. Are you able to control it and scroll<br/>5 through it?<br/>6 A. I am not. I'm able to see it. I am not<br/>7 able to control it. Wait, I think I -- I am moving<br/>8 it now, yes.<br/>9 Q. Okay. Wonderful. So this is your<br/>10 declaration that you submitted in this proceeding,<br/>11 correct?<br/>12 A. Yes.<br/>13 Q. Can you scroll to the last page, please.<br/>14 MS. DANEK: Counsel, I think I'm out of<br/>15 the meeting. Have I -- do you see me still in the<br/>16 meeting? On my end, it looks like I've dropped out.<br/>17 THE VIDEOGRAPHER: Counsel, this is the<br/>18 videographer. I can still see you in the meeting.<br/>19 MS. DANEK: Okay.<br/>20 MS. PATEL: But you are not on camera,<br/>21 Counsel.<br/>22 MS. DANEK: It looks like I'm frozen.</p> | <p>Page 13</p> <p>1 Q. Okay.<br/>2 A. My apologies.<br/>3 Q. Understood. How long ago was that<br/>4 deposition?<br/>5 A. I don't know exactly. It was during<br/>6 COVID. It was probably around 2021 maybe.<br/>7 Q. Okay. And do you remember what parties<br/>8 were involved? The names of the parties that were<br/>9 involved?<br/>10 A. I don't. I mean, I know the name of the<br/>11 patient, which obviously I can't share, but the rest<br/>12 I don't know.<br/>13 Q. Okay. And you testified on behalf of the<br/>14 patient, is that right?<br/>15 A. Yes.<br/>16 Q. Okay. All right. Dr. Spurgeon, when we<br/>17 took a break just now, did you speak with your<br/>18 counsel at all?<br/>19 A. No.<br/>20 Q. Do you have in front of you Exhibit 2014,<br/>21 your declaration in this case?<br/>22 A. I do.</p>                                                                                                   |

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| <p>Page 14</p> <p>1 Q. And you have the last page in front of you<br/>2 there?<br/>3 A. Yes.<br/>4 Q. Okay. And that's your signature at the<br/>5 bottom, is that correct?<br/>6 A. Yes.<br/>7 Q. Before signing your declaration, did you<br/>8 review the text to make sure everything was accurate<br/>9 and complete?<br/>10 A. Yes.<br/>11 Q. And when did you start preparing your<br/>12 declaration?<br/>13 A. I'm not sure of the exact date, but the<br/>14 process probably started maybe eight months ago.<br/>15 Q. Did you draft the declaration yourself?<br/>16 A. I drafted it in conjunction with counsel.<br/>17 Q. Let's turn to page 7 of your declaration.<br/>18 And you can use your hard copy, if that's easier for<br/>19 you, or what we have up on the screen. It's up to<br/>20 you.<br/>21 A. I have my hard copy here.<br/>22 Q. Okay, great. So starting at page 7 and</p>                                                                                      | <p>Page 16</p> <p>1 today?<br/>2 A. So spent two days with counsel preparing<br/>3 for what a deposition would be like.<br/>4 Q. How many meetings did you have with<br/>5 counsel?<br/>6 A. Specifically related to the preparation,<br/>7 two meetings and one phone call.<br/>8 Q. Who was present?<br/>9 A. Latham Watkins counsel and a member from<br/>10 AbbVie's legal team. Actually, a couple of members.<br/>11 I can't recall specific names off the top of my head<br/>12 right now, but a couple members of AbbVie's legal<br/>13 counsel in the most recent --<br/>14 Q. Okay. So Ms. Danek, a couple members from<br/>15 AbbVie's legal counsel and maybe other counsel from<br/>16 Latham, is that right?<br/>17 A. Correct.<br/>18 Q. Have you talked to anyone else other than<br/>19 your attorneys about this case?<br/>20 A. No.<br/>21 Q. Let's turn to paragraph 7 of your<br/>22 declaration. Let me know when you get there.</p> |
| <p>Page 15</p> <p>1 then through 8, 9, 10, 11, all the way through 13,<br/>2 those are your list of materials that you reviewed<br/>3 and considered in forming your opinions, is that<br/>4 right?<br/>5 A. Correct.<br/>6 Q. Did you consider any other documents in<br/>7 forming your opinions?<br/>8 A. No.<br/>9 Q. Did you speak to anyone before forming<br/>10 your opinions, anyone other than counsel?<br/>11 A. No.<br/>12 Q. What did you do to prepare for this<br/>13 deposition?<br/>14 A. The whole process of this declaration<br/>15 helped prepare for this deposition, so assuming that<br/>16 that timeline is correct, it was probably around<br/>17 eight months ago, working on this declaration and<br/>18 then discussing things with counsel on a regular<br/>19 basis and working on different drafts of the<br/>20 declaration along the way.<br/>21 Q. So other than preparing your declaration,<br/>22 what did you do to prepare to sit for this deposition</p> | <p>Page 17</p> <p>1 A. I'm there.<br/>2 Q. So you state here that you did your<br/>3 internship and your residency in internal medicine at<br/>4 Oregon Health and Science University, is that right?<br/>5 A. Yes.<br/>6 Q. OHSU, right?<br/>7 MS. DANEK: I think, Dr. Spurgeon, you<br/>8 might need to speak up a little.<br/>9 THE WITNESS: Oh, yeah.<br/>10 BY MS. PATEL:<br/>11 Q. And you completed your residency in 2006?<br/>12 A. Yes.<br/>13 Q. And then you did your fellowship in<br/>14 hematology and medical oncology at OHSU and you<br/>15 completed that in 2009, is that right?<br/>16 A. Yes.<br/>17 Q. During your residency and fellowship, did<br/>18 you study or treat CLL or SLL patients?<br/>19 A. I want to qualify your question a little<br/>20 bit. If you're asking if I took care of patients<br/>21 with CLL/SLL as a resident, I did, yes.<br/>22 Q. Did you treat CLL/SLL patients as a</p>                         |

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| <p>1 resident?</p> <p>2 A. I'll qualify that again, too. Treating</p> <p>3 has a broad meaning there. So treating for</p> <p>4 complications from their disease, yes. Given I was a</p> <p>5 resident, I was not able to prescribe medications to</p> <p>6 treat their cancer.</p> <p>7 Q. Okay. Did you ever administer medications</p> <p>8 to treat their cancer that were already prescribed by</p> <p>9 other doctors?</p> <p>10 A. No.</p> <p>11 Q. So you did not administer any BTKIs to any</p> <p>12 CLL or SLL patients during your internship or</p> <p>13 residency, is that right?</p> <p>14 A. That's correct. And none were available,</p> <p>15 too, so --</p> <p>16 Q. What treatments were used at that time?</p> <p>17 A. Chemoimmunotherapy. Sorry, did you hear</p> <p>18 me?</p> <p>19 Q. I did. I did.</p> <p>20 A. Oh, okay.</p> <p>21 Q. Okay. Let's turn to paragraph 10 of your</p> <p>22 declaration.</p>                                                                             | <p>Page 18</p> | <p>1 second year fellow, I began to specialize more on</p> <p>2 hematologic malignancies.</p> <p>3 THE REPORTER: I'm sorry, you said a broad</p> <p>4 range of what cases?</p> <p>5 THE WITNESS: Hematology oncology cases.</p> <p>6 MS. DANEK: Dr. Spurgeon, I think you'd do</p> <p>7 best to speak -- just continue to speak up so that</p> <p>8 the court reporter can hear you.</p> <p>9 THE WITNESS: Okay.</p> <p>10 BY MS. PATEL:</p> <p>11 Q. Okay. When you said you began to</p> <p>12 specialize, in your second year of fellowship, in</p> <p>13 hematological malignancies, what specific</p> <p>14 malignancies did you begin to specialize in in your</p> <p>15 second year?</p> <p>16 A. So this is not an exhaustive list by any</p> <p>17 means, but as examples off the top of my head,</p> <p>18 lymphoma, different leukemias, multiple myeloma,</p> <p>19 Waldenstrom's macroglobulinemia, bone marrow failure.</p> <p>20 Those are examples of what I began to focus on my</p> <p>21 second year of fellowship.</p> <p>22 Q. Okay. So since your fellowship and since</p> | <p>Page 20</p> |
| <p>1 A. Okay. I'm here.</p> <p>2 Q. You state here that you've worked as a</p> <p>3 physician since 2009, right?</p> <p>4 A. I would qualify that. Again, I've worked</p> <p>5 as a physician since I was an intern in 2002. This</p> <p>6 is as a faculty member, yes, in 2009.</p> <p>7 Q. Okay. Did you begin treating patients and</p> <p>8 prescribing medications in 2009?</p> <p>9 A. No. I began treating patients during my</p> <p>10 fellowship as a hematology oncology fellow.</p> <p>11 Q. As a fellow, did you treat CLL/SLL</p> <p>12 patients?</p> <p>13 A. Yes.</p> <p>14 Q. Did you treat them with BTKIs?</p> <p>15 A. No.</p> <p>16 Q. How many CLL or SLL patients would you</p> <p>17 estimate that you treated during your fellowship?</p> <p>18 A. I honestly don't recall.</p> <p>19 Q. What other types of patients did you treat</p> <p>20 during your fellowship?</p> <p>21 A. A broad range of hematology oncology</p> <p>22 lymphoma cases that span the spectrum. And then as a</p> | <p>Page 19</p> | <p>1 becoming a faculty member in 2009, you state that</p> <p>2 you've been treating a broad range of lymphoma</p> <p>3 patients with a special emphasis on CLL and MCL,</p> <p>4 right?</p> <p>5 A. Right.</p> <p>6 Q. What other types of lymphomas do you</p> <p>7 treat?</p> <p>8 A. Diffuse large B-cell lymphoma. Again, not</p> <p>9 an exhaustive list because I may leave some off</p> <p>10 inadvertently. But off the top of my head, diffuse</p> <p>11 large B-cell lymphoma, high grade B-cell lymphoma,</p> <p>12 Hodgkin's lymphoma, follicular lymphoma. Those are</p> <p>13 the main examples.</p> <p>14 Q. How much of your practice involves</p> <p>15 treating patients with those other types of lymphomas</p> <p>16 that you just mentioned?</p> <p>17 A. About 25 percent of my practice.</p> <p>18 Q. And how much of your practice involves</p> <p>19 treating patients with MCL?</p> <p>20 A. Probably, I believe, 10 percent, if I had</p> <p>21 to estimate. Again, this is just a pure estimation.</p> <p>22 Q. Okay. And what about the remaining</p>              | <p>Page 21</p> |

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| <p>1 patients that you treat. What types of conditions</p> <p>2 are you treating there?</p> <p>3 A. So the majority of my patient population</p> <p>4 is CLL/SLL. And then the other -- the remainder is</p> <p>5 made up of mantle cell and other lymphomas, some of</p> <p>6 which I just mentioned.</p> <p>7 Q. And you say here that you've treated --</p> <p>8 that since 2009 to the present day, you've treated</p> <p>9 hundreds of patients with SLL and CLL using various</p> <p>10 therapies, is that right?</p> <p>11 A. Correct.</p> <p>12 Q. How many hundreds? Two hundred? Less</p> <p>13 than 500?</p> <p>14 A. I honestly don't know.</p> <p>15 Q. You don't know if you've treated closer to</p> <p>16 a thousand patients or closer to 200 patients?</p> <p>17 A. I mean, I can come up with a range. It's</p> <p>18 less than a thousand.</p> <p>19 Q. Okay. Is it less than 500?</p> <p>20 A. I don't know.</p> <p>21 Q. Is it around 500?</p> <p>22 A. Yeah, I think -- so I think one of the</p>                                                                                                                                                                                               | <p>Page 22</p> <p>1 saying. What I'm saying is I have treated hundreds</p> <p>2 with the agents listed below in the rest of that</p> <p>3 paragraph. But what I'm saying is -- the</p> <p>4 clarification is I've followed or managed or cared</p> <p>5 for or am responsible for the care of many -- of more</p> <p>6 than hundreds. Again, I can't qualify that with a</p> <p>7 specific number.</p> <p>8 BY MS. PATEL:</p> <p>9 Q. And the only BTKIs that you have used to</p> <p>10 treat patients are Imbruvica, Brukinsa and</p> <p>11 acalabrutinib, right?</p> <p>12 A. Can you reframe the question, please, or</p> <p>13 ask that again?</p> <p>14 Q. Sure you've treated patients with</p> <p>15 Imbruvica, Brukinsa and acalabrutinib, right?</p> <p>16 A. Yes.</p> <p>17 Q. And those are the only BTKIs you've</p> <p>18 treated patients with, is that right?</p> <p>19 A. No.</p> <p>20 Q. What other BTKIs have you administered to</p> <p>21 treat CLL or SLL?</p> <p>22 A. Off the top of my head -- the others are</p>                                                                                                          |
| <p>1 reasons this is challenging to come up with a number</p> <p>2 is the way CLL works is that we have a period of</p> <p>3 observation (watchful waiting) that many patients</p> <p>4 when they get diagnosed, that's what's done. And so</p> <p>5 if you think about it that way, it's easily greater</p> <p>6 than a thousand, but not all those patients are</p> <p>7 needing treatment at the same time or even, you know,</p> <p>8 some never need treatment. So that's why it's a</p> <p>9 little hard to come up with that number.</p> <p>10 Q. Okay. That's a --</p> <p>11 A. Yeah. So a number of those -- so many,</p> <p>12 many CLL patients have been -- and SLL patients have</p> <p>13 been under my care, but that doesn't necessarily mean</p> <p>14 they're all getting treatment.</p> <p>15 Q. Okay. So when you say, in paragraph 10,</p> <p>16 that you've treated hundreds of patients with</p> <p>17 SLL/CLL, you're including those patients who you</p> <p>18 haven't yet administered a treatment but are in that</p> <p>19 wait and see period that you just described, is that</p> <p>20 right?</p> <p>21 MS. DANEK: Objection, form.</p> <p>22 THE WITNESS: No, that's not what I'm</p> | <p>Page 23</p> <p>1 not approved inhibitors. They've been done on</p> <p>2 clinical trials, but include tirabrutinib and then</p> <p>3 not on trial would be pirtobrutinib, which in this</p> <p>4 case is not an irreversible BTK inhibitor.</p> <p>5 Q. Okay. During your first few years</p> <p>6 treating CLL and SLL patients, approximately what</p> <p>7 percentage of your patients did you treat with</p> <p>8 Imbruvica?</p> <p>9 MS. DANEK: Objection, form.</p> <p>10 THE WITNESS: Can you be more specific</p> <p>11 about -- the first couple of years, you said? Are</p> <p>12 you saying first two years?</p> <p>13 BY MS. PATEL:</p> <p>14 Q. First few years, early in your practice,</p> <p>15 you know, what percentage approximately of patients</p> <p>16 did you treat with Imbruvica?</p> <p>17 A. I would need you to be more specific about</p> <p>18 the actual timeline as it relates to -- you might</p> <p>19 define "early career" different than I do.</p> <p>20 Q. Sure. Let's say 2010-2011 time period, a</p> <p>21 few years after that, that range.</p> <p>22 A. Around that range, I don't think I treated</p> |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <p>Page 24</p> <p>Page 25</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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| <p>1 any patients with Imbruvica at that time.</p> <p>2 Q. When did you start treating patients with</p> <p>3 Imbruvica?</p> <p>4 A. I don't know exact timelines.</p> <p>5 Q. Before Brukinsa was approved in 2019,</p> <p>6 would you say the majority of your patients you</p> <p>7 treated with Imbruvica?</p> <p>8 A. Yes.</p> <p>9 Q. After 2019, what percentage of your</p> <p>10 patients do you now treat with Imbruvica?</p> <p>11 A. So I'm going to -- if I may, can I ask you</p> <p>12 to qualify the question or can I clarify based on</p> <p>13 some little different dates. So it's a little</p> <p>14 different from 2019 until the more acalabrutinib --</p> <p>15 head-to-head data came out with acalabrutinib and the</p> <p>16 head-to-head data with zanubrutinib.</p> <p>17 So in 2019, I still used a significant</p> <p>18 amount of ibrutinib. And then it really wasn't until</p> <p>19 more recently when those other studies came out that</p> <p>20 I started using more of acalabrutinib and</p> <p>21 zanubrutinib.</p> <p>22 Q. Okay. So after those studies came out,</p>                                                                                   | Page 26 | <p>1 than not to start a newly diagnosed patient on</p> <p>2 Brukinsa?</p> <p>3 A. Because of the Alpine data.</p> <p>4 Q. What about the Alpine data?</p> <p>5 A. The Alpine trial showed improvements in</p> <p>6 progression-free survival as well as certain</p> <p>7 toxicities in the zanubrutinib arm.</p> <p>8 Q. So the conclusions in the Alpine trial</p> <p>9 prompted you to prefer zanubrutinib over any other</p> <p>10 BTKI, is that right?</p> <p>11 A. Outside of a clinical trial, that's</p> <p>12 correct.</p> <p>13 Q. Okay. Let's turn to -- oh, wait.</p> <p>14 When -- you were treating CLL/SLL patients</p> <p>15 starting in the 2010-2011 time period, is that right?</p> <p>16 A. Yes.</p> <p>17 Q. During that time period, would you have</p> <p>18 administered a BTKI to a patient that had not been</p> <p>19 tested for undue adverse side effects?</p> <p>20 MS. DANEK: Objection, form.</p> <p>21 THE WITNESS: Can you restate the</p> <p>22 question, please?</p>                                                                   | Page 28 |
| <p>1 what percentage of patients did you continue treating</p> <p>2 with Imbruvica?</p> <p>3 A. I don't know exact percentages, but to</p> <p>4 contextualize things, there are a couple of ways to</p> <p>5 think about that. So there are patients that are --</p> <p>6 have been on ibrutinib for a long time and there are</p> <p>7 patients that are new starts.</p> <p>8 Q. Right.</p> <p>9 A. So the patients that -- my practice has</p> <p>10 been the patients that are on ibrutinib doing well</p> <p>11 has been to keep them on ibrutinib. The practice</p> <p>12 otherwise is I have tended to use more zanubrutinib,</p> <p>13 as a new start.</p> <p>14 Q. So if you have newly diagnosed CLL/SLL</p> <p>15 patients who have not previously been on any BTKI</p> <p>16 treatment, you're more likely than not to choose</p> <p>17 Brukinsa as their -- as a treatment, is that right?</p> <p>18 A. That is correct. And for further context,</p> <p>19 that's if I deem them appropriate for BTKI because</p> <p>20 there are some other therapies as well.</p> <p>21 Q. Sure. Why is that? Or sorry, let me just</p> <p>22 clarify. Why is it that you would be more likely</p> | Page 27 | <p>1 BY MS. PATEL:</p> <p>2 Q. What about the question is confusing to</p> <p>3 you?</p> <p>4 A. If you would just repeat it, then, please.</p> <p>5 Q. Sure. So during the 2010-2011 time</p> <p>6 period, would you have administered an irreversible</p> <p>7 BTKI to a patient that had not been tested for undue</p> <p>8 adverse side effects?</p> <p>9 A. I -- honestly, it's such a hypothetical</p> <p>10 that I can't really comment.</p> <p>11 Q. Have you ever treated a patient -- a CLL</p> <p>12 or SLL patient with an irreversible BTKI that had not</p> <p>13 been tested for undue adverse side effects?</p> <p>14 A. I have in clinical trials, yes. Outside</p> <p>15 of clinical trials, it's not something that's</p> <p>16 possible because those -- it's not something</p> <p>17 possible.</p> <p>18 Q. Why is it not possible?</p> <p>19 A. Because the FDA wouldn't let us administer</p> <p>20 such a drug. The drug wouldn't exist. That's why</p> <p>21 I'm struggling with the hypothetical, because the</p> <p>22 drug wouldn't exist.</p> | Page 29 |

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| <p>1 Q. Is the FDA the only reason that you've<br/>2 never administered an irreversible BTKI that has not<br/>3 been tested for undue adverse side effects in<br/>4 practice?<br/>5 MS. DANEK: Objection, form.<br/>6 THE WITNESS: I'm still struggling to give<br/>7 you an answer because it's a scenario that is<br/>8 beyond -- just would never happen. It's not --<br/>9 BY MS. PATEL:<br/>10 Q. So -- yeah. And you don't need to imagine<br/>11 the scenario at least right now for this question. I<br/>12 just want to know if the only reason that you<br/>13 wouldn't do so is because of FDA regulations or if<br/>14 there are other reasons as well.<br/>15 MS. DANEK: Objection, form.<br/>16 THE WITNESS: There's standard practice in<br/>17 oncology that we would have patients treated in a<br/>18 well-designed clinical trial with a new agent. So<br/>19 again, this is hard to, again, imagine a scenario<br/>20 that would not present itself.<br/>21 BY MS. PATEL:<br/>22 Q. So your answer is that another reason you</p>        | Page 30 | <p>1 administer an irreversible BTK to a CLL/SLL patient<br/>2 that had not previously been tested for undue adverse<br/>3 side effects.<br/>4 MS. DANEK: Objection, form.<br/>5 THE WITNESS: And you're talking about<br/>6 today or 2011?<br/>7 MS. PATEL: Both.<br/>8 MS. DANEK: Same objections.<br/>9 THE WITNESS: I can't provide a<br/>10 comprehensive list. But what I can say is, in<br/>11 relation to this case, given the specifications<br/>12 outlined in the patent about irreversible inhibitors,<br/>13 the -- and going back to 2011, it really establishes,<br/>14 especially in relation to chemotherapy, as a safe<br/>15 approach, using irreversible BTK inhibitors.<br/>16 BY MS. PATEL:<br/>17 Q. So you're saying that you would in fact<br/>18 treat a CLL/SLL patient with an irreversible<br/>19 inhibitor that had not been tested for undue adverse<br/>20 side effects, right?<br/>21 A. I'm still having trouble defining that<br/>22 question because without the specification in 2011</p>                                                                                   | Page 32 |
| <p>1 wouldn't do so is because it would go against<br/>2 standard practice in oncology?<br/>3 MS. DANEK: Objection, form.<br/>4 THE WITNESS: No, my main answer is that<br/>5 it's too hypothetical to provide an opinion on.<br/>6 BY MS. PATEL:<br/>7 Q. What are the reasons that you sitting here<br/>8 today would not administer an irreversible BTKI to a<br/>9 CLL/SLL patient that had not previously been tested<br/>10 for undue adverse side effects?<br/>11 MS. DANEK: Objection, form.<br/>12 THE WITNESS: Again, I think about it a<br/>13 little differently in that I would have no problem<br/>14 putting a patient on a clinical trial with an<br/>15 irreversible BTK inhibitor, even if it hadn't been<br/>16 tested.<br/>17 BY MS. PATEL:<br/>18 Q. Well, that doesn't really answer my<br/>19 question. I just want you to -- I want you to list<br/>20 all the different reasons why you wouldn't do what I<br/>21 said, that you wouldn't -- and I'll repeat it. I<br/>22 want you to list the reasons that you would not today</p> | Page 31 | <p>1 that was -- you know, had clinical data showing the<br/>2 therapeutic efficacy and outlining safety, we<br/>3 wouldn't be where we are today. So it's really hard<br/>4 to -- to answer that question definitively other than<br/>5 to say, yes, it's a safe class of drugs.<br/>6 Q. So you're saying that with the<br/>7 specification of the '803 patent, you would feel<br/>8 comfortable treating one of your CLL/SLL patients<br/>9 with an irreversible BTKI that had not been tested<br/>10 for undue adverse side effects, right?<br/>11 A. That's a hypothetical that never exists.<br/>12 So, again, I can't really answer that question other<br/>13 than saying I would feel comfortable with the<br/>14 toxicity profile of an ibrutinib-like irreversible<br/>15 BTK inhibitor. Otherwise, this scenario, it doesn't<br/>16 exist.<br/>17 Q. Dr. Spurgeon, you understand you're here<br/>18 today to discuss your declaration in which you<br/>19 provided opinions from the perspective of a POSA,<br/>20 right?<br/>21 A. Correct.<br/>22 Q. And when you were forming your opinions,</p> | Page 33 |

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| <p>1 did you put yourself into the mindset of a POSA</p> <p>2 looking at the specification that was available in</p> <p>3 2011?</p> <p>4 A. Can you be more specific?</p> <p>5 Q. Sure. What further specificity can I</p> <p>6 provide?</p> <p>7 A. I guess just what is your definition of</p> <p>8 mindset of a POSA?</p> <p>9 Q. Another word is perspective. Did you put</p> <p>10 yourself in the shoes of a POSA when forming your</p> <p>11 opinions in this case?</p> <p>12 A. Yes. And it would be -- the POSA is</p> <p>13 outlined as a team.</p> <p>14 THE REPORTER: I'm sorry, could you repeat</p> <p>15 that?</p> <p>16 THE WITNESS: Yes. Sorry. Yes. It's --</p> <p>17 in our case the POSA is a team of members.</p> <p>18 BY MS. PATEL:</p> <p>19 Q. Right. Sure. So when forming your</p> <p>20 opinions in this case, you put yourself in the shoes</p> <p>21 of the clinical member of the POSA team, right?</p> <p>22 A. Correct.</p>                                                                                                                                                                                                                                                                       | <p>Page 34</p> <p>1 it -- you know, does it inhibit BTK at certain doses?</p> <p>2 What are the dose ranges? We would have to do that</p> <p>3 to define that as a community. So that's why it</p> <p>4 would be on a clinical trial. That's the primary</p> <p>5 reason.</p> <p>6 Q. And you wouldn't do it outside the context</p> <p>7 of a clinical trial, right?</p> <p>8 A. If you're asking if I would just take any</p> <p>9 drug off the shelf, not knowing anything about its</p> <p>10 characteristics other than it was an irreversible BTK</p> <p>11 inhibitor and put it in a patient, the answer is no,</p> <p>12 I would not, outside of a clinical trial.</p> <p>13 But when we do clinical trials, we have a</p> <p>14 good -- you know, the FDA requires a broad range of</p> <p>15 routine tests that are done to -- so we have a better</p> <p>16 understanding of what starting doses would be or --</p> <p>17 it depends on the specifics of the drug, too.</p> <p>18 Q. Why wouldn't you do so outside of a</p> <p>19 clinical trial?</p> <p>20 A. Well, let me think about that a little</p> <p>21 different way, contextualize that further. So if</p> <p>22 there was -- again, because I could be giving a dose</p> <p>Page 36</p> |
| <p>1 Q. So that's what I'm asking you to do right</p> <p>2 now. Being in the shoes of a clinical member of the</p> <p>3 POSA team, would you treat one of your CLL/SLL</p> <p>4 patients with an irreversible BTKI that had not been</p> <p>5 tested for undue adverse side effects?</p> <p>6 MS. DANEK: Objection, form.</p> <p>7 THE WITNESS: Again, understanding what</p> <p>8 I've already said as far as this being hypothetical,</p> <p>9 I would have no problem putting a patient on an</p> <p>10 irreversible ibrutinib-like BTK inhibitor. But to</p> <p>11 contextualize this, remember this is something that</p> <p>12 would be done on a clinical trial and so that's --</p> <p>13 I'm done with my answer.</p> <p>14 BY MS. PATEL:</p> <p>15 Q. Okay. So you're saying you would do so,</p> <p>16 but you would only do so in the context of the</p> <p>17 clinical trial, is that right?</p> <p>18 A. I would do so in the context of a clinical</p> <p>19 trial. But it's not as simple as, you know, just</p> <p>20 putting someone -- the reason we want to do a</p> <p>21 clinical trial is so we understand, again, as the</p> <p>22 specification teaches us, we want to understand does</p> <p>Page 35</p> | <p>1 to the patient whether either it's too low a dose or</p> <p>2 too high a dose and I have no idea what that dose is.</p> <p>3 But if -- another way -- if you're asking</p> <p>4 if someone came to me and said, look, I have an</p> <p>5 ibrutinib-like compound, this is the dose, I know it</p> <p>6 to inhibit BTK, this is the dose range, then I would</p> <p>7 have -- I wouldn't have an issue putting the patient</p> <p>8 on that drug. But we can't get there without the</p> <p>9 other stuff I mentioned already. So that's why it</p> <p>10 needs to be on a clinical trial and that's why it's</p> <p>11 really hard to answer this hypothetical question.</p> <p>12 Q. Okay.</p> <p>13 MS. PATEL: This might be a good time for</p> <p>14 a break.</p> <p>15 THE VIDEOGRAPHER: Going off the record at</p> <p>16 9:38 a.m.</p> <p>17 (Recess.)</p> <p>18 THE VIDEOGRAPHER: Back on the record at</p> <p>19 9:46 a.m.</p> <p>20 BY MS. PATEL:</p> <p>21 Q. Let's turn to paragraph 12 of your</p> <p>22 declaration. So you state here that you've received</p> <p>Page 37</p>                                                                                                                                                              |

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| <p>1 federal grants to study novel therapeutics in</p> <p>2 hematological malignancies, right?</p> <p>3 A. Correct.</p> <p>4 Q. And you call a couple of those studies out</p> <p>5 in this paragraph, right?</p> <p>6 A. Correct.</p> <p>7 Q. And then in paragraph 13, you discuss how</p> <p>8 you participated in clinical trials as a site or</p> <p>9 clinical PI for ibrutinib, acalabrutinib and</p> <p>10 zanubrutinib, right?</p> <p>11 A. Correct.</p> <p>12 Q. Discuss how you designed, initiated and</p> <p>13 completed CLL lymphoma studies and serve as a PI for</p> <p>14 numerous other clinical trials concerning treatments</p> <p>15 for CLL/SLL or other blood cancers, right?</p> <p>16 A. Correct.</p> <p>17 Q. And then in paragraph 14, you note that</p> <p>18 you're a named author on peer-reviewed scientific</p> <p>19 articles, many involving CLL, SLL or other blood</p> <p>20 cancers, right?</p> <p>21 A. Correct.</p> <p>22 Q. And you've published several review</p>                   | <p>Page 38</p> | <p>1 for publication?</p> <p>2 A. Yes. There's usually a couple of</p> <p>3 categories. You provide your review, you may -- it</p> <p>4 depends on the journal what the categories are, but</p> <p>5 you may, you know, say -- you may ask for major</p> <p>6 revisions, minor revisions, you may not publish it at</p> <p>7 all. You may not ask for any of those things.</p> <p>8 So, yes, typically you're not the only</p> <p>9 reviewer either. You know, you're part of a number</p> <p>10 of -- depends on the journal how many peer reviewers</p> <p>11 they have.</p> <p>12 Q. When you're reviewing the methodologies of</p> <p>13 some of these papers, what are the key things that</p> <p>14 you look for in a paper that you would recommend for</p> <p>15 publication?</p> <p>16 A. Are you talking a clinical paper or are</p> <p>17 you talking a basic science paper?</p> <p>18 Q. Let's start with a basic science paper.</p> <p>19 And sorry, actually before that, can you let us --</p> <p>20 could you let me know what is the distinction that</p> <p>21 you are drawing between a clinical paper and a basic</p> <p>22 science paper?</p> | <p>Page 40</p> |
| <p>1 articles, a book chapter, other abstracts and posters</p> <p>2 that focus on kinase inhibitors and B-cell</p> <p>3 malignancies, right?</p> <p>4 A. Yes.</p> <p>5 Q. And then in paragraph 15, you discuss how</p> <p>6 you've been an ad hoc reviewer for some oncology</p> <p>7 journals, right?</p> <p>8 A. Yes.</p> <p>9 Q. What's your role as an ad hoc reviewer?</p> <p>10 A. I'm not on the editorial board of any of</p> <p>11 those journals, but they will send me papers to</p> <p>12 review.</p> <p>13 Q. And do you provide your feedback on those</p> <p>14 papers to the journals?</p> <p>15 A. I peer review the paper, yes.</p> <p>16 Q. What kind -- what do you review the papers</p> <p>17 for?</p> <p>18 A. It depends on the paper, but generally</p> <p>19 scientific merit, methodology and conclusions.</p> <p>20 Q. Do you make recommendations based off of</p> <p>21 scientific merit, methodology and conclusions to the</p> <p>22 journals as to whether or not to accept these papers</p> | <p>Page 39</p> | <p>1 A. Only in that one has clinical data and the</p> <p>2 other does not.</p> <p>3 Q. Okay. So then let's start with a basic</p> <p>4 science paper.</p> <p>5 A. I'm going to give you a broad answer</p> <p>6 because it really depends on the specifics of the</p> <p>7 topic or the paper, but is it -- and this is not an</p> <p>8 exhaustive list by any means. But from off the top</p> <p>9 of my head, number would be what is the question</p> <p>10 being asked? Is it a valid question to ask? What is</p> <p>11 the hypothesis? Does the data support the hypothesis</p> <p>12 and has it been done in a way that is appropriate,</p> <p>13 and does the data support the conclusions.</p> <p>14 Q. When you say you consider has the data</p> <p>15 been done in a way that is appropriate, are you</p> <p>16 referring to the methodology of the paper?</p> <p>17 A. Yes.</p> <p>18 Q. What are some hallmarks of appropriate</p> <p>19 methodologies?</p> <p>20 A. Again, very broad here, but it depends on</p> <p>21 the context. But some general hallmarks off the top</p> <p>22 of my head would be is the assay being performed</p>         | <p>Page 41</p> |

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| <p>1 something that can -- is it the right assay being</p> <p>2 done to answer the question and is it reproducible in</p> <p>3 that assay and are the results interpretable. And if</p> <p>4 the results are interpretable, does it support the</p> <p>5 conclusion of the paper.</p> <p>6 Q. What affects whether results are</p> <p>7 interpretable or not?</p> <p>8 A. It's a lot of things. Again, not an</p> <p>9 exhaustive list by any means. But are the</p> <p>10 conclusions being drawn, do they match up with the</p> <p>11 data presented.</p> <p>12 So a hypothetical paper -- which again,</p> <p>13 this is all hypothetical -- that, you know, if you</p> <p>14 were looking at a drug and it killed 10 percent of</p> <p>15 cancer cells or didn't kill any, but then the</p> <p>16 conclusion was, oh, based on our data, it killed</p> <p>17 things, the data didn't show that and so have they</p> <p>18 chosen the right assays to really show that result.</p> <p>19 That's just a random example.</p> <p>20 Q. What is a class effect?</p> <p>21 A. In what context?</p> <p>22 Q. In the scientific industry.</p> | Page 42 | <p>1 a class of drugs that are similar enough to have the</p> <p>2 same effects.</p> <p>3 Q. Have you ever been involved in</p> <p>4 establishing a class effect?</p> <p>5 MS. DANEK: Objection, form.</p> <p>6 THE WITNESS: I'm not sure what you mean</p> <p>7 by established class effect.</p> <p>8 BY MS. PATEL:</p> <p>9 Q. No. So I asked, have you ever been</p> <p>10 involved in establishing a class effect?</p> <p>11 A. I still don't understand the question.</p> <p>12 Q. Okay. Class effects would need to be</p> <p>13 confirmed, right, by some amount of testing, is that</p> <p>14 right?</p> <p>15 MS. DANEK: Objection, form.</p> <p>16 THE WITNESS: So I think that depends on</p> <p>17 the context. I don't think we can make that</p> <p>18 generalization and it depends on the situation.</p> <p>19 So as an example, as we're talking about</p> <p>20 here, the specification provided in the patents does</p> <p>21 provide information that's fairly detailed on a class</p> <p>22 of this irreversible ibrutinib-like BTK inhibitors.</p> | Page 44 |
| <p>1 A. So related to a drug, is that what you're</p> <p>2 asking?</p> <p>3 Q. Sure. You used the term "class effect" in</p> <p>4 your declaration, right?</p> <p>5 A. Can you show me the part you're referring</p> <p>6 to?</p> <p>7 Q. You don't recall right now whether you</p> <p>8 used the term "class effect" in your declaration?</p> <p>9 A. I just don't know exactly where I might</p> <p>10 find it.</p> <p>11 Q. Sure. But do you use the term "class</p> <p>12 effect" in your declaration? You can look at</p> <p>13 paragraph 90. But I would still like you to answer</p> <p>14 my question. Do you know sitting here today whether</p> <p>15 you use the term "class effect" in your declaration?</p> <p>16 A. Yes.</p> <p>17 Q. And do you in fact use that term in your</p> <p>18 declaration?</p> <p>19 A. Yes.</p> <p>20 Q. What does that term mean to you?</p> <p>21 A. So as related to what we're discussing</p> <p>22 here, the class effect related to drugs would be that</p>                                                                                                                              | Page 43 | <p>1 So in that situation, the blueprint for that class</p> <p>2 has already been created. So that would be very</p> <p>3 different than a drug that didn't already have that</p> <p>4 blueprint.</p> <p>5 BY MS. PATEL:</p> <p>6 Q. Have you ever been involved in the process</p> <p>7 of creating a blueprint for a class effect?</p> <p>8 MS. DANEK: Objection, form.</p> <p>9 THE WITNESS: Are you asking if I've been</p> <p>10 involved in developing a patent?</p> <p>11 BY MS. PATEL:</p> <p>12 Q. No. You just said that, you know, there's</p> <p>13 a certain blueprint that you need that would</p> <p>14 establish a class effect, is that right?</p> <p>15 MS. DANEK: Objection, form.</p> <p>16 THE WITNESS: I think as relates to here,</p> <p>17 we're talking about the specification of patents, and</p> <p>18 I have not been involved in designing a patent.</p> <p>19 BY MS. PATEL:</p> <p>20 Q. Okay. Class effects would need to be</p> <p>21 discovered, is that right?</p> <p>22 MS. DANEK: Objection, form.</p>                              | Page 45 |

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| <p>1 THE WITNESS: I would say that compounds<br/>2 within a class would need to be discovered.<br/>3 BY MS. PATEL:<br/>4 Q. But how would one know that a class effect<br/>5 exists if it was never established or shown or<br/>6 discovered at all?<br/>7 MS. DANEK: Objection, form.<br/>8 THE WITNESS: I can't speak to that in<br/>9 this case because here the class has been discovered.<br/>10 BY MS. PATEL:<br/>11 Q. Okay. My question is, for other types of<br/>12 class effects, have you ever been involved in<br/>13 discovering those?<br/>14 A. I've not been involved in discovering<br/>15 specific compounds, i.e., using medicinal chemistry<br/>16 or pharmacologic -- identifying specific compounds<br/>17 because that's outside my area of expertise. I have<br/>18 been involved in testing agents in the clinic that<br/>19 are part of a given class.<br/>20 Q. So are you saying you've been involved in<br/>21 testing agents in a clinic that are part of a given<br/>22 class to assess whether they fall within the class</p> | <p>Page 46</p> <p>1 BY MS. PATEL:<br/>2 Q. And I'm not asking you to distinguish<br/>3 whether a particular compound is part of X class or Y<br/>4 class. But, as you stated, a class effect is the<br/>5 understanding that a group of like compounds will<br/>6 behave -- will all have a particular effect, is that<br/>7 right?<br/>8 A. Absolutely.<br/>9 Q. Okay. In order to establish that<br/>10 correlation, there has to be some kind of testing<br/>11 that's done, right?<br/>12 MS. DANEK: Objection, form.<br/>13 THE WITNESS: Yes. I mean, you would need<br/>14 to see that the -- the confirmation that -- the<br/>15 confirmation of what is known about agents in that<br/>16 class.<br/>17 BY MS. PATEL:<br/>18 Q. Have you ever seen confirmation of a class<br/>19 effect based on data from a single species that falls<br/>20 within that class?<br/>21 A. Can you repeat the question, please?<br/>22 Q. Sure. So in all of your career and your</p> <p>Page 48</p>                                                                                                                                                                                                            |
| <p>1 effect?<br/>2 MS. DANEK: Objection, form.<br/>3 THE WITNESS: No, not exactly because<br/>4 that's not what we're doing in a clinical trial per<br/>5 se. We're not doing the clinical trial to determine<br/>6 if it's a class effect. We're doing the clinical<br/>7 trial to understand the properties of the drug, to<br/>8 understand dosing, to define safety and understand<br/>9 clinical activity.<br/>10 BY MS. PATEL:<br/>11 Q. So you've never been a part of a study or<br/>12 a testing or anything to determine if there is a<br/>13 class effect?<br/>14 MS. DANEK: Objection, form.<br/>15 THE WITNESS: I would say that the<br/>16 clinical trial can help determine if it is -- it can<br/>17 confirm, it can be confirmatory of a specific class<br/>18 effect. But I don't have the expertise to understand<br/>19 looking at a compound if that's going to be the same<br/>20 class of drug from the very nascent stages based on<br/>21 structure. And that would be a critical component to<br/>22 define any of that.</p>         | <p>Page 47</p> <p>1 experiences on clinical trials and being a coauthor<br/>2 on numerous papers and being an ad hoc reviewer for<br/>3 journals, have you ever seen a situation where a<br/>4 class effect is confirmed based solely on data from a<br/>5 single species that falls within that class?<br/>6 MS. DANEK: Objection, form.<br/>7 THE WITNESS: I don't think it can be<br/>8 broken down into such a black and white question<br/>9 because there's a lot of things that go into that.<br/>10 So you can have confirmation based on studies that<br/>11 have been done, you know, preclinically that support<br/>12 the narrative.<br/>13 And if we think about that for the case of<br/>14 irreversible ibrutinib-like BTK inhibitors, I think,<br/>15 you know, as the field has progressed, we've seen<br/>16 that there can be more confirmatory studies that<br/>17 highlight what is in the specification and that, in<br/>18 this case, it's -- you know, over the last decade,<br/>19 it's really affirmed that the specification was<br/>20 right.<br/>21 So I think that you can see, you know, a<br/>22 broad range of possibilities, but you can't break it</p> <p>Page 49</p> |

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| <p>1 down into just black or white because, you know,<br/>2 obviously there's a lot of scientific progress along<br/>3 the way.<br/>4 BY MS. PATEL:<br/>5 Q. And I'm not asking you if you can confirm<br/>6 a class effect with a single species falling within<br/>7 that class. I'm asking if you've ever seen a<br/>8 situation where a class effect has been confirmed by<br/>9 a single species that falls within the class effect.<br/>10 MS. DANEK: Objection, form.<br/>11 BY MS. PATEL:<br/>12 Q. So I'll ask you again. Have you, in your<br/>13 career and all your experiences, ever seen a<br/>14 situation in an article or in a clinical trial where<br/>15 a class effect was confirmed in the industry based<br/>16 solely on data from a single species within that<br/>17 class?<br/>18 MS. DANEK: Objection, form.<br/>19 THE WITNESS: Again, I think that's hard<br/>20 to give a black and white answer because science<br/>21 builds on itself. And generally the nature of<br/>22 science is if there is a class and there is a</p>                                                           | <p>Page 50</p> | <p>1 BY MS. PATEL:<br/>2 Q. Okay. It helped lay the groundwork, but<br/>3 it didn't confirm the class, is that right?<br/>4 MS. DANEK: Objection, form.<br/>5 THE WITNESS: I think I would answer<br/>6 that -- I think since we're kind of thinking about<br/>7 some of these questions hypothetically. To think<br/>8 about it another way, if we were in a situation that<br/>9 the specification was all we had and ibrutinib was<br/>10 all we had, yes, that ibrutinib would -- or<br/>11 ibrutinib-like compound would singularly establish<br/>12 that class.<br/>13 BY MS. PATEL:<br/>14 Q. And then do you recall -- and this is not<br/>15 a hypothetical question. I want you to think back in<br/>16 your memory. Do you recall a single situation where<br/>17 a single species within a class confirmed and<br/>18 established a class effect other than this case?<br/>19 MS. DANEK: Objection, form.<br/>20 THE WITNESS: Again, it's a continuum. So<br/>21 I think there are examples where a class has been<br/>22 established and then things are built on that class.</p> | <p>Page 52</p> |
| <p>1 specific single compound within that class that has a<br/>2 certain behavior and leads to a certain effect, then<br/>3 it goes from a single thing to becoming a class. It<br/>4 goes from a single species to becoming a class.<br/>5 And so there are -- you know, again, not<br/>6 being a medicinal chemist, it is my understanding,<br/>7 though, that drug developers such as chemists,<br/>8 structural biologists, whatever their training might<br/>9 be, can look at compounds and understand does it fit<br/>10 in a specific class. And so subsequent to that,<br/>11 testing using agents that have that structure can<br/>12 further confirm or validate that class.<br/>13 BY MS. PATEL:<br/>14 Q. So you're saying more than a single<br/>15 species is required to confirm or validate a class<br/>16 effect?<br/>17 MS. DANEK: Objection, form.<br/>18 THE WITNESS: What I'm saying is with this<br/>19 current case and the specification is that this is an<br/>20 example of a situation where targeting BTK in an<br/>21 irreversible way helped lay the groundwork for a<br/>22 class.</p> | <p>Page 51</p> | <p>1 So it's -- and so I can provide an example.<br/>2 If you think about Gleevec and CML. So<br/>3 that's a BCR-ABL tyrosine-kinase inhibitor that<br/>4 was -- or Imatinib. It was the first drug, published<br/>5 in 2001, that truly established a class. And so if<br/>6 that -- if no other drugs came out, that class would<br/>7 have been defined by that single species. So I think<br/>8 the reason --<br/>9 BY MS. PATEL:<br/>10 Q. So --<br/>11 MS. DANEK: Excuse me, Counsel. Please<br/>12 let Dr. --<br/>13 BY MS. PATEL:<br/>14 Q. Dr. Spurgeon, finish your question --<br/>15 finish your answer.<br/>16 A. So again, the reason that's hard to<br/>17 delineate and say it's black or white is because<br/>18 scientific progress moves forward. And so what ends<br/>19 up happening is more and more drugs are in a class<br/>20 and if by happens -- you know, as the drugs develop,<br/>21 they then are in a class and they provide<br/>22 confirmation of that class.</p>                                                                                            | <p>Page 53</p> |

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| <p>1 Q. Okay. So I think I'm understanding now.</p> <p>2 It's a spectrum, a continuum, right? You have the</p> <p>3 first species that discovers the class effect exists,</p> <p>4 right? And then other drugs within that class are</p> <p>5 created or discovered and those end up confirming the</p> <p>6 class effect, right?</p> <p>7 A. Correct.</p> <p>8 Q. And in your experience, when you have that</p> <p>9 first species that results in the discovery of the</p> <p>10 class effect, does the scientific community establish</p> <p>11 that class effect based only on that first species or</p> <p>12 is it only after the additional compounds within that</p> <p>13 class confirm it?</p> <p>14 MS. DANEK: Objection, form.</p> <p>15 THE WITNESS: I would say the former</p> <p>16 because -- and I think ibrutinib is a good example of</p> <p>17 this -- because if ibrutinib was the only agent, it</p> <p>18 would be confirmed that BT -- irreversibly inhibiting</p> <p>19 BTK is a therapeutically effective -- you could dose</p> <p>20 through lymphocytosis continuously and you could use</p> <p>21 an assay to understand if it was inhibiting BTK.</p> <p>22 So I think -- so I would go with your</p> | Page 54 | <p>1 you're looking at?</p> <p>2 A. I was just looking at -- I wasn't really</p> <p>3 looking at much. I was just doodling more than --</p> <p>4 or, you know, messing with the papers.</p> <p>5 Q. Okay.</p> <p>6 A. Can you repeat the question?</p> <p>7 Q. Okay. Let me -- hang on one second. It's</p> <p>8 your opinion that lymphocytosis is a class effect for</p> <p>9 irreversible BTK inhibitors, correct?</p> <p>10 A. Yes.</p> <p>11 Q. Do you know when the scientific community</p> <p>12 updated its guidelines to reflect that discovery?</p> <p>13 A. Yes.</p> <p>14 Q. When was that?</p> <p>15 A. There's really two -- the official</p> <p>16 guidelines were updated in 2018. There was a</p> <p>17 communication in 2012. But the official iwCLL</p> <p>18 guidelines were updated in 2018.</p> <p>19 Q. Okay. Why did it take so long for the</p> <p>20 guidelines to be updated?</p> <p>21 A. I'm not sure. I can speculate that, you</p> <p>22 know, guideline groups are not -- you know, meet on a</p>                                                                                                                                      | Page 56 |
| <p>1 former characterization that you could have a single</p> <p>2 species in a class to define a class.</p> <p>3 BY MS. PATEL:</p> <p>4 Q. To define a class or to define a class</p> <p>5 effect?</p> <p>6 A. I guess I don't fully understand the</p> <p>7 distinction.</p> <p>8 Q. Is it your view that a class and a class</p> <p>9 effect are the same or interchangeable terms?</p> <p>10 A. I mean, they're not interchangeable in my</p> <p>11 mind. I guess if you're in a class, you're going to</p> <p>12 result in a class effect.</p> <p>13 Q. And you said it's your view that</p> <p>14 irreversible inhibition with a BTKI will induce</p> <p>15 lymphocytosis and that that is not a sign of disease</p> <p>16 progression, right?</p> <p>17 MS. DANEK: Objection, form. Did you say</p> <p>18 clinical cytosis?</p> <p>19 MS. PATEL: Lymphocytosis.</p> <p>20 BY MS. PATEL:</p> <p>21 Q. Dr. Spurgeon, I see that you're reading</p> <p>22 something in front of you. Can you tell me what</p>                                                                                                                                                                                                                    | Page 55 | <p>1 typical basis. So I'd have to go back and look at</p> <p>2 the prior guidelines, the 2018. I don't remember the</p> <p>3 exact date, but I think it was 2009. So the</p> <p>4 guidelines often take a long time to sort of update.</p> <p>5 That's just kind of the nature of the beast.</p> <p>6 And I suspect, even though I wasn't part</p> <p>7 of this, in formulating anything from the Chessum</p> <p>8 Communication that this is why that was done in 2012,</p> <p>9 but there was, to my knowledge, no reconvening of</p> <p>10 discussing officially changing the guidelines until</p> <p>11 later.</p> <p>12 Q. Do you know if the guidelines were</p> <p>13 established after the committee considered the</p> <p>14 clinical trials for Imbruvica -- for Brukinsa?</p> <p>15 Sorry, let me ask -- strike that.</p> <p>16 Do you know if the guidelines were</p> <p>17 established after the committee considered the</p> <p>18 clinical trial data from Brukinsa?</p> <p>19 MS. DANEK: Objection, form.</p> <p>20 THE WITNESS: I don't know.</p> <p>21 MS. PATEL: Okay. Can we pull up tab 12</p> <p>22 which we can mark as Spurgeon Exhibit 1.</p> | Page 57 |

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| <p>1 (Spurgeon Exhibit No. 1 was marked<br/>2 for identification.)<br/>3 MS. DANEK: Is this a new document not<br/>4 previously marked?<br/>5 MS. PATEL: Yes.<br/>6 MS. DANEK: Priya, if you would email that<br/>7 to me or if it can be dropped so I can download it<br/>8 and print it in case we have issues navigating the<br/>9 document as we have with the earlier --<br/>10 MS. PATEL: Sure. Kathryn can email that<br/>11 to you.<br/>12 BY MS. PATEL:<br/>13 Q. But Dr. Spurgeon, why don't you try and<br/>14 see if you can navigate it.<br/>15 A. Okay.<br/>16 Q. Are you able to scroll through it? Looks<br/>17 like you are.<br/>18 A. Slowly but surely, yeah.<br/>19 Q. Okay. So this is an article titled<br/>20 Pevonedistat, a Nedd8-activating enzyme inhibitor, in<br/>21 combination with ibrutinib in patients with<br/>22 relapsed/refractory B-cell non-Hodgkin lymphoma.</p>                                                                                                                      | Page 58 | <p>1 yet, so I was just curious as to whether or not there<br/>2 was some other -- if the deposition platform is not<br/>3 able to provide that either.<br/>4 THE REPORTER: If I could interject, I<br/>5 think the witness has control of the document on the<br/>6 screen.<br/>7 MS. DANEK: I agree, I agree. I'm<br/>8 asking -- so Kathryn -- no, you're not Kathryn. Did<br/>9 Liz drop off? Is there no one from the deposition<br/>10 who is sort of in charge?<br/>11 MS. PATEL: We have emailed it to you. We<br/>12 have emailed the document to you. You will receive<br/>13 it, as long as your internet is working.<br/>14 MS. DANEK: Okay. It came in.<br/>15 BY MS. PATEL:<br/>16 Q. Dr. Spurgeon, do you recognize this<br/>17 article?<br/>18 A. Yes.<br/>19 Q. You are listed as one of the coauthors,<br/>20 right?<br/>21 A. Yes.<br/>22 Q. And this was published in January of 2023,</p> | Page 60 |
| <p>1 Do you see that?<br/>2 MS. DANEK: Actually, we don't see it on<br/>3 the screen right now.<br/>4 THE WITNESS: I see it.<br/>5 MS. PATEL: Do you not see it, Brenda?<br/>6 MS. DANEK: I don't see it. And is there<br/>7 some way we can get the file? Like these are not the<br/>8 documents electronically. Usually they're available<br/>9 somehow for download.<br/>10 MS. PATEL: I think we're emailing you the<br/>11 document, but Dr. Spurgeon is able to see it on his<br/>12 screen.<br/>13 MS. DANEK: Right, I know. But typically<br/>14 there's sort of like a counsel copy that's provided,<br/>15 so I thought that the -- frequently there's like an<br/>16 exhibit jockey with the platform that will have<br/>17 either a link for exhibits or put them in the chat.<br/>18 Is that not available through this service?<br/>19 MS. PATEL: It is -- I mean, it may be,<br/>20 but I think we just agreed to email it to you as a<br/>21 courtesy copy.<br/>22 MS. DANEK: Right. I haven't received it</p> | Page 59 | <p>1 correct?<br/>2 A. Yes.<br/>3 Q. And it's a study investigating a<br/>4 combination therapy of Pevonedistat with ibrutinib,<br/>5 is that right?<br/>6 A. Yes.<br/>7 Q. Okay. Do you see the abstract in front of<br/>8 you there in the gray box?<br/>9 A. Yes.<br/>10 Q. Okay. Do you see where it states that,<br/>11 "This open-label, phase 1, multicenter,<br/>12 investigator-sponsored study enrolled patients with<br/>13 relapsed/refractory NHL and chronic lymphocytic<br/>14 leukemia (CLL)"?<br/>15 A. I do, yes.<br/>16 Q. And it also states -- do you see where it<br/>17 also states, "18 patients with NHL were enrolled<br/>18 including eight patients with mantle cell lymphoma<br/>19 (MCL) and 4 patients with CLL"?<br/>20 A. Yes.<br/>21 Q. Can you scroll to page 2, please, of the<br/>22 document.</p>                                                                        | Page 61 |

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| <p>1 A. Okay.</p> <p>2 Q. Under the heading statistical analysis, do</p> <p>3 you see the second sentence in the second paragraph</p> <p>4 that states, "Response was evaluated per Lugano</p> <p>5 criteria in patients with NHL and per IWCLL 2008</p> <p>6 criteria in CLL"?</p> <p>7 A. Yes.</p> <p>8 Q. All right. This indicates that response</p> <p>9 in CLL patients was evaluated by using the IWCLL 2008</p> <p>10 criteria, right?</p> <p>11 A. Yes.</p> <p>12 Q. And then on that same page, under patient</p> <p>13 characteristics, in the second paragraph, do you see</p> <p>14 where it says, "Three patients each were treated on</p> <p>15 dose levels 1 through 4 and 6 patients were treated</p> <p>16 on dose level 5"?</p> <p>17 A. Yes.</p> <p>18 Q. And then let's turn to page 3. Do you see</p> <p>19 a heading titled Efficacy?</p> <p>20 A. Yes.</p> <p>21 Q. And that first sentence there says, "The</p> <p>22 ORR was 65 percent for all patients (N equals 17</p>                                                      | <p>Page 62</p> <p>1 that mean?</p> <p>2 A. So as an example, often, you know, you'll</p> <p>3 treat a patient and then you'll do a CT scan at some</p> <p>4 juncture to assess disease response. And so, you</p> <p>5 know, in a patient, you may have labs and things like</p> <p>6 that, but if they don't make it to the assessment</p> <p>7 response, they're not evaluable. So if they don't</p> <p>8 make it to that two-month scan, they're not</p> <p>9 evaluable. So if they come off because of the</p> <p>10 toxicity or they withdraw consent, those would be</p> <p>11 examples of the patient is not evaluable for</p> <p>12 response.</p> <p>13 So often they have to have had that</p> <p>14 initial -- they have to have had that imaging test,</p> <p>15 that CT scan. And again, this is just an example. I</p> <p>16 don't remember the details of the study, when scans</p> <p>17 were or anything like that. But as a generalization,</p> <p>18 you are tracking response using a number of factors</p> <p>19 including imaging, typically CT scans or PET scans,</p> <p>20 whatever. And if the patient is not assessed at that</p> <p>21 two-month mark, for example, then they're not</p> <p>22 evaluable. Or if, again, they decide they don't want</p> |
| <p>1 response evaluable)"?</p> <p>2 A. Yes.</p> <p>3 Q. So this shows that only 17 patients had</p> <p>4 evaluable responses, right, in this study?</p> <p>5 A. Correct.</p> <p>6 Q. What does it mean to have an evaluable</p> <p>7 response?</p> <p>8 A. An evaluable response is, as it implies,</p> <p>9 just someone you can accurately evaluate for a</p> <p>10 response. So, for example, if someone's on the study</p> <p>11 for four weeks and then gets hit by a bus or</p> <p>12 something, then they're not evaluable. So that would</p> <p>13 like, you know, be an extreme example.</p> <p>14 Q. Okay. What's sort of a more common</p> <p>15 example?</p> <p>16 A. If someone for some reason withdrew</p> <p>17 consent or had a toxicity, then therefore was not</p> <p>18 able to have an evaluation, whether it be a scan --</p> <p>19 so trials like this will incorporate imaging. So if</p> <p>20 a patient doesn't have the imaging, they may not be</p> <p>21 evaluable.</p> <p>22 Q. They don't have the imaging, what does</p> | <p>Page 63</p> <p>1 to be on the study or they have a toxicity, that</p> <p>2 would be an example.</p> <p>3 Q. Okay. So basically it's anything that</p> <p>4 prevents the patient from attending a milestone</p> <p>5 assessment. So it could be that they withdrew the</p> <p>6 consent or they had toxicity or they got, as you</p> <p>7 said, hit by a bus, something that prevents them from</p> <p>8 attending that assessment, is that right?</p> <p>9 A. I think that's fair.</p> <p>10 Q. Okay. Is it common in most studies to</p> <p>11 have, you know, a subset of patients that don't have</p> <p>12 evaluable responses?</p> <p>13 A. Yes. And it varies by study. I can't</p> <p>14 give you a percentage or anything like that. But</p> <p>15 related to this study, you may have mentioned it, but</p> <p>16 I missed the total number versus the -- those that</p> <p>17 were evaluable.</p> <p>18 So I know you said 17 were evaluable,</p> <p>19 but --</p> <p>20 Q. Yeah, 17 were evaluable. If you look</p> <p>21 at -- I think in the abstract, they said it was --</p> <p>22 A. Yeah.</p>                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <p>Page 64</p> <p>Page 65</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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| <p>1 Q. -- 30 patients?</p> <p>2 A. Yeah. The other thing that factors into</p> <p>3 that analysis is, when you're doing the report, so,</p> <p>4 for example, you may have patients that -- again, I</p> <p>5 can't -- I don't recall the exact details of this</p> <p>6 study related to that -- but you can have patients,</p> <p>7 for example, that are one month in the study, but</p> <p>8 your study abstract or report -- you know, let's say</p> <p>9 you've got 30 patients on a study. You may have five</p> <p>10 patients that haven't gotten to the evaluation yet.</p> <p>11 So they may get there, but they just haven't gotten</p> <p>12 there yet. So that's another example.</p> <p>13 Q. And is that because those patients were</p> <p>14 started on a different timeline? They just started</p> <p>15 later?</p> <p>16 A. Yes.</p> <p>17 Q. Is that right?</p> <p>18 A. Yes.</p> <p>19 Q. Why wouldn't all the patients be started</p> <p>20 on the same -- at the same time?</p> <p>21 A. It's just the nature of enrolling</p> <p>22 patients. So you may -- you know, it's just the</p>                                                                        | <p>Page 66</p> | <p>1 it's 18. It's 18.</p> <p>2 MS. DANEK: Dr. Spurgeon, I have a hard</p> <p>3 copy available for you as well.</p> <p>4 THE WITNESS: Yes, 18. Yeah. So I would</p> <p>5 say that's fairly -- that's a fairly common amount of</p> <p>6 patients that wouldn't be evaluable.</p> <p>7 BY MS. PATEL:</p> <p>8 Q. Okay. So at least one patient in a cohort</p> <p>9 may not be evaluable, is that right?</p> <p>10 MS. DANEK: Objection, form.</p> <p>11 THE WITNESS: In this study, one patient</p> <p>12 was not evaluable.</p> <p>13 BY MS. PATEL:</p> <p>14 Q. When you're designing a study, is there</p> <p>15 anything you can do to mitigate the likelihood of</p> <p>16 having patients that aren't evaluable?</p> <p>17 A. Not that I can really think of right now.</p> <p>18 I think generally it's -- it goes along with doing</p> <p>19 clinical trials, you may have patients that are not</p> <p>20 evaluable.</p> <p>21 Q. Let's turn to page 7 of the document. And</p> <p>22 you can feel free to use your hard copy --</p> | <p>Page 68</p> |
| <p>1 nature of these studies. No one gets started at the</p> <p>2 exact same time. I shouldn't say no one, but</p> <p>3 generally speaking, it's uncommon to put everyone on</p> <p>4 at the same time just because that's the way patients</p> <p>5 present and the patients need treatment.</p> <p>6 Q. So the timeline in these studies cannot be</p> <p>7 dictated by the patient's own need in their</p> <p>8 treatment, is that right?</p> <p>9 A. I would say that the timeline of a</p> <p>10 study -- for an individual, yes, that is true. But</p> <p>11 the timeline for a study typically, if you don't have</p> <p>12 a patient going on then, you have a patient -- a</p> <p>13 different patient going on the study, right? So, you</p> <p>14 know, on an individual basis, it can affect things</p> <p>15 and that can differ from timeline -- or patient to</p> <p>16 patient, week to week.</p> <p>17 Q. And apologies. I think I said 30 earlier,</p> <p>18 but it looks like it might just be 18 total patients</p> <p>19 that were enrolled, is that right?</p> <p>20 A. That sounds --</p> <p>21 Q. Okay.</p> <p>22 A. I'd have to go back and look again, but</p> | <p>Page 67</p> | <p>1 A. Okay.</p> <p>2 Q. -- if that's easier to navigate for you.</p> <p>3 A. Okay.</p> <p>4 Q. Take a look at that second full paragraph</p> <p>5 on the right-hand side.</p> <p>6 A. That starts with Pevonedistat?</p> <p>7 Q. Yeah. It begins with, "The study is</p> <p>8 limited."</p> <p>9 A. Oh, okay.</p> <p>10 Q. Do you see that? Do you see that</p> <p>11 paragraph?</p> <p>12 A. Yes.</p> <p>13 Q. Okay. So that paragraph says, "The study</p> <p>14 is limited by small sample size at this time and</p> <p>15 short follow-up."</p> <p>16 Do you see that?</p> <p>17 A. Yes.</p> <p>18 Q. So here you and your coauthors concluded</p> <p>19 that 17 evaluable patients is a limited sample size,</p> <p>20 correct?</p> <p>21 MS. DANEK: Objection, form.</p> <p>22 THE WITNESS: In this context, yes. So I</p>                                                                                                                                                                                                            | <p>Page 69</p> |

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| <p>1 would qualify that, though, because this is a study</p> <p>2 that included many different histologies and the size</p> <p>3 of the -- making conclusions off of a specific</p> <p>4 number -- there's not necessarily a specific number.</p> <p>5 So this had many different disease types and it looks</p> <p>6 like there were four patients with CLL. So I do</p> <p>7 agree based on the statement -- with the statement</p> <p>8 here in this paper.</p> <p>9 BY MS. PATEL:</p> <p>10 Q. And that's the next sentence that you're</p> <p>11 talking about, right? It says, "The CLL/PLL cohort,</p> <p>12 in particular, has only four patients</p> <p>13 and thus conclusions of efficacy in this cohort are</p> <p>14 limited," right?</p> <p>15 A. Yes.</p> <p>16 Q. So here you and your coauthors further</p> <p>17 concluded that a limited sample size of only four</p> <p>18 patients with CLL/SLL is insufficient to conclude</p> <p>19 efficacy.</p> <p>20 MS. DANEK: Objection, form.</p> <p>21 THE WITNESS: No, my conclusion is the</p> <p>22 same as the sentence there, which is that the</p> | <p>Page 70</p> <p>1 the results shown, yes.</p> <p>2 Q. How many patients would have been</p> <p>3 sufficient to make conclusions regarding efficacy?</p> <p>4 MS. DANEK: Objection, form.</p> <p>5 THE WITNESS: I don't know. I don't think</p> <p>6 there's a specific number.</p> <p>7 BY MS. PATEL:</p> <p>8 Q. Is one patient sufficient?</p> <p>9 A. Sufficient for what?</p> <p>10 Q. Is one patient a sufficient sample size to</p> <p>11 form conclusions of efficacy?</p> <p>12 MS. DANEK: Objection, form.</p> <p>13 THE WITNESS: I think you'd have to</p> <p>14 qualify it a little bit there because conclusions</p> <p>15 implies -- it depends on the context. So we do, for</p> <p>16 example, publish case reports of one patient where it</p> <p>17 is a meaningful conclusion --</p> <p>18 BY MS. PATEL:</p> <p>19 Q. Dr. Spurgeon, I'm sorry to interrupt you,</p> <p>20 but I think --</p> <p>21 A. Yeah.</p> <p>22 Q. Could you come a little closer to the</p> <p>Page 72</p>                                                                                                                                                                                                          |
| <p>1 conclusions of efficacy in this cohort are limited.</p> <p>2 BY MS. PATEL:</p> <p>3 Q. Okay. Why are the conclusions of efficacy</p> <p>4 in the cohort limited?</p> <p>5 A. Well, I'd have to look at the specifics of</p> <p>6 each of those CLL patients. They may have gotten</p> <p>7 different dose ranges, too. And there were four</p> <p>8 patients.</p> <p>9 Q. Okay. If you were to assume that all four</p> <p>10 CLL/SLL patients got the same dose, would you still</p> <p>11 conclude that the conclusions of the efficacy in the</p> <p>12 cohort are limited?</p> <p>13 MS. DANEK: Objection, form.</p> <p>14 THE WITNESS: Based on the results of this</p> <p>15 paper, yes, I agree with what's written.</p> <p>16 BY MS. PATEL:</p> <p>17 Q. So your answer is yes, even if all four</p> <p>18 patients had the same dose?</p> <p>19 MS. DANEK: Objection, form.</p> <p>20 BY MS. PATEL:</p> <p>21 Q. Your conclusions would still be limited?</p> <p>22 A. In this paper with this combination with</p> <p>Page 71</p>                                                                       | <p>1 microphone?</p> <p>2 A. Oh, I'm sorry. I'm sorry. Yes. So what</p> <p>3 I was going to say, I think this is related to</p> <p>4 context and when one defines conclusion, what that</p> <p>5 means.</p> <p>6 So I think as it relates to -- there are</p> <p>7 times, for example, we publish case reports because</p> <p>8 we think the conclusion is important. And that could</p> <p>9 be based on one, two or three patients. However,</p> <p>10 there are other times when you may be designing a</p> <p>11 different clinical trial and have different</p> <p>12 parameters where it is limited.</p> <p>13 So I think the context matters and what</p> <p>14 the conclusion -- what you're looking for in that</p> <p>15 conclusion because obviously the, you know, benchmark</p> <p>16 of understanding things is very different when we're</p> <p>17 talking about looking for a novel agent or novel</p> <p>18 pathway as compared to FDA approval, which is a</p> <p>19 different benchmark.</p> <p>20 Q. When you publish case reports based on one</p> <p>21 or two or three patients, do you make conclusions</p> <p>22 with regard to efficacy in those types of papers?</p> <p>Page 73</p> |

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| <p>Page 74</p> <p>1 A. In relation to those patients, yes.</p> <p>2 Q. Can you make broader conclusions for all</p> <p>3 patients in those case reports?</p> <p>4 MS. DANEK: Objection, form.</p> <p>5 THE WITNESS: Can you be more specific,</p> <p>6 "Broader conclusions for all patients"? I think</p> <p>7 that's what you said.</p> <p>8 BY MS. PATEL:</p> <p>9 Q. In those types of papers with the smaller</p> <p>10 sample sizes, do you make conclusions that are</p> <p>11 applicable to all patients that have the malignancies</p> <p>12 that that sample size has?</p> <p>13 MS. DANEK: Objection, form.</p> <p>14 THE WITNESS: I don't think I characterize</p> <p>15 as all patients. However, I might use those data to</p> <p>16 treat another patient with the same treatment.</p> <p>17 BY MS. PATEL:</p> <p>18 Q. In the context of this paper, what in your</p> <p>19 opinion would have been the ideal sample size to</p> <p>20 sufficiently conclude efficacy?</p> <p>21 MS. DANEK: Objection, form.</p> <p>22 THE WITNESS: I don't have an ideal sample</p>                                                                                                                          | <p>Page 76</p> <p>1 Q. Sure.</p> <p>2 MS. PATEL: Yeah, we can take a break</p> <p>3 right now.</p> <p>4 THE VIDEOGRAPHER: Off the record at 10:55</p> <p>5 a.m.</p> <p>6 (Recess.)</p> <p>7 THE VIDEOGRAPHER: Back on the record at</p> <p>8 11:02 a.m.</p> <p>9 MS. PATEL: Okay. Let's pull up tab 13.</p> <p>10 We can mark it as Spurgeon Exhibit 2.</p> <p>11 (Spurgeon Exhibit No. 2 was marked</p> <p>12 for identification.)</p> <p>13 MS. PATEL: And could you drop it into the</p> <p>14 chat, Eric, please, for opposing counsel.</p> <p>15 THE VIDEOGRAPHER: Yes, one moment.</p> <p>16 BY MS. PATEL:</p> <p>17 Q. Dr. Spurgeon, do you see this article in</p> <p>18 front of you?</p> <p>19 A. I do, yes.</p> <p>20 Q. It's titled Hypertension treatment for</p> <p>21 patients receiving ibrutinib: A multicenter</p> <p>22 retrospective study, right?</p>           |
| <p>Page 75</p> <p>1 size from this paper. This is an early phase study</p> <p>2 trying to show a novel combination, but I think it's</p> <p>3 hard to apply a specific sample size. And as I</p> <p>4 mentioned before, there are going to be different</p> <p>5 benchmarks depending on the development of the drug,</p> <p>6 early phase versus Phase 2 versus Phase 3, and that</p> <p>7 often has to do -- when we talk about sample size and</p> <p>8 efficacy, that's really Phase -- you know, and</p> <p>9 approval, that's different, right?</p> <p>10 And that's based on also how the clinical</p> <p>11 trial is written and what power is needed and what</p> <p>12 effect size is deemed appropriate in conjunction with</p> <p>13 discussions with the FDA. So that's -- that's very</p> <p>14 different than drawing specific conclusions from --</p> <p>15 from, you know, the number of patients in an early</p> <p>16 phase study like this.</p> <p>17 BY MS. PATEL:</p> <p>18 Q. But you agree that four is too limited of</p> <p>19 a sample size here?</p> <p>20 A. In this study, I agree with what's</p> <p>21 written, yes. May I ask for a break? Would that be</p> <p>22 okay?</p> | <p>Page 77</p> <p>1 A. Correct.</p> <p>2 Q. Do you recognize this article?</p> <p>3 A. I do.</p> <p>4 Q. You're listed as one of the coauthors,</p> <p>5 right?</p> <p>6 A. Yes.</p> <p>7 Q. And this article was pre-published online</p> <p>8 in February of 2024, right?</p> <p>9 A. That sounds correct.</p> <p>10 Q. And this article investigates treatments</p> <p>11 for BTKI-associated hypertension in patients on</p> <p>12 ibrutinib, right?</p> <p>13 A. Yes.</p> <p>14 Q. Okay. Can you scroll to page 3?</p> <p>15 A. I seem to have lost --</p> <p>16 Q. There you go. That page.</p> <p>17 A. This page, okay.</p> <p>18 Q. Yes. Do you see the heading Results?</p> <p>19 A. Yes.</p> <p>20 Q. And that first sentence states, "Overall,</p> <p>21 196 patients were included in the study: 118</p> <p>22 received treatment for diagnosed hypertension before</p> |

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| <p>1 starting BTKI (prior hypertension), and 78 were<br/>2 diagnosed after BTKI initiation (de novo<br/>3 hypertension)."</p> <p>4 Do you see that?</p> <p>5 A. Yes.</p> <p>6 Q. Let's take a look at table 1 right<br/>7 underneath. And there that table shows that the<br/>8 entire CLL/SLL cohort was 184 patients, right?</p> <p>9 A. Yes.</p> <p>10 Q. And then let's turn to page 2091. And<br/>11 then do you see the heading Limitations?</p> <p>12 A. Yes.</p> <p>13 Q. And you see that first sentence which<br/>14 states, "Our study had several limitations beyond the<br/>15 constraints of a small sample size, retrospective<br/>16 data, and relatively few patients on<br/>17 second-generation BTKIs"?</p> <p>18 A. Yes.</p> <p>19 Q. And here you and your coauthors are<br/>20 characterizing one of the limitations of the study as<br/>21 being the small sample size, is that right?</p> <p>22 A. Yes.</p>                                                                                                | <p>Page 78</p> <p>1 A. Right.</p> <p>2 Q. How many patients would be involved in a<br/>3 large prospective study?</p> <p>4 A. It depends.</p> <p>5 Q. Would it be more than 184 CLL/SLL<br/>6 patients?</p> <p>7 A. I don't know.</p> <p>8 Q. But you agree that you and your coauthors<br/>9 concluded that 184 CLL/SLL patients was too limited<br/>10 of a sample size to confirm your conclusions, right?</p> <p>11 MS. DANEK: Objection, form.</p> <p>12 THE WITNESS: I'd agree that it's one of<br/>13 the limitations of this retrospective analysis,<br/>14 indeed, in that a prospective study would be needed<br/>15 to better understand the issue and define the issue<br/>16 and the number of patients -- this kind of goes back<br/>17 to the -- what we were talking about before, it<br/>18 really shows that context is everything.</p> <p>19 So it depends how you'd want to design<br/>20 that study, what difference you'd want to see, what<br/>21 agent, you know, how many arms you would want. So it<br/>22 could be a simple study where you're looking at two</p> |
| <p>1 Q. And then scroll down to the heading<br/>2 Conclusion. In that last paragraph, you and your<br/>3 coauthors provide your conclusions regarding the best<br/>4 anti-hypertension regimens, right?</p> <p>5 A. Yes. We -- with apparent benefit, yeah.</p> <p>6 Q. And then that last statement of the<br/>7 conclusions states that, "Large prospective studies<br/>8 are needed to formulate formal guidelines on the best<br/>9 anti-hypertension regimens to use in patients taking<br/>10 BTKI," correct?</p> <p>11 A. Yes.</p> <p>12 Q. So you and your coauthors noted there<br/>13 that, to confirm your conclusions, large<br/>14 retrospective studies would be needed, right?</p> <p>15 A. Large --</p> <p>16 MS. DANEK: Objection, form.</p> <p>17 THE WITNESS: Large prospective studies, I<br/>18 think you meant to say?</p> <p>19 BY MS. PATEL:</p> <p>20 Q. Yes. So you and your coauthors noted<br/>21 there that to confirm your conclusions, large<br/>22 prospective studies would be needed, right?</p> | <p>Page 79</p> <p>1 arms where you use one treatment regimen versus<br/>2 another, one agent versus two or you could add in<br/>3 another arm that showed three anti-hypertensive.</p> <p>4 So again, I think it's -- again, this is<br/>5 all about context and what you're looking for and<br/>6 this just highlights that it's difficult to define<br/>7 the patient number, you know, as a broader -- as a<br/>8 broader statement.</p> <p>9 BY MS. PATEL:</p> <p>10 Q. How many patients would you want in a<br/>11 single arm?</p> <p>12 MS. DANEK: Objection, form.</p> <p>13 THE WITNESS: Again, I don't know because<br/>14 it's still all about the context.</p> <p>15 BY MS. PATEL:</p> <p>16 Q. In this context.</p> <p>17 A. Right. So -- yes, that's -- that still<br/>18 applies, even if it was a single arm.</p> <p>19 Q. So you're saying you wouldn't be able to<br/>20 tell me sitting here today what would be a sufficient<br/>21 sample size in a large prospective study to confirm<br/>22 your conclusions in this paper?</p>                                       |
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| <p>1 MS. DANEK: Objection, form.</p> <p>2 THE WITNESS: I'm telling you, yes, I</p> <p>3 wouldn't be able to come up with a patient number</p> <p>4 unless I sat down and really thought about it and</p> <p>5 came up with a statistical plan that supported my</p> <p>6 hypothesis and potential conclusions.</p> <p>7 BY MS. PATEL:</p> <p>8 Q. So you're saying that it's a complex</p> <p>9 assessment when determining the number of patients</p> <p>10 you would want to include in any particular cohort,</p> <p>11 is that right?</p> <p>12 MS. DANEK: Objection, form.</p> <p>13 THE WITNESS: No, in this case, it</p> <p>14 wouldn't be complex. It would be routine. It's just</p> <p>15 something that I would have to think about and come</p> <p>16 up with a more formal approach than giving a number</p> <p>17 off the top of my head.</p> <p>18 BY MS. PATEL:</p> <p>19 Q. So you're saying it would take you a long</p> <p>20 time to think about, longer than we have here today,</p> <p>21 is that right?</p> <p>22 MS. DANEK: Objection, form.</p> | Page 82 | <p>1 confirm, you understand that whether challenged</p> <p>2 claims have adequate written description support and</p> <p>3 are enabled is considered from the perspective of a</p> <p>4 person of ordinary skill in the art, right?</p> <p>5 A. Yes.</p> <p>6 Q. And when I say POSA, you understand that</p> <p>7 that means person of ordinary skill in the art,</p> <p>8 right?</p> <p>9 A. Yes.</p> <p>10 Q. So in paragraph 74 of your declaration,</p> <p>11 you state that a clinical member is a member that had</p> <p>12 at least a medical degree with training in hematology</p> <p>13 and oncology, including several years of clinical</p> <p>14 experience in treating hematologic malignancies,</p> <p>15 right?</p> <p>16 A. Yes.</p> <p>17 Q. You agree with this definition of a</p> <p>18 clinical member, right?</p> <p>19 A. Yes.</p> <p>20 Q. And you believe you qualify as a clinical</p> <p>21 member of a POSA team, right?</p> <p>22 A. Yes.</p> | Page 84 |
| <p>1 THE WITNESS: No, not what I'm saying.</p> <p>2 BY MS. PATEL:</p> <p>3 Q. How long would it take you to think about?</p> <p>4 A. I can't give you an absolute number. That</p> <p>5 would be hypothetical.</p> <p>6 Q. Just an estimate. Just an estimate. A</p> <p>7 few hours?</p> <p>8 A. I don't know. I really don't. I mean, it</p> <p>9 could take less than an hour. It could take a day.</p> <p>10 It depends what -- I can't really speculate. It's</p> <p>11 not fair for me to speculate in this situation.</p> <p>12 Q. Okay. So it's situation-specific, is that</p> <p>13 right?</p> <p>14 A. Yes.</p> <p>15 Q. Okay. We can take that down. Can you</p> <p>16 turn back to your declaration, please. It's Exhibit</p> <p>17 2014.</p> <p>18 A. I have it here, yes.</p> <p>19 Q. Turn to paragraph 74. Let me know when</p> <p>20 you're there.</p> <p>21 A. I'm here.</p> <p>22 Q. Okay. We touched on this earlier, but to</p>                                                                                                                     | Page 83 | <p>1 Q. And you're not an expert in chemistry,</p> <p>2 right?</p> <p>3 A. Correct.</p> <p>4 Q. Nor are you an expert in medicinal</p> <p>5 chemistry?</p> <p>6 A. Correct.</p> <p>7 Q. And you're not an expert in chemical</p> <p>8 structures, right?</p> <p>9 A. Correct.</p> <p>10 Q. Or protein structures, right?</p> <p>11 A. Correct.</p> <p>12 Q. And you're not an expert in the chemical</p> <p>13 structure of small molecules, right?</p> <p>14 A. Correct.</p> <p>15 Q. And you're not an expert in structural</p> <p>16 interactions between small molecule drugs and</p> <p>17 proteins including kinases, right?</p> <p>18 A. Correct. I would need to rely on someone</p> <p>19 with that expertise within the POSA team to tell me</p> <p>20 if one drug was in the same class as another drug.</p> <p>21 Q. And you're not an expert in the</p> <p>22 structure-function relationship between BTKI and BTK,</p>                                          | Page 85 |

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| <p>1 right?</p> <p>2 A. Can you be more specific? If you're</p> <p>3 asking if -- can I look at a structure of a BTKI and</p> <p>4 know what it would do functionally? No, I'm not an</p> <p>5 expert in that. If you asked me to see if someone</p> <p>6 tells you that is an expert in a POSA team that it's</p> <p>7 an irreversible BTK inhibitor, what can we expect, I</p> <p>8 would be the expert in that.</p> <p>9 Q. And you're not an expert in assessing the</p> <p>10 physical chemical properties of a compound, right?</p> <p>11 A. Correct.</p> <p>12 Q. And you're not an expert in assessing how</p> <p>13 different structures may affect those physiochemical</p> <p>14 properties, right?</p> <p>15 A. That's correct. I wouldn't. But where I</p> <p>16 would be an expert again is where if someone told me</p> <p>17 that it was an irreversible BTK inhibitor, I would</p> <p>18 have expertise in understanding the impacts of that</p> <p>19 on -- in the clinical context.</p> <p>20 Q. Okay.</p> <p>21 MS. PATEL: Well, let's pull up tab 3.</p> <p>22 This is going to be Exhibit 1001, the '803 patent.</p> | Page 86 | <p>1 A. June 2011, yes.</p> <p>2 Q. You compared Imbruvica to other</p> <p>3 irreversible BTKIs including Brukinsa, acalabrutinib,</p> <p>4 tirabrutinib throughout your declaration, right?</p> <p>5 MS. DANEK: Objection, form.</p> <p>6 THE WITNESS: There's a portion of my</p> <p>7 declaration that I discuss the compounds you</p> <p>8 mentioned.</p> <p>9 BY MS. PATEL:</p> <p>10 Q. But as of June 2011, Brukinsa,</p> <p>11 acalabrutinib and tirabrutinib were not known to</p> <p>12 irreversibly inhibit BTK, right?</p> <p>13 A. As of 2011, to my knowledge, we don't have</p> <p>14 any clinical data that suggests that. I can't be</p> <p>15 exhaustive to say that there may not have been some</p> <p>16 preclinical data or some structures, AKA, like in the</p> <p>17 specification which includes the class of</p> <p>18 ibrutinib-like and also includes zanubrutinib, that</p> <p>19 those structures weren't known or that people, you</p> <p>20 know -- at that juncture, there was no clinical --</p> <p>21 that is true there was no clinical data for those</p> <p>22 compounds.</p> |
| <p>1 (Spurgeon Exhibit No. 1001 was</p> <p>2 identified for the record.)</p> <p>3 BY MS. PATEL:</p> <p>4 Q. Let me know when you have that in front of</p> <p>5 you, Dr. Spurgeon.</p> <p>6 A. Okay. I have it.</p> <p>7 Q. Okay. You understand that BeiGene is</p> <p>8 challenging certain claims of the '803 patent?</p> <p>9 A. Yes.</p> <p>10 Q. That those are claims 1 through 8, 12 and</p> <p>11 20 of the '803 patent? You know, it's okay. I'll</p> <p>12 represent to you that claims 1 through 8, 12 and 20</p> <p>13 are the claims that BeiGene is challenging of the</p> <p>14 '803 patent. And I'll refer to those throughout this</p> <p>15 deposition as the challenged claims.</p> <p>16 A. Okay.</p> <p>17 Q. Do you understand? Okay.</p> <p>18 A. Yes.</p> <p>19 Q. Your opinions regarding written</p> <p>20 description and enablement of the challenged claims</p> <p>21 are considered from the perspective of a POSA as of</p> <p>22 2010-2011, right?</p>                                                                                                                                                    | Page 87 | <p>1 Q. Were you aware of any data whatsoever</p> <p>2 suggesting that Brukinsa, acalabrutinib or</p> <p>3 tirabrutinib would irreversibly inhibit BTK as of</p> <p>4 June 2011?</p> <p>5 MS. DANEK: Objection, form.</p> <p>6 THE WITNESS: I was not aware, but I would</p> <p>7 suggest that just because I wasn't aware doesn't mean</p> <p>8 that something wasn't happening that I just was</p> <p>9 unaware of.</p> <p>10 But from my perspective, again, no</p> <p>11 clinical data that I had seen or preclinical data</p> <p>12 that I had seen specific to those compounds, then</p> <p>13 again, at that stage I wouldn't know the differences</p> <p>14 because that's not my area of expertise related to</p> <p>15 the compound structures.</p> <p>16 BY MS. PATEL:</p> <p>17 Q. You in your declaration haven't offered</p> <p>18 any opinions regarding whether the challenged claims</p> <p>19 are anticipated or obvious, right?</p> <p>20 A. Correct.</p> <p>21 Q. You have the '803 patent in front of you,</p> <p>22 right?</p>                                                                 |

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| <p>1 A. I do.</p> <p>2 Q. Can you turn to claim 1. That should be</p> <p>3 at the back of the patent.</p> <p>4 A. Okay.</p> <p>5 Q. So looking at claim 1, it recites a method</p> <p>6 for treating CLL or SLL in an individual comprising</p> <p>7 orally administering a therapeutically effective</p> <p>8 amount of an irreversible BTK inhibitor on a</p> <p>9 continuous daily regimen until progression of the</p> <p>10 CLL, SLL or unacceptable toxicity, right?</p> <p>11 A. Yes.</p> <p>12 Q. You agree that the challenged claims</p> <p>13 require a step of administering a therapeutic</p> <p>14 effective amount of the BTKI to a patient who has CLL</p> <p>15 or SLL?</p> <p>16 A. Yes.</p> <p>17 Q. And you agree that claim 1 requires doing</p> <p>18 so until disease progression or unacceptable</p> <p>19 toxicity, right?</p> <p>20 A. Yes.</p> <p>21 Q. And claim 1 also recites that</p> <p>22 lymphocytosis is not considered as progression of CLL</p> | Page 90 | <p>1 A. Oh, I see it.</p> <p>2 Q. Okay.</p> <p>3 A. Yes, okay. Sorry. I didn't go to the top</p> <p>4 of the other column. Okay.</p> <p>5 Q. Oh, I see. Okay. And you didn't offer</p> <p>6 any opinions regarding that limitation, right?</p> <p>7 A. About whether it binds to Cys 481?</p> <p>8 Q. Any opinions. You did not offer any</p> <p>9 opinions regarding the limitation that recites</p> <p>10 wherein the irreversible inhibitor BTK forms a</p> <p>11 covalent bond with cysteine 481 of a BTK.</p> <p>12 A. I did not provide any opinion on the</p> <p>13 characteristics of actual -- of the structural</p> <p>14 characteristics of the compound and therefore its</p> <p>15 binding interactions.</p> <p>16 Instead, I was asked to sort of --</p> <p>17 starting from the framework of there's an</p> <p>18 irreversible inhibitor that binds BTK and has --</p> <p>19 and/or a class of medications like -- that are</p> <p>20 ibrutinib-like, that's where I was asked to comment,</p> <p>21 at that portion forward.</p> <p>22 Q. Okay. And then claim 1 also recites</p> |
| <p>1 or SLL, right?</p> <p>2 A. Yes.</p> <p>3 Q. And it also recites that BTKI forms a</p> <p>4 covalent bond with cysteine 481 of BTK, right?</p> <p>5 A. Where do you see that in the claim?</p> <p>6 Q. The very last limitation, wherein the</p> <p>7 irreversible inhibitor BTK performs a covalent bond</p> <p>8 with cysteine 481 of a Bruton's tyrosine kinase. Let</p> <p>9 me know where you're having trouble. I can help</p> <p>10 navigate you.</p> <p>11 A. I can't find the part specifically that</p> <p>12 mentions the cysteine 481.</p> <p>13 Q. Okay. Do you see the structure of the</p> <p>14 molecule in claim 1? Do you see that depiction?</p> <p>15 A. Yes.</p> <p>16 Q. And then you see that there's a "wherein"</p> <p>17 underneath that?</p> <p>18 A. Yep.</p> <p>19 Q. And then there's a second "wherein"</p> <p>20 underneath that one?</p> <p>21 A. Yep.</p> <p>22 Q. And then there's a third "wherein."</p>                                     | Page 91 | <p>1 structural components of the irreversible BTKI,</p> <p>2 right? There's the structure that's shown -- that's</p> <p>3 depicted in claim 1. You see that, right?</p> <p>4 A. Yes.</p> <p>5 Q. Okay. That's one of the structural</p> <p>6 limitations, right?</p> <p>7 A. Yes. It mentions structure, yes.</p> <p>8 Q. Right. And then there are two limitations</p> <p>9 underneath that depiction, one that starts with</p> <p>10 wherein Z prime is optionally substituted and goes</p> <p>11 on, is that right?</p> <p>12 A. Yes.</p> <p>13 Q. And then there's a second limitation</p> <p>14 underneath that that starts with, "Wherein the</p> <p>15 optionally substituted fused heterocyclic ring," and</p> <p>16 goes on to list a couple of structural limitations</p> <p>17 there.</p> <p>18 Do you see that?</p> <p>19 A. I do.</p> <p>20 Q. Both of those limitations are structural</p> <p>21 limitations as well, right?</p> <p>22 A. Yes.</p>                                                                                                                                 |

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| <p>1 Q. And you didn't offer opinions regarding</p> <p>2 how many BTKIs satisfy the structural limitations of</p> <p>3 those --</p> <p>4 A. Correct.</p> <p>5 Q. -- of claim 1, right?</p> <p>6 A. That is correct.</p> <p>7 Q. You rely on Dr. Eck's opinion regarding</p> <p>8 the scope of the structural limitations of the</p> <p>9 challenged claims, right?</p> <p>10 A. That is correct.</p> <p>11 Q. And you haven't offered any opinion</p> <p>12 regarding how a structure of a BTKI may impact the</p> <p>13 functions of the BTKI, right?</p> <p>14 A. Correct.</p> <p>15 Q. Have you ever performed this type of</p> <p>16 analysis?</p> <p>17 A. Which type of analysis specifically?</p> <p>18 Q. An analysis of how a structure of a BTKI</p> <p>19 may impact the functions of the BTKI.</p> <p>20 A. No, I have not performed that.</p> <p>21 Q. And you haven't offered any opinion</p> <p>22 regarding how the geometry, electron distribution and</p>                                                                                                                                                                                                                       | Page 94 | <p>1 Q. Yes. Ibrutinib -- you understand that</p> <p>2 ibrutinib satisfies the structural limitations of the</p> <p>3 claim, right?</p> <p>4 A. Yes. So -- yes.</p> <p>5 Q. And you understand that it satisfies the</p> <p>6 cysteine 481 binding limitation of the claim, right?</p> <p>7 A. Yes.</p> <p>8 Q. So then when you treat CLL/SLL patients,</p> <p>9 do you orally administer to any one of those patients</p> <p>10 a therapeutically effective amount of ibrutinib on a</p> <p>11 continuous daily regimen until progression of the CLL</p> <p>12 or SLL or unacceptable toxicity wherein lymphocytosis</p> <p>13 is not considered progression of the CLL or SLL?</p> <p>14 A. Yes.</p> <p>15 Q. Have you ever had to stop treatment of any</p> <p>16 of your patients on ibrutinib due to unacceptable</p> <p>17 toxicity?</p> <p>18 A. Yes. And I've done -- had to do that with</p> <p>19 other chemotherapeutics as well.</p> <p>20 Q. Okay.</p> <p>21 A. Or targeted agents. Same.</p> <p>22 Q. What are some examples of unacceptable</p>                                                                                                                                                             | Page 96 |
| <p>1 H bonding properties of the BTKI impact the</p> <p>2 therapeutically effective dose of BTK, right?</p> <p>3 A. That is correct.</p> <p>4 Q. And you haven't offered any opinion</p> <p>5 regarding how the geometry, electron distribution and</p> <p>6 H bonding properties as in hydrogen bonding</p> <p>7 properties of a BTKI impact whether the BTKI will</p> <p>8 result in lymphocytosis when administered to CLL/SLL</p> <p>9 patients, right?</p> <p>10 A. That is correct. What I've commented on</p> <p>11 is if there is an ibrutinib-like irreversible BTK</p> <p>12 inhibitor that can inhibit BTK, it will lead to the</p> <p>13 elements outlined in the specification.</p> <p>14 Q. When treating your own patients with</p> <p>15 ibrutinib, do you follow the ibrutinib regimen</p> <p>16 described in claim 1?</p> <p>17 A. You mean specifically -- just to clarify,</p> <p>18 specifically orally administering to the individual a</p> <p>19 therapeutically effective amount on a continuous</p> <p>20 daily regimen until progression wherein lymphocytosis</p> <p>21 is not considered progression? Is that the part</p> <p>22 you're referring to in claim 1?</p> | Page 95 | <p>1 toxicities that have prompted you to stop treatment?</p> <p>2 A. So one can stop treatment for a number of</p> <p>3 reasons. This is not exhaustive by any means, but</p> <p>4 off the top of my head, can range from things like</p> <p>5 what we would call financial toxicity where the</p> <p>6 patient can no longer afford the drug or get the</p> <p>7 drug. It can range -- so that could be an example.</p> <p>8 It can be related to side effects,</p> <p>9 specific side effects, namely, things like diarrhea,</p> <p>10 skin rash, arthralgias, atrial fibrillation,</p> <p>11 development of hypertension that we cannot control.</p> <p>12 Those would all be examples of reasons to stop</p> <p>13 treatment.</p> <p>14 Q. Have you ever treated a patient with</p> <p>15 ibrutinib for a year or longer and then had to stop</p> <p>16 treatment after that due to unacceptable toxicity?</p> <p>17 A. I can't think of a patient off the top of</p> <p>18 my head, but I'm sure I have, yes.</p> <p>19 Q. So it can take a year or more sometimes</p> <p>20 for a patient to present unacceptable toxicity to a</p> <p>21 treatment like ibrutinib, right?</p> <p>22 MS. DANEK: Objection, form.</p> | Page 97 |

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| <p>Page 98</p> <p>1 THE WITNESS: It is possible to develop<br/>2 toxicity with any of these agents -- and when I say<br/>3 these acts, any of the BTK inhibitors -- yes, beyond<br/>4 a year of therapy.<br/>5 BY MS. PATEL:<br/>6 Q. How can treatment with ibrutinib result in<br/>7 unacceptable toxicity when the patient is<br/>8 administered only a therapeutically effective amount?<br/>9 MS. DANEK: Objection, form.<br/>10 THE WITNESS: I think one way to think<br/>11 about that is that therapeutically effective -- and<br/>12 also in this case -- but in general, therapeutically<br/>13 effective does not always equate to toxicity and<br/>14 often does not equate to toxicity. It doesn't mean<br/>15 that drugs don't have toxicities. They do. That's<br/>16 just part of cancer treatment.<br/>17 BY MS. PATEL:<br/>18 Q. Okay. Could you turn to paragraph 77 of<br/>19 your declaration.<br/>20 A. Okay.<br/>21 Q. Do you see there you state that, "I<br/>22 understand from Dr. Eck that the class of</p> | <p>Page 98</p> <p>1 regarding the scope of the claimed -- of the<br/>2 challenged claims, correct?<br/>3 MS. DANEK: Objection, form.<br/>4 THE WITNESS: Can you clarify that<br/>5 question, please? Or repeat the question.<br/>6 BY MS. PATEL:<br/>7 Q. As you're stating in paragraph 77 and 115,<br/>8 you're relying on Dr. Eck to identify the<br/>9 irreversible inhibitors that are within the scope of<br/>10 the claims, right?<br/>11 A. As I'm not a medicinal chemist or<br/>12 structural biologist, I am relying on Dr. Eck to<br/>13 define what compounds irreversibly inhibit BTK, yes.<br/>14 Q. Okay. And did Dr. Eck tell you how many<br/>15 compounds irreversibly inhibit BTK?<br/>16 A. No.<br/>17 Q. Okay. Do you have any sense of how many<br/>18 compounds within the scope of the claim irreversibly<br/>19 inhibit BTK?<br/>20 A. No.<br/>21 Q. Did you have any sense of that when you<br/>22 were forming your opinions in this case?</p>                                                                                                |
| <p>Page 99</p> <p>1 irreversible BTK inhibitors in the claims have common<br/>2 structural features to ibrutinib that convey the<br/>3 ability to irreversibly inhibit BTK." And then you<br/>4 make your conclusion regarding the specification.<br/>5 Do you see that?<br/>6 A. I do, yes.<br/>7 Q. And can you also flip to paragraph 115 of<br/>8 your declaration.<br/>9 A. Okay.<br/>10 Q. And do you see there you state that you<br/>11 understand that Dr. Eck opines that a POSA would have<br/>12 been able to identify irreversible inhibitors within<br/>13 the scope of the claims?<br/>14 Do you see that?<br/>15 A. Yes.<br/>16 Q. And then next you state that in your<br/>17 opinion, the specification as filed in June 2011<br/>18 would have enabled a POSA to practice the full scope<br/>19 of the claimed methods.<br/>20 Do you see that?<br/>21 A. Yes.<br/>22 Q. You haven't yourself offered any opinion</p>                                                                                               | <p>Page 101</p> <p>1 A. No. My opinion's based on that there were<br/>2 compounds with ibrutinib-like properties in a class<br/>3 and one of which was zanubrutinib.<br/>4 Q. So you just know that a POSA like Eck<br/>5 could identify -- Dr. Eck could identify the number<br/>6 of BTKIs falling within the scope of the claims that<br/>7 would irreversibly inhibit BTK, right?<br/>8 MS. DANEK: Objection, form.<br/>9 THE WITNESS: My understanding is that he<br/>10 would have the expertise to define what irreversible<br/>11 BTK inhibitors were ibrutinib-like.<br/>12 BY MS. PATEL:<br/>13 Q. But he wouldn't be able to tell you the<br/>14 breadth of the claims?<br/>15 MS. DANEK: Objection, form.<br/>16 THE WITNESS: I can't speculate because<br/>17 I'm, again, not a structural biologist, but -- so I<br/>18 don't know if that's -- you know, how many compounds<br/>19 Dr. Eck would look at. You would have to ask him<br/>20 that.<br/>21 But in looking at those compounds, my<br/>22 understanding is, as a POSA, as part of the team,</p> |

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| <p>1 that he would have the expertise to tell me which of</p> <p>2 these agents are ibrutinib-like and fall within that</p> <p>3 class that we're discussing today that applies to the</p> <p>4 specification.</p> <p>5 BY MS. PATEL:</p> <p>6 Q. Okay. Can you turn to paragraph 84,</p> <p>7 please.</p> <p>8 A. Okay.</p> <p>9 Q. So here you state that, "Together, the</p> <p>10 above data in the specification detail that ibrutinib</p> <p>11 occupies BTK, inhibits BTK-dependent processes, and</p> <p>12 has remarkable clinical results in CLL/SLL patients,</p> <p>13 including the particularly difficult-to-treat</p> <p>14 relapsed/refractory patients. A POSA reading this</p> <p>15 disclosure would understand that inhibiting BTK</p> <p>16 results in treating CLL/SLL patients."</p> <p>17 A. Yes.</p> <p>18 Q. So it's your opinion that if you know that</p> <p>19 a certain -- that certain claimed BTKIs inhibit BTK,</p> <p>20 then those same BTKIs would effectively treat CLL/SLL</p> <p>21 patients, is that right?</p> <p>22 MS. DANEK: Objection, form.</p> | <p>Page 102</p> | <p>1 THE WITNESS: I don't know any evidence of</p> <p>2 ibrutinib-like BTK inhibitors that don't effectively</p> <p>3 inhibit BTK or at least the ones that we've studied</p> <p>4 clinically that don't have activity in CLL/SLL. I</p> <p>5 don't know of any evidence of that.</p> <p>6 BY MS. PATEL:</p> <p>7 Q. So you're saying it's possible that even</p> <p>8 if an ibrutinib-like BTK inhibitor does not inhibit</p> <p>9 BTK, then it would still effectively treat CLL/SLL?</p> <p>10 MS. DANEK: Objection, form.</p> <p>11 THE WITNESS: No. What I'm saying is that</p> <p>12 if there was -- if Dr. Eck came to me and said here's</p> <p>13 some compounds, they irreversibly inhibit BTK, that I</p> <p>14 would expect them to treat CLL/SLL, if they're</p> <p>15 ibrutinib-like. That's what I'm saying.</p> <p>16 BY MS. PATEL:</p> <p>17 Q. Okay. So let me rephrase this question.</p> <p>18 A. Okay.</p> <p>19 Q. So say Dr. Eck came to you and said here</p> <p>20 is a compound that satisfies the structural</p> <p>21 limitations of the claims, you know the ones that we</p> <p>22 went through today, but it does not irreversibly</p>                            | <p>Page 104</p> |
| <p>1 THE WITNESS: It is my understanding</p> <p>2 that -- to qualify that a little further would be</p> <p>3 ibrutinib-like irreversible BTK inhibitors.</p> <p>4 BY MS. PATEL:</p> <p>5 Q. Right. So claimed BTKIs, the claimed</p> <p>6 BTKIs, right, ibrutinib-like, is that what --</p> <p>7 A. Yes.</p> <p>8 Q. I guess what are you defining as</p> <p>9 ibrutinib-like BTKIs?</p> <p>10 A. It would rely on Dr. Eck for that based on</p> <p>11 the structure.</p> <p>12 Q. So we'll use your phrasing here. If you</p> <p>13 know that certain ibrutinib-like inhibitors inhibit</p> <p>14 BTK, then it's your opinion that those same BTKIs</p> <p>15 would effectively treat CLL or SLL, right?</p> <p>16 A. Yes. If they're irreversible</p> <p>17 ibrutinib-like inhibitors, yes.</p> <p>18 Q. And do you believe the inverse is true as</p> <p>19 well, if certain BTKIs do not inhibit BTK, then it's</p> <p>20 your opinion they would not effectively treat</p> <p>21 CLL/SLL?</p> <p>22 MS. DANEK: Objection, form.</p>                                                      | <p>Page 103</p> | <p>1 inhibit BTK. Would you conclude that it would</p> <p>2 therefore not effectively treat CLL or SLL?</p> <p>3 A. If it was -- it wouldn't -- I mean, in</p> <p>4 that scenario, it wouldn't satisfy the claim, would</p> <p>5 it? Because aren't we talking irreversible</p> <p>6 inhibitors?</p> <p>7 Q. Well, that -- my question isn't whether it</p> <p>8 would satisfy the claims. My question is, if Dr. Eck</p> <p>9 said here is a compound that satisfies the structure</p> <p>10 that's defined in the claims, but does not itself</p> <p>11 irreversibly inhibit BTK, what conclusion would you</p> <p>12 draw with regard to whether that compound would treat</p> <p>13 CLL or SLL?</p> <p>14 MS. DANEK: Objection, form.</p> <p>15 THE WITNESS: I'm honestly having trouble</p> <p>16 wrapping my head around this hypothetical because by</p> <p>17 definition, an irreversible ibrutinib-like BTK</p> <p>18 inhibitor is going to irreversibly inhibit BTK. And</p> <p>19 so in that case, I would expect it to treat CLL/SLL.</p> <p>20 BY MS. PATEL:</p> <p>21 Q. Right. And I'm not saying that Dr. Eck is</p> <p>22 coming to you with an irreversible BTK inhibitor.</p> | <p>Page 105</p> |

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| <p>Page 106</p> <p>1 I'm saying he's coming to you with a compound that</p> <p>2 satisfies the structural limitations of the claims.</p> <p>3 It has the structure that's shown in the picture of</p> <p>4 claim 1, it has two to four nitrogen atoms, it has</p> <p>5 optional substitutions as defined in the claim. All</p> <p>6 of those structural limitations are satisfied in that</p> <p>7 compound. But when you actually dock that compound</p> <p>8 to BTK, it does not show irreversible inhibition.</p> <p>9 What conclusion would you draw with regard</p> <p>10 to efficacy in CLL/SLL patients based off of that</p> <p>11 information?</p> <p>12 A. If the inhibitor did not inhibit BTK, I</p> <p>13 would -- in that situation, I would think it would</p> <p>14 not be effective for CLL/SLL, that is correct.</p> <p>15 Q. Okay.</p> <p>16 A. Is that what you're asking?</p> <p>17 Q. Yes. Thank you.</p> <p>18 MS. PATEL: Okay. Let's take a quick</p> <p>19 break. I want to see if I want to wrap this.</p> <p>20 Maybe -- yeah, let's go off the record.</p> <p>21 THE VIDEOGRAPHER: Off the record at 11:50</p> <p>22 a.m.</p> | <p>Page 108</p> <p>1 a clinical trial in reality. So it's hard to</p> <p>2 navigate in hypotheticals.</p> <p>3 Q. Could you turn to page 63 of your</p> <p>4 declaration, please.</p> <p>5 A. Did you say page 63 or paragraph 63?</p> <p>6 Q. Page 63 this time.</p> <p>7 A. Page 63.</p> <p>8 Q. Yes. Usually I say paragraph, but this</p> <p>9 time it was easier to refer to the page.</p> <p>10 A. Okay.</p> <p>11 Q. Do you see heading B there?</p> <p>12 A. Yes.</p> <p>13 Q. So that heading is the section that</p> <p>14 contains the entirety of your opinions regarding</p> <p>15 enablement, correct?</p> <p>16 A. I think the whole declaration includes</p> <p>17 things that outline why it would be enabled, but that</p> <p>18 is the heading, yes.</p> <p>19 Q. Where else in your declaration do you have</p> <p>20 opinions regarding enablement?</p> <p>21 A. I just think that the context of</p> <p>22 everything leads to the section about enablement.</p>                                                            |
| <p>Page 107</p> <p>1 (Recess.)</p> <p>2 THE VIDEOGRAPHER: Back on the record at</p> <p>3 12:00 p.m.</p> <p>4 BY MS. PATEL:</p> <p>5 Q. Okay. Dr. Spurgeon, do you still have</p> <p>6 paragraph 84 in front of you?</p> <p>7 A. I do.</p> <p>8 Q. It says specifically in that paragraph you</p> <p>9 conclude that based on the ibrutinib data in the</p> <p>10 specification, a POSA would understand that</p> <p>11 inhibiting BTK results in treating CLL/SLL patients,</p> <p>12 right?</p> <p>13 A. Yes.</p> <p>14 Q. So putting aside all regulatory issues,</p> <p>15 you know, in a world where the FDA is not relevant,</p> <p>16 if Dr. Eck represented to you that a specific</p> <p>17 compound irreversibly inhibits BTK, would you treat</p> <p>18 one of your CLL/SLL patients with it?</p> <p>19 A. It's the same answer as before, which</p> <p>20 would be if I knew a dose where BTK was inhibited,</p> <p>21 AKA something that was therapeutically effective,</p> <p>22 then yes. But again, that would be in the context of</p>                                                                                                    | <p>Page 109</p> <p>1 Q. Okay. But these are your actual opinions</p> <p>2 regarding whether the patent is enabled, right?</p> <p>3 A. Yes.</p> <p>4 Q. Okay. Take a look at paragraph 119 to</p> <p>5 120.</p> <p>6 A. Yes.</p> <p>7 Q. You state here that the specification</p> <p>8 teaches identifying therapeutically effective doses,</p> <p>9 right?</p> <p>10 A. Yes. It documents the data, yes.</p> <p>11 Q. And you state that that's because example</p> <p>12 7 of the specification teaches how to measure the</p> <p>13 occupancy of BTK using specific assays, right?</p> <p>14 A. I'm referencing example 7.</p> <p>15 Q. You're referencing example 7 in that</p> <p>16 paragraph of your declaration to support your opinion</p> <p>17 that the specification teaches how to measure the</p> <p>18 occupancy of BTK using specific assays, right?</p> <p>19 A. Yes.</p> <p>20 Q. So let's turn to example 7 of the</p> <p>21 specification. That's Exhibit 1001. Do you have</p> <p>22 that in front of you, Dr. Spurgeon?</p> |

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| <p>Page 110</p> <p>1 A. I do. Yes.</p> <p>2 Q. It's at column 136. Do you see it?</p> <p>3 A. Yes.</p> <p>4 Q. So example 7 is titled a clinical trial to</p> <p>5 determine safety and efficacy of compounds of Formula</p> <p>6 (D), is that right?</p> <p>7 A. Yes.</p> <p>8 Q. Compounds of Formula (D) just refers to</p> <p>9 Imbruvica, right?</p> <p>10 A. Yes.</p> <p>11 Q. So example 7 is limited to Imbruvica?</p> <p>12 MS. DANEK: Object to form.</p> <p>13 THE WITNESS: Clinical trial results are</p> <p>14 with ibrutinib in this section.</p> <p>15 BY MS. PATEL:</p> <p>16 Q. And no other BTKI is discussed in example</p> <p>17 7, right?</p> <p>18 A. There's no clinical data that I know of in</p> <p>19 example 7 other than ibrutinib.</p> <p>20 Q. And are there other BTKIs discussed there</p> <p>21 that you're aware of?</p> <p>22 A. No.</p>                                                                                                                                                                                                          | <p>Page 112</p> <p>1 support your conclusion that the specification</p> <p>2 teaches how to identify a therapeutically effective</p> <p>3 amount, right?</p> <p>4 A. I agree that's what I cite in the section,</p> <p>5 yes.</p> <p>6 Q. So this example discloses that a</p> <p>7 therapeutically effective dose of ibrutinib can be</p> <p>8 identified by measuring BTK occupancy during a</p> <p>9 clinical trial, right?</p> <p>10 A. Yes.</p> <p>11 Q. You were involved in some trials</p> <p>12 investigating Imbruvica, right?</p> <p>13 A. Yes.</p> <p>14 Q. Were you involved in this one?</p> <p>15 A. No.</p> <p>16 Q. Okay. Let's take a look at column 136,</p> <p>17 starting at line 23. Let me know when you see that.</p> <p>18 A. Okay.</p> <p>19 Q. So that first sentence there states that</p> <p>20 "Cohorts of six patients each receive a compound of</p> <p>21 Formula (D), which you agree is Imbruvica, at 1.25,</p> <p>22 2.5, 5.0, 12.5 and 17.5 milligrams per kilogram per</p>                          |
| <p>Page 111</p> <p>1 Q. And example 7 is what you rely on to</p> <p>2 demonstrate that the specification teaches how to</p> <p>3 identify a therapeutically effective amount or dose,</p> <p>4 right?</p> <p>5 MS. DANEK: Objection, form.</p> <p>6 THE WITNESS: Example 7, yes, is what I</p> <p>7 cite as a reference for how to use -- it mentions</p> <p>8 occupancy and to come up with a dose.</p> <p>9 BY MS. PATEL:</p> <p>10 Q. So example 7 is what you rely on to</p> <p>11 demonstrate that the specification teaches how to</p> <p>12 identify a therapeutically effective amount, right?</p> <p>13 MS. DANEK: Objection, form.</p> <p>14 THE WITNESS: I think it's important to</p> <p>15 note that the totality of the specification informs</p> <p>16 the treatment using ibrutinib. But example 7, yes,</p> <p>17 is an example that discusses the BTKI.</p> <p>18 BY MS. PATEL:</p> <p>19 Q. Sure. But this is what you rely on.</p> <p>20 A. This is what I reference is how I would</p> <p>21 phrase it.</p> <p>22 Q. It's what you cite in that paragraph to</p> | <p>Page 113</p> <p>1 day until MTD is established."</p> <p>2 MS. DANEK: Objection, form.</p> <p>3 THE WITNESS: I see that here, yes.</p> <p>4 BY MS. PATEL:</p> <p>5 Q. And MTD means maximum tolerated dose,</p> <p>6 right?</p> <p>7 A. Yes.</p> <p>8 Q. And that refers to the highest dose that</p> <p>9 you could administer of a compound that does not</p> <p>10 cause unacceptable side effects, right?</p> <p>11 A. Yes.</p> <p>12 Q. What are some examples of such</p> <p>13 unacceptable side effects?</p> <p>14 A. For treatments in general or for BTK</p> <p>15 inhibitors at this time in 2011?</p> <p>16 Q. BTK inhibitors at this time in 2011.</p> <p>17 A. So I think it's important to contextualize</p> <p>18 2011 because if you think about chemoimmunotherapy,</p> <p>19 which is our standard, there are a lot of potential</p> <p>20 side effects and toxicities. And so it's</p> <p>21 difficult -- that would be infections, that would be</p> <p>22 myelosuppression, so suppression of the bone marrow</p> |

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| <p>1 function and pancytopenias, inability to give<br/>2 therapies because of really effects on the bone<br/>3 marrow and bone marrow health. This is not<br/>4 exhaustive again, things like, you know, admissions<br/>5 for infection.<br/>6 So that was kind of -- that was the<br/>7 standard at the time and so it wasn't uncommon to see<br/>8 very high rates of some of the things I mentioned.<br/>9 And so that was really the kind of the benchmark<br/>10 paradigm at the time of 2011 was looking for some of<br/>11 these severe toxicities. And if you look at some of<br/>12 the most effective therapies at the time with<br/>13 chemoimmunotherapy, they could -- you know, CLL is a<br/>14 disease of -- typically a disease of the elderly, but<br/>15 many of the elderly were even not candidates for the<br/>16 most effective therapy due to its toxicities.<br/>17 So I mention that just to put it in<br/>18 context because, you know, what we accept in one<br/>19 category of treatment may not be something we accept<br/>20 in another category of treatment or what we accept in<br/>21 -- one treatment setting may be different in another<br/>22 treatment setting or different in one population of</p> | <p>Page 114</p> <p>1 THE WITNESS: Again, it's context and this<br/>2 initial trial does inform that, but the specification<br/>3 here really informs the development of other BTK --<br/>4 irreversible BTK inhibitors.<br/>5 And I think importantly, you know, in this<br/>6 case, even though there was a broad range of doses<br/>7 indicated using this assay at low doses, there were<br/>8 higher -- you know, there was BTK occupancy. So I<br/>9 think it was realized that it didn't need to go up to<br/>10 the -- to the MTD.<br/>11 BY MS. PATEL:<br/>12 Q. So like you said, there are five doses<br/>13 listed here, right?<br/>14 MS. DANEK: Objection, mischaracterizing<br/>15 the document.<br/>16 THE WITNESS: Six. I actually count six<br/>17 listed.<br/>18 BY MS. PATEL:<br/>19 Q. You're saying there are six doses listed?<br/>20 A. That's what I count.<br/>21 Q. Right. So 1.25, 2.5, 5.0, 8.3, 12.5 and<br/>22 17.5, right?</p>                                        |
| <p>1 the other. So I just think that's important to keep<br/>2 in mind. But those would be examples of things we<br/>3 might be looking for and anything where it impacted<br/>4 the therapeutic efficacy for the patient.<br/>5 Q. So here in example 7 -- so example 7<br/>6 indicates that when determine a therapeutically<br/>7 effective dose for Imbruvica, the protocol considered<br/>8 unacceptable side effects, right?<br/>9 MS. DANEK: Objection, form.<br/>10 THE WITNESS: So as is the case for any<br/>11 Phase 1 study, that was how the trial was designed<br/>12 starting with the dose range. And traditionally that<br/>13 idea of MTD really applied to cytotoxic<br/>14 chemoimmunotherapy and so this was -- this is baked<br/>15 into all Phase 1 clinical trials at the time.<br/>16 BY MS. PATEL:<br/>17 Q. Right. And this protocol that's baked<br/>18 into all Phase 1 clinical trials at the time is what<br/>19 you rely on to support your position that the<br/>20 specification teaches how to identify a<br/>21 therapeutically effective amount, right?<br/>22 MS. DANEK: Objection to form.</p>                                                                                                       | <p>Page 115</p> <p>1 A. Yes.<br/>2 Q. Six different doses are listed here. So<br/>3 does that mean each cohort is assigned one of the six<br/>4 doses?<br/>5 A. Each patient in the cohort? No.<br/>6 Q. No, that wasn't my question.<br/>7 A. Okay.<br/>8 Q. Is each separate cohort assigned a<br/>9 different dosage amount?<br/>10 A. That's -- that is how it's designed, yes.<br/>11 You would enroll at the lowest dose cohort a certain<br/>12 number of patients and look for toxicities.<br/>13 Q. Okay.<br/>14 A. And then you would do a stepwise approach.<br/>15 And then assuming you're not seeing any MTD, you<br/>16 know, maximum tolerated dose, you would potentially<br/>17 go up to the highest dose.<br/>18 Q. Okay. And here it says that each cohort<br/>19 had six people, right?<br/>20 A. Seeing the way it's designed, it could<br/>21 have up to six patients based on the toxicity design<br/>22 and using -- using the number of DLTs to define</p> <p>Page 117</p> |

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| <p>1 whether you go up to the next dose. And that's</p> <p>2 pretty --</p> <p>3 Q. Do you see that first sentence we just</p> <p>4 read? Cohorts of six patients each receive a</p> <p>5 compound of Formula (D) at 1.25, 2.5, 5.0, 8.3, 12.5</p> <p>6 and 17.5.</p> <p>7 Do you see that?</p> <p>8 A. I do.</p> <p>9 Q. So I read that to mean that each cohort</p> <p>10 has six patients in it. Do you read that any</p> <p>11 differently?</p> <p>12 A. You are correct, yes. You are correct.</p> <p>13 It's designed so you enroll six and you use that six</p> <p>14 to define the toxicity, yes.</p> <p>15 Q. So you could have ultimately 36</p> <p>16 different -- 36 total people that are enrolled in</p> <p>17 this trial, right? That would be six cohorts of six</p> <p>18 people each, right?</p> <p>19 MS. DANEK: Object to form.</p> <p>20 THE WITNESS: Yes, if you enrolled all the</p> <p>21 cohorts, you could have six patients you could -- it</p> <p>22 appears based on what's written here, you would have</p>                                                            | <p>Page 118</p> <p>1 start with the first cohort, is that right?</p> <p>2 MS. DANEK: Objection, form.</p> <p>3 THE WITNESS: Yeah. I mean, that's --</p> <p>4 it's not that scientific, but yeah, you could.</p> <p>5 BY MS. PATEL:</p> <p>6 Q. Okay. And do you know if that's what</p> <p>7 occurred here?</p> <p>8 A. I don't know the inner workings of how</p> <p>9 they did slot assign -- or slot allotment.</p> <p>10 Q. Not slot allotment. Do you know if they</p> <p>11 identified 36 people who would be part of the</p> <p>12 study -- at the start of the study?</p> <p>13 A. I don't know. But typically, to put</p> <p>14 further context on that, what would happen is if, you</p> <p>15 know, you would put people on the 1.25 and then you</p> <p>16 would start a waiting list for the next cohort and</p> <p>17 the next cohort and the next cohort.</p> <p>18 So there could have been 25 people on that</p> <p>19 waiting list. There could have been 200 on that</p> <p>20 waiting list, depending on how many sites where it</p> <p>21 was open and how accrual was going and things like</p> <p>22 that.</p> <p>Page 120</p>                                                                                                                                                                          |
| <p>1 36 patients.</p> <p>2 BY MS. PATEL:</p> <p>3 Q. Would you recruit all -- identify or</p> <p>4 recruit all 36 people at the start of the study or</p> <p>5 would you do it on a rolling basis?</p> <p>6 A. Well, you would identify patients for the</p> <p>7 study, but you couldn't enroll the next cohort until</p> <p>8 one cohort had closed.</p> <p>9 Q. Okay. So you would -- sorry, did you</p> <p>10 finish your answer?</p> <p>11 A. I was just going to say you could enroll</p> <p>12 on the first dose level. You couldn't enroll on the</p> <p>13 second dose level until the parameters for the first</p> <p>14 dose level had been reached.</p> <p>15 Q. Right. And so when you use the word</p> <p>16 "enroll," you mean you couldn't start patients on the</p> <p>17 next dose level until the parameters of the first</p> <p>18 dose level had been achieved, right?</p> <p>19 A. Yes.</p> <p>20 Q. But you could -- and it sounds like that</p> <p>21 is what occurs -- identify the 36 people that would</p> <p>22 be a part of the subsequent cohorts before you even</p> | <p>Page 119</p> <p>1 Q. Okay. What is the process of identifying</p> <p>2 people to put into a cohort?</p> <p>3 A. So typically, if you have a multicenter</p> <p>4 study, you would -- I would see a patient and I would</p> <p>5 have the study open and I would say this patient</p> <p>6 needs treatment and I would identify the patient,</p> <p>7 notify the sponsor that I had a patient that needed</p> <p>8 treatment and I wanted to enroll the patient on the</p> <p>9 study. And the sponsor would tell me either yes, we</p> <p>10 have a slot or no, we don't have a slot.</p> <p>11 Q. So in this situation, the sponsor is the</p> <p>12 one that is pulling together the patients that would</p> <p>13 be part of the study, is that right?</p> <p>14 A. They are -- in this situation, it's really</p> <p>15 true for all studies that are sponsor-initiated</p> <p>16 studies, in my experience, is that especially if</p> <p>17 there's an early phase study where enrollment is what</p> <p>18 we would call competitive because they only have so</p> <p>19 many slots, yes, you would contact the sponsor and</p> <p>20 the sponsor ultimately has -- has a list of patients</p> <p>21 and they may or may not offer up slots when the slots</p> <p>22 are unavailable at the time.</p> <p>Page 121</p> |

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| <p>1 Q. Okay. And are there certain inclusion<br/>2 criteria that a patient would have to satisfy to<br/>3 become part of the study?<br/>4 A. Yes.<br/>5 Q. And who designs those inclusion criteria?<br/>6 A. It's usually the sponsor in collaboration<br/>7 with experts in the field, typically clinical<br/>8 trialists, in collaboration with the FDA.<br/>9 Q. And what types of considerations go into<br/>10 designing inclusion criteria for a particular study?<br/>11 A. It really depends on the context of the<br/>12 study again. But as we're talking about here, an<br/>13 early phase study, it's a dose-finding study,<br/>14 typically it's a relapsed to refractory population<br/>15 that has had the appropriate number of standard of<br/>16 care therapies and/or has limited treatment options.<br/>17 Q. And are there exclusion criteria as well?<br/>18 A. There are, yes.<br/>19 Q. And what goes into, you know, identifying<br/>20 exclusion criteria for a particular study?<br/>21 A. Off the top of my head, these inclusion<br/>22 and exclusion criteria are linked, right? For</p>                                                                                                        | <p>Page 122</p> <p>1 signed to the sponsor that included all the<br/>2 supporting documents from my assessment. And then if<br/>3 there was a slot available, they would sign off on<br/>4 eligibility. That is true. They would have the<br/>5 final signoff on eligibility.<br/>6 If they had concerns, they would contact<br/>7 me and we would discuss the specific concerns for<br/>8 that particular patient.<br/>9 Q. Okay. And so when it comes to a list of<br/>10 individuals that the sponsor would be pulling from,<br/>11 that list is essentially created by doctors who are<br/>12 treating patients and who pass along those patients'<br/>13 eligibility packages to add to the wait list, is that<br/>14 right?<br/>15 A. Essentially, yes. I mean, the eligibility<br/>16 may not have been confirmed yet, right. So the<br/>17 patient -- the sponsor -- and of course this is all<br/>18 de-identified. The sponsor may have a subject number<br/>19 from a subject site -- or, excuse me, from a site<br/>20 number. And then, if they develop a slot, then you<br/>21 bring the patient back to sign consent, then you<br/>22 screen for eligibility, then you send it to the</p> <p>Page 124</p> |
| <p>1 example, if they didn't meet that threshold for the<br/>2 number of prior therapies, they would be ineligible.<br/>3 If they had certain organ dysfunction, they wouldn't<br/>4 be eligible. If they had active infection, they<br/>5 wouldn't be eligible. If they had a poor performance<br/>6 status, they wouldn't be eligible.<br/>7 These are just a number of examples and<br/>8 that is inclusion criteria, again, that has been<br/>9 looked at by the FDA.<br/>10 Q. Okay. And so when -- here in example 7,<br/>11 when coming up with the six individuals, the six<br/>12 patients who would be a part of cohort 1, the sponsor<br/>13 would need to look at each potential candidate on the<br/>14 wait list and assess whether they meet these<br/>15 exclusion or inclusion criteria and then from there<br/>16 decide whether they would be allotted a spot in<br/>17 cohort 1, is that right?<br/>18 A. Basically the process would be me as the<br/>19 local investigator, I would evaluate my patient, I<br/>20 would evaluate the eligibility criteria, I would<br/>21 determine if they were eligible or not. And then I<br/>22 would send along an eligibility packet that I had</p> <p>Page 123</p> | <p>1 sponsor.<br/>2 Q. How long does it take to recruit a single<br/>3 person to a cohort from the moment that the doctor<br/>4 sees the patient and assesses that they might be a<br/>5 good candidate to the moment that they are<br/>6 administered the drug?<br/>7 A. There's no such standard, right, so -- but<br/>8 what I can tell you typically often is the case,<br/>9 if -- when you're going from signing consent to<br/>10 enrolling the patient, typically you have a month for<br/>11 that screening period to take place. So you can<br/>12 enroll -- if the patient needs therapy soon, you<br/>13 could potentially enroll them on a Monday and treat<br/>14 them by the end of the week.<br/>15 If the patient can wait and logistically<br/>16 you need to take longer to do the screening studies<br/>17 like CAT scans and evaluations, you know, you may<br/>18 have decided to use up that whole 28-day window.<br/>19 There are a lot of, you know, personal circumstances<br/>20 and things that go into that -- those specifics. But<br/>21 oftentimes the screening window is about a month, so<br/>22 you have a month to complete the screening studies.</p> <p>Page 125</p>              |

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| <p>1 Q. How many individuals are involved in the<br/>2 process of screening a single patient?<br/>3 A. That's very -- that would be very<br/>4 site-specific.<br/>5 Q. Okay. But it sounds like you would need<br/>6 at least the doctor who sees that patient and then<br/>7 someone to screen that patient and then the ultimate<br/>8 sponsor to evaluate their package, is that right?<br/>9 A. I mean, sometimes those can be all the<br/>10 same person, but -- other than the sponsor, right.<br/>11 So, you know, there may be some practices where the<br/>12 doctor enrolls the patient, you know, and then orders<br/>13 all the tests for screening and then enrolls the<br/>14 patient. There may be other places where they have<br/>15 study coordinators to do that job.<br/>16 Q. Okay. And we discussed how the protocol<br/>17 here in example 7 contemplates a potential total of<br/>18 36 people, but it actually could be more than that,<br/>19 right, if the dosing levels could be increased beyond<br/>20 17.5, right?<br/>21 A. It does. And it highlights, I think, how<br/>22 novel it was at the time to have an assay -- as</p> | <p>Page 126</p> <p>1 related to how they chose these. But there's<br/>2 typically a dose range that's low and then one that<br/>3 goes -- and then you have increasing dose levels<br/>4 because the low dose, you know, it's balancing that<br/>5 toxicity with efficacy.<br/>6 Q. What factors are considered when selecting<br/>7 the doses?<br/>8 A. It would be the characteristics of the<br/>9 drug. So there may be preclinical data looking at<br/>10 the on-target occupancy. There may be preclinical<br/>11 data to help identify or evaluate pharmacokinetics.<br/>12 There may be solubility questions, all of the things,<br/>13 but this is very standard for drug development.<br/>14 Q. When you say preclinical data, what<br/>15 specifically are you referring to?<br/>16 A. That could be in vitro cellular models,<br/>17 that could be animal data. It could be -- and then<br/>18 you could have stage zero clinical studies which are<br/>19 giving doses that are felt to be subtherapeutic to<br/>20 understand the PK. Those would be examples.<br/>21 Q. Could you select doses for this kind of<br/>22 study in example 7 without doing any of this testing</p> <p>Page 128</p> |
| <p>1 described in the specification -- to have an assay<br/>2 that you could actually, you know, see what doses<br/>3 were effectively inhibiting BTK. Because prior to<br/>4 this time in the CLL space, that's not how studies<br/>5 were designed. They were designed with cytotoxic<br/>6 chemotherapy really in escalating doses until you<br/>7 reached an MTD.<br/>8 Q. Do you know how each of the six doses in<br/>9 example 7 were chosen?<br/>10 A. Not specifically.<br/>11 Q. Are these standard doses that every dosing<br/>12 study starts with?<br/>13 A. No.<br/>14 Q. How are doses typically selected for a<br/>15 study like this?<br/>16 A. It really depends on the compounds. And<br/>17 so there are a series of tests that are very standard<br/>18 required for drug development in the FDA where<br/>19 different doses that are deemed necessary to inhibit<br/>20 the target in this case or have efficacy, and it's<br/>21 going to be so variable.<br/>22 So I can't speculate on doses at all</p>                                                                                                                               | <p>Page 127</p> <p>1 that you described?<br/>2 A. So I think in this study, that -- so there<br/>3 are a couple of distinctions here. One is what's<br/>4 required. And so all the things I mentioned are<br/>5 required by the FDA, coming up with these dose ranges<br/>6 and things like that, okay? So that is what's<br/>7 required. You'd submit your package to the FDA to<br/>8 get your IND so you can treat patients. So there's<br/>9 that element.<br/>10 And in this case, prior to the<br/>11 characteristics outlined in the specification, also<br/>12 it was needed to design a study like this because<br/>13 there wasn't that same experience with identifying<br/>14 MTD. Was MTD an issue. But that's very different<br/>15 than sort of the specifications outlined that we're<br/>16 talking about.<br/>17 The specifications here are that is the<br/>18 drug therapeutic or is it therapeutically effective.<br/>19 And that's a very different requirement based on the<br/>20 studies you would have to do. That's not a<br/>21 regulatory requirement.<br/>22 And it's my opinion that what's described</p> <p>Page 129</p>                                                       |

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| <p>1 in the specification prevents the blueprints and the<br/>2 knowledge so subsequent trials would have a leg up<br/>3 because they would understand that, you know, if you<br/>4 target -- if you can simply show that you're going to<br/>5 irreversibly inhibit BTK, that you're going to have<br/>6 an assay that has an on-target effect, that if you<br/>7 can show that, you're going to effectively treat<br/>8 CLL/SLL.</p> <p>9 So the doses may be totally different<br/>10 based on the properties of the drug, meaning that if<br/>11 it's a more potent drug, it's going to require less<br/>12 of an overall milligram dose versus a less potent<br/>13 drug, which will require a higher milligram dose.<br/>14 But it's a question of dosing and not a question of,<br/>15 you know, really more than that because it's a<br/>16 question of you have an assay. Are you inhibiting<br/>17 BTK, yes or no, at a given dose. And if you can show<br/>18 that, you know you're going to be inhibiting BTK.</p> <p>19 And then further the specification shows<br/>20 that if you effectively inhibit BTK, it leads to<br/>21 therapeutic efficacy.</p> <p>22 MS. DANEK: Counsel, if there's a good</p> | Page 130 | <p>1 A. Similarly, it could affect the dose that<br/>2 would inhibit BTK.</p> <p>3 Q. Would IC50 values be something that could<br/>4 likewise affect the dose that would inhibit BTK?</p> <p>5 A. Yes.</p> <p>6 Q. Is there anything else that could impact<br/>7 the doses that you would select when conducting a<br/>8 study like the study in example 7?</p> <p>9 A. I think we touched on the things that<br/>10 could factor into dosing. But again, off the top of<br/>11 my head, I'm not thinking of any others at the<br/>12 moment.</p> <p>13 Q. Is it always six doses that are selected<br/>14 in a study like the study in example 7 or can it be<br/>15 less or more?</p> <p>16 A. It can be less or more.</p> <p>17 Q. Does the number of doses depend on the<br/>18 compound that's being administered?</p> <p>19 A. Generally speaking, yes. But also in the<br/>20 context of, you know, in the context of the -- as the<br/>21 specification teaches in this case, it's the<br/>22 development of that on-target assay that can really</p>                                                                   | Page 132 |
| <p>1 time to stop in the next couple of minutes so we can<br/>2 grab a -- we could grab lunch quickly to keep moving,<br/>3 but just wanted to check where you were.</p> <p>4 MS. PATEL: One moment. Yeah, can we keep<br/>5 going for about 15 more minutes and then maybe we can<br/>6 wrap for lunch?</p> <p>7 Does that work for you, Dr. Spurgeon?</p> <p>8 MS. DANEK: Is 15 minutes okay for lunch?</p> <p>9 Are you all right? Let's go.</p> <p>10 MS. PATEL: Okay.</p> <p>11 BY MS. PATEL:</p> <p>12 Q. You mentioned certain preclinical tests.<br/>13 You mentioned evaluating solubility. How would that<br/>14 affect the dose that you would use in a study like<br/>15 example 7? Or the doses you would use in a study<br/>16 like example 7?</p> <p>17 A. So it could impact the dose that is<br/>18 available to effectively inhibit BTK.</p> <p>19 Q. And you mentioned pharmacodynamics and<br/>20 pharmacokinetics. How would that impact the dose<br/>21 that you would -- the doses that you would use in an<br/>22 example -- in a study like example 7?</p>                                                                                                                                    | Page 131 | <p>1 inform the number of doses for future similar class<br/>2 drugs.</p> <p>3 Q. So do you mean that because there were six<br/>4 doses selected here in example 7, that same number of<br/>5 doses would be selected for future similar class<br/>6 drugs?</p> <p>7 A. No. I can't speculate on the number of<br/>8 doses that would have been required, dose ranges, for<br/>9 any given compound. It's simply does the drug<br/>10 effectively inhibit BTK. And if those invivo --<br/>11 those translational studies in the patient show that<br/>12 it effectively inhibits BTK, then it would satisfy<br/>13 the specification mentioned in the claims. So I<br/>14 think it's impossible to know that hypothetical dose<br/>15 range.</p> <p>16 Q. So you say, you know, as long as you have<br/>17 the translational studies in the patient showing that<br/>18 it effectively inhibits BTK, then that would be<br/>19 enough to identify the dose?</p> <p>20 A. So again, I want to separate a couple of<br/>21 things here. There's dose related to FDA, approval,<br/>22 safety, all of that. That's one element.</p> | Page 133 |

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| <p>1 But the other element that I believe is</p> <p>2 more appropriate here is, is it therapeutically</p> <p>3 effective for treating CLL and SLL? And the</p> <p>4 answer -- so in that scenario, the answer is yes. If</p> <p>5 you are effectively targeting BTK irreversibly with a</p> <p>6 ibrutinib-like BTK inhibitor, then, yes, that's what</p> <p>7 you would need to see.</p> <p>8 Q. We're -- but we're talking right now about</p> <p>9 a therapeutically effective amount, right?</p> <p>10 A. We are. And that would be a</p> <p>11 therapeutically effective amount.</p> <p>12 Q. Okay. And how would you -- and you would</p> <p>13 identify the therapeutically effective amount by</p> <p>14 following what's described here in example 7, right?</p> <p>15 MS. DANEK: Objection, form.</p> <p>16 THE WITNESS: If I had the specification,</p> <p>17 it would help me inform what I needed to do to</p> <p>18 identify the therapeutically effective amount.</p> <p>19 BY MS. PATEL:</p> <p>20 Q. And it's your opinion that what you would</p> <p>21 do is what's described in example 7 of the</p> <p>22 specification, correct?</p> | <p>Page 134</p> <p>1 Q. And in order to measure the occupancy, you</p> <p>2 would need to first administer that BTKI to the</p> <p>3 patient, right, and then draw their blood and run the</p> <p>4 assay, correct?</p> <p>5 A. That is correct.</p> <p>6 Q. So at what dose would you administer the</p> <p>7 BTKI to the patient before you draw their blood and</p> <p>8 run the assay?</p> <p>9 A. I don't know the specific dose.</p> <p>10 Q. Why not?</p> <p>11 A. Because I don't have access to the --</p> <p>12 ready access or complete access to the preclinical</p> <p>13 data.</p> <p>14 MS. PATEL: Why don't we go ahead and take</p> <p>15 a break.</p> <p>16 THE VIDEOGRAPHER: Off the record at 12:55</p> <p>17 p.m.</p> <p>18 (Whereupon, at 12:55 p.m., the deposition</p> <p>19 in the above-entitled matter was recessed, to</p> <p>20 reconvene at 1:22 p.m., this same day.)</p> <p>21</p> <p>22</p> |
| <p>1 MS. DANEK: Objection, form.</p> <p>2 THE WITNESS: It's my opinion that</p> <p>3 specifically, if you had a drug that irreversibly</p> <p>4 inhibited BTK and you could show that in the patient</p> <p>5 using techniques as described in example 7, that show</p> <p>6 on-target occupancy in an irreversible manner and</p> <p>7 show disruption of BTK-mediated cellular processes,</p> <p>8 then yes, that would be incredibly helpful. That's</p> <p>9 what you would need to have to define what doses you</p> <p>10 were going to do.</p> <p>11 BY MS. PATEL:</p> <p>12 Q. And so to show that in the patient, you</p> <p>13 would have to actually administer that BTKI to the</p> <p>14 patient -- to a patient, right?</p> <p>15 A. Yes.</p> <p>16 Q. At what dose would you administer the BTKI</p> <p>17 to the patient?</p> <p>18 A. Well, based on what the specification</p> <p>19 teaches, I would administer the dose that caused BTK</p> <p>20 inhibition based on the assay and based on the</p> <p>21 specification, so that had greater than 90 percent</p> <p>22 BTK occupancy in PBMCs. That's the dose I would use.</p>       | <p>Page 135</p> <p>1 AFTERNOON SESSION</p> <p>2 (1:22 p.m.)</p> <p>3 THE VIDEOGRAPHER: Back on the record at</p> <p>4 1:22 p.m.</p> <p>5 EXAMINATION BY COUNSEL FOR PETITIONERS (RESUMED)</p> <p>6 BY MS. PATEL:</p> <p>7 Q. Dr. Spurgeon, did you speak with your</p> <p>8 counsel during the break today?</p> <p>9 A. No.</p> <p>10 Q. Have you spoken with your counsel during</p> <p>11 any of the breaks today?</p> <p>12 A. I've said hello. I mean, I've had a</p> <p>13 conversation, but nothing related to the case.</p> <p>14 Q. Okay.</p> <p>15 A. Is that what you're asking?</p> <p>16 Q. Okay. So do you still have the patent in</p> <p>17 front of you, Dr. Spurgeon?</p> <p>18 A. I do, yes.</p> <p>19 Q. If you flip back to example 7. Let me</p> <p>20 know when that's in front of you.</p> <p>21 A. Okay.</p> <p>22 Q. Can you just take a look at column 136,</p>                                    |
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| <p>1 lines 23 through 41 and let me know when you're done?</p> <p>2 A. Twenty-three through 31, you said?</p> <p>3 Q. Forty-one.</p> <p>4 A. Forty-one. Okay.</p> <p>5 Q. So I just want to walk through that</p> <p>6 paragraph with you. So in that paragraph, it defines</p> <p>7 a single cycle for a single cohort as being 28 days</p> <p>8 of treatment plus seven days of rest, is that right?</p> <p>9 A. Yes.</p> <p>10 Q. So a single cycle for one cohort lasts</p> <p>11 five weeks, right?</p> <p>12 A. Yes.</p> <p>13 Q. And so the paragraph describes taking the</p> <p>14 first cohort of six patients, administering Imbruvica</p> <p>15 daily for 28 days at a dose of 1.25, right?</p> <p>16 A. Yes.</p> <p>17 Q. And then those six patients rest for seven</p> <p>18 days, right?</p> <p>19 A. Yes.</p> <p>20 Q. And then during that first cycle, each of</p> <p>21 the six patients come in to have their blood drawn on</p> <p>22 five different days, right, day 1, 2, 8, 15 and 29?</p>                                                   | <p>Page 138</p> <p>1 inhibition of BCR signaling, right?</p> <p>2 A. I put it a little differently. It's</p> <p>3 not -- it's the effect of that given drug level.</p> <p>4 Q. Okay. Understood. What is considered</p> <p>5 maximal occupancy?</p> <p>6 A. I can't speculate based on what's</p> <p>7 described here, what's determined maximal occupancy</p> <p>8 because it's not determined here. What I can say is</p> <p>9 that, you know, one could envision a range of</p> <p>10 possible occupancies, but I don't know the</p> <p>11 characteristics well enough of the assay to truly</p> <p>12 define what that looks like other than the results</p> <p>13 demonstrate that occupancy did take place and it did</p> <p>14 result in therapeutic efficacy.</p> <p>15 Q. Around what amount of occupancy would you</p> <p>16 want to see to feel confidence that the therapeutic</p> <p>17 results in efficacy?</p> <p>18 MS. DANEK: Objection, form.</p> <p>19 THE WITNESS: I think as related to the</p> <p>20 specification in this clinical trial, it was an</p> <p>21 investigation. So I don't think we knew what that</p> <p>22 level would be or the specification or what the</p> |
| <p>1 A. Yes.</p> <p>2 Q. And then on each of those days, BCR</p> <p>3 biomarker assays are run on the blood samples, right?</p> <p>4 A. Yes.</p> <p>5 Q. And those are two assays, right, one that</p> <p>6 measures occupancy and one that measures inhibition,</p> <p>7 correct?</p> <p>8 A. Yes.</p> <p>9 Q. What is -- oh. And you run both of those</p> <p>10 assays to determine what drug levels are required to</p> <p>11 achieve maximal occupancy of BTK and maximal</p> <p>12 inhibition of BCR signaling, right?</p> <p>13 A. I'm sorry, in example 7, can you show me</p> <p>14 where it says maximal occupancy or maximal</p> <p>15 inhibition?</p> <p>16 Q. Yeah. Look at -- sorry -- 137, line 22,</p> <p>17 it talks about the PD biomarkers and it says these</p> <p>18 assays determine what drug levels are required --</p> <p>19 A. Yes. I see it, yes. Okay.</p> <p>20 Q. Okay. So you agree that both those assays</p> <p>21 are done to determine what drug levels are required</p> <p>22 to achieve maximal occupancy of BTK and maximal</p> | <p>Page 141</p> <p>1 clinical trial says knew what that would be.</p> <p>2 So I don't think at the time in 2011, when</p> <p>3 this was occurring, that there was any sort of</p> <p>4 specific number in mind. But the results showed that</p> <p>5 it inhibited -- or it had occupancy of greater than</p> <p>6 90 percent and that it inhibited the BCR-mediated</p> <p>7 cellular processes.</p> <p>8 BY MS. PATEL:</p> <p>9 Q. What does an occupancy of 90 percent tell</p> <p>10 you about efficacy?</p> <p>11 A. Prior to the specification, it wouldn't</p> <p>12 have told us much. But because of the specification,</p> <p>13 it tells us a lot.</p> <p>14 Q. And what is it that it tells us?</p> <p>15 A. It tells us that if you inhibit BTK</p> <p>16 irreversibly with ibrutinib or ibrutinib-like</p> <p>17 compounds, that you will see clinical activity in</p> <p>18 therapeutic efficacy.</p> <p>19 Q. I'm just trying to understand which one</p> <p>20 comes first. Does occupancy confirm efficacy or --</p> <p>21 MS. DANEK: Objection, form.</p> <p>22 BY MS. PATEL:</p>                                                                                                  |

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| <p>1 Q. -- or does clinical efficacy at a certain<br/>2 occupancy determine -- strike that.<br/>3 Okay. Do you know what's considered<br/>4 maximal inhibition?<br/>5 A. I don't know specifically from the<br/>6 specification. One would assume max inhibition is<br/>7 fully inhibiting the process 100 percent/ but within<br/>8 any assay, you're going to have a range there, the<br/>9 confidence interval of what that range could be,<br/>10 within the operating characteristics of the assay<br/>11 most likely, but I can't speak to the specifics<br/>12 related to that assay.<br/>13 Q. Can you walk me through what happens from<br/>14 the point where a patient in cohort 1 comes in on<br/>15 cycle day 2 to have their blood drawn all the way to<br/>16 the point where you have the data you need from the<br/>17 assays.<br/>18 MS. DANEK: Objection, form.<br/>19 THE WITNESS: Since I don't have the lab<br/>20 manual for the protocol, the clinical trial, I can't<br/>21 be too granular in walking you through that.<br/>22 BY MS. PATEL:</p> | <p>Page 142</p> <p>1 A. Not specifically, but my -- I would think<br/>2 they actually don't take that long.<br/>3 Q. But you haven't done one of these<br/>4 yourself?<br/>5 A. I have not done these specific assays. I<br/>6 have done assays where you stimulate the B-cell<br/>7 receptor with anti-IGM and then you assay cell<br/>8 surface -- then you do -- subject the cells to flow<br/>9 cytometry. And that generally is a fairly<br/>10 straightforward test.<br/>11 Q. Did you speak with anyone who's ran one of<br/>12 these assays before?<br/>13 A. Specifically for BTK inhibitors?<br/>14 Q. Yes.<br/>15 A. No.<br/>16 Q. So you yourself, in forming your opinions,<br/>17 were not aware of how long it takes to run each of<br/>18 these assays, right?<br/>19 A. I have not run those specific assays, but,<br/>20 again, I've run a very similar assay by using<br/>21 anti-IGM to stimulate cells. Typically you don't<br/>22 have to do that for very long. And then subjecting</p> <p>Page 144</p>                                                                                              |
| <p>1 Q. Well, can you provide at a high level what<br/>2 occurs?<br/>3 MS. DANEK: Objection, form.<br/>4 THE WITNESS: I mean, I think what I can<br/>5 provide is what's stated here, is that the patient<br/>6 has been dosed with, in this case, ibrutinib and then<br/>7 a sample is drawn four to six hours later, a<br/>8 peripheral blood sample in this case. And that same<br/>9 thing happens on day two and the other days mentioned<br/>10 here that we already talked about, days 1, 2, 8, 15<br/>11 and 29 during cycle one, and that those<br/>12 pharmacodynamic parameters or markers, excuse me, are<br/>13 tested based on those lab draws.<br/>14 BY MS. PATEL:<br/>15 Q. And the assays are run on the blood<br/>16 samples, right?<br/>17 A. Yes.<br/>18 Q. Okay. Have you ever done one of these<br/>19 assays before?<br/>20 A. Not these specific assays, no.<br/>21 Q. Are you aware of how long each of these<br/>22 assays takes?</p>                                                                                                           | <p>Page 143</p> <p>1 the cells to flow cytometry, which also is a<br/>2 relatively quick test.<br/>3 But there's a lot -- it's not<br/>4 necessarily -- there's a lot of different contexts,<br/>5 meaning that you could batch the samples, you could<br/>6 do them all at once, you could do them in real time.<br/>7 There's a number of different ways they could be<br/>8 done, so it's difficult to quantify. But what I can<br/>9 tell you is it's not extensive and it's reasonable.<br/>10 Q. But you yourself haven't confirmed how<br/>11 long it would take?<br/>12 A. I have not performed those specific tests<br/>13 as relates to BTK -- or, excuse me, as it relates to<br/>14 ibrutinib, how they did it on this study.<br/>15 Q. Okay. And then back to column 136, it<br/>16 says, "If less than or equal to 1 DLT (dose limiting<br/>17 toxicity) is observed in the cohort during cycle 1,<br/>18 escalation to the next cohort will proceed," right?<br/>19 A. Yes.<br/>20 Q. What are examples of dose limiting<br/>21 toxicity?<br/>22 A. Generally dose limiting toxicity, it</p> <p>Page 145</p> |

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| <p>1 varies from protocol to protocol and treatment to<br/>2 treatment and disease to disease. So how you define<br/>3 that's going to be different per different protocols.<br/>4 But dose limiting toxicity is something that's<br/>5 defined before you treat patients on a clinical<br/>6 trial. It's well defined on the protocol on the<br/>7 trial.<br/>8 And so as is mentioned -- as is mentioned<br/>9 in any trial, there can be these DLTs, but as an<br/>10 example, in the time with chemoimmunotherapy, because<br/>11 that was the standard that we were going off of, DLTs<br/>12 might be defined as prolonged periods of what we<br/>13 would call neutropenia with low white blood cells<br/>14 that fight infection or significant infection<br/>15 requiring hospitalization. A DLT is different<br/>16 necessarily than a side effect.<br/>17 Q. So what are some examples of DLTs in the<br/>18 context of irreversible BTK inhibitor treatments for<br/>19 CLL/SLL?<br/>20 A. So some of those DLTs are -- and again,<br/>21 this is not an exhaustive list -- but off the top of<br/>22 my head, some of these DLTs would be things that are</p>  | <p>Page 146</p> <p>1 that's the DLT period. In seeing that patient, you<br/>2 know, on a scheduled or unscheduled visit, if they<br/>3 had laboratories that met the criteria for a DLT<br/>4 based on prespecified criteria in the protocol, or if<br/>5 they had clinical findings. So let's -- again, this<br/>6 is all just theoretical. But if someone came in and<br/>7 had a new pneumonia when you saw them, so they had<br/>8 fever, shortness of breath and needed admission to<br/>9 the hospital for IV antibiotics, and if that was a<br/>10 defining DLT, then that patient would satisfy<br/>11 criteria for DLT.<br/>12 Q. So when they come in on the predetermined<br/>13 days, it's not just to draw their blood. They're<br/>14 also being evaluated for DLTs as well, is that right?<br/>15 A. They're being evaluated whether they're<br/>16 coming in or not. So sometimes a patient will come<br/>17 in to an outside hospital, to the ER with a new<br/>18 problem. And so that would also, if it meets the<br/>19 criteria, would go down as a DLT.<br/>20 So a DLT is not necessarily determined in<br/>21 real time. It's kind of assessed to see does it meet<br/>22 the protocol definition of DLT.</p> <p>Page 148</p> |
| <p>1 relevant to CLL in general. So like I mentioned,<br/>2 infection, grade 3 or higher events related to the<br/>3 drug. So typically grade 3 means severe enough to<br/>4 require hospitalization and that could include organ<br/>5 damage, that could include infection, that could<br/>6 include low blood counts, that could include<br/>7 bleeding, it could include diarrhea. But I don't<br/>8 have the definition specifically related to this<br/>9 study, how they define DLTs going into the study.<br/>10 These are all generalities.<br/>11 Q. How do you evaluate if a patient is<br/>12 experiencing a dose limiting toxicity?<br/>13 A. So much of it is how we define toxicities<br/>14 in patient getting any cancer treatment. And so it's<br/>15 a combination of laboratories and a combination of<br/>16 symptoms and a combination of signs and/or events or<br/>17 diagnoses.<br/>18 Q. So practically speaking, how do you<br/>19 identify if a particular patient in a cohort is<br/>20 experiencing dose limiting toxicities?<br/>21 A. So as related to the example here, if it's<br/>22 a 35-day window or cycle, for that first cycle,</p> | <p>Page 147</p> <p>1 Q. And so if the patient went to an outside<br/>2 hospital, how do you become aware of the DLT having<br/>3 occurred?<br/>4 A. It varies. But this is -- it's fairly --<br/>5 it's a routine thing. So we have patients that go on<br/>6 study. We'd counsel them. If there's anything that<br/>7 comes up, you call us, let us know. If they're<br/>8 admitted -- I mean, and we're constantly, you know,<br/>9 in contact and understanding. And there are<br/>10 certain -- depending on the protocol, there may be<br/>11 certain reporting requirements, too, within a certain<br/>12 amount of time, which is very standard.<br/>13 Q. So it's standard that those conducting the<br/>14 study and the patients that are part of the study are<br/>15 in constant contact?<br/>16 A. It's really standard on any patients we're<br/>17 treating, including trial patients, they're advised<br/>18 to communicate their symptoms with us and advised to<br/>19 follow up. And it's not uncommon for our team,<br/>20 whether they be on a trial or not, to give them a<br/>21 call to see how they're doing.<br/>22 Q. Are there members of the team who are</p> <p>Page 149</p>                                            |

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| <p>1 assigned particular patients to keep track of?</p> <p>2 A. It really depends on the center and the</p> <p>3 institution where the patient is being treated. What</p> <p>4 I can tell you is our practice is I have a research</p> <p>5 nurse I work with. I have a standard of care nurse I</p> <p>6 work with that's involved in the care of these</p> <p>7 patients.</p> <p>8 Q. And how many patients -- I'm sorry, that's</p> <p>9 for -- in studies and trials that are being</p> <p>10 conducted, you have a standard of care nurse and you</p> <p>11 have a research nurse?</p> <p>12 A. In the clinical trials in our practice, in</p> <p>13 the way we're set up, is that the majority of the</p> <p>14 nursing care that takes place on those patients is</p> <p>15 done by the research nurse. There may be a little</p> <p>16 that's done by the standard of care nurse, but</p> <p>17 typically the standard of care nurse is taking care</p> <p>18 of patients on standard of care therapies.</p> <p>19 Q. Okay. And so if one -- only one or no DLT</p> <p>20 is observed, then another cohort of six other</p> <p>21 patients are enrolled, right, for the next higher</p> <p>22 dose and they begin cycle 1?</p> | <p>Page 150</p> <p>1 occupancy by the drug are performed on day 1, 2, 8,</p> <p>2 15, 29 during cycle 1 and on day 1 and 15 of cycles</p> <p>3 3, 5, 7, 9 and 11."</p> <p>4 Do you see that?</p> <p>5 A. Yes, that's the area that I was inferring</p> <p>6 based on that language that it's 11 cycles, yes.</p> <p>7 Q. And why is it that they would need to come</p> <p>8 in for 11 cycles?</p> <p>9 MS. DANEK: Objection, form.</p> <p>10 THE WITNESS: Can I ask you a question?</p> <p>11 So can you clarify what is unusual about that to you?</p> <p>12 BY MS. PATEL:</p> <p>13 Q. I don't know if it's unusual or not. I</p> <p>14 actually was wondering if that's typical that, you</p> <p>15 know, one cohort would go through 11 cycles --</p> <p>16 A. Okay.</p> <p>17 Q. -- for the second study.</p> <p>18 A. So I can't comment specifically to 11</p> <p>19 cycles, why it's 11, why it's not ongoing, why it's</p> <p>20 not six cycles. I can't comment on that. But</p> <p>21 typically it's just prespecified in the protocol.</p> <p>22 And most -- there are very few studies, especially</p>                                                                                                                       |
| <p>1 A. Correct.</p> <p>2 Q. And that second cohort will go through the</p> <p>3 same steps we just discussed, right?</p> <p>4 A. Yes.</p> <p>5 Q. And the first cohort, do they continue</p> <p>6 through additional -- multiple additional cycles at</p> <p>7 the 1.25 dose?</p> <p>8 A. In this case, yes. I say it that way</p> <p>9 because there may be other studies where patients are</p> <p>10 treated at different doses. But yes, based on this</p> <p>11 design, it appears that the study was patients would</p> <p>12 continue therapy at the dose they were assigned at</p> <p>13 the time.</p> <p>14 Q. And they would continue therapy for up to</p> <p>15 11 cycles, is that right?</p> <p>16 A. It appears it's inferred in that they come</p> <p>17 in the blood draw on cycle 11, but that's the -- it</p> <p>18 looks like here it's through cycle 11. That's what</p> <p>19 it looks like. But I don't -- unless you can point</p> <p>20 me in the specific area, I don't see that.</p> <p>21 Q. Yeah. So here it says in column 136, line</p> <p>22 28, the first full sentence begins, "Tests for BTK</p>                                                                                                    | <p>Page 151</p> <p>1 early phase studies, that are designed -- you know,</p> <p>2 there may be some biomarker studies where patients</p> <p>3 are only treated for one cycle. But the overwhelming</p> <p>4 majority of studies will continue -- you know,</p> <p>5 especially if it's -- if it's a targeted drug, things</p> <p>6 like that, it is doing continuous dosing in some</p> <p>7 capacity, it will continue treatments. But it's</p> <p>8 very -- to contextualize it further, it's very</p> <p>9 dependent on the drug being studied in the clinical</p> <p>10 trial.</p> <p>11 Q. So how does one determine how many cycles</p> <p>12 makes sense for a particular drug being studied? You</p> <p>13 mentioned continuous dosing. If the regimen for that</p> <p>14 particular drug would involve continuous dosing, then</p> <p>15 would that influence the number of cycles that would</p> <p>16 be conducted in a study like this?</p> <p>17 A. It could. I think there are a lot of</p> <p>18 factors that can go in, some practical and some</p> <p>19 clinical and some best guess.</p> <p>20 Q. What are some clinical factors that would</p> <p>21 go into it?</p> <p>22 A. So as an example, in 2011, cytotoxic</p> |

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| <p>1 chemotherapy was the norm for this disease and so</p> <p>2 we're limited on how much cytotoxic chemotherapy you</p> <p>3 can give. And so that's why you give it in fixed</p> <p>4 duration, you don't do continuous dosing, you take</p> <p>5 time off of therapy. That's the standard. And so</p> <p>6 you can't continue further on because the host</p> <p>7 can't -- the normal tissues can't tolerate it. And</p> <p>8 so there's an example of you've got a finite number</p> <p>9 of treatment cycles.</p> <p>10 Q. But if you have the option, you would opt</p> <p>11 towards more like 11 cycles like was done for</p> <p>12 Imbruvica, right?</p> <p>13 A. I couldn't specify a specific number of</p> <p>14 cycles. I think not enough was known in this Phase 1</p> <p>15 study. And that's often the case, too, in a Phase 1</p> <p>16 study. You know, as drugs get developed, they may</p> <p>17 change their duration of therapy. And so at the</p> <p>18 time, I can't speak to why they specifically chose 11</p> <p>19 cycles. I don't know.</p> <p>20 Q. Well, so now having the specification and</p> <p>21 seeing that they chose 11 cycles for example 7, in</p> <p>22 any future BTK treatments, would you recommend around</p> | <p>Page 154</p> <p>1 you're hitting the target.</p> <p>2 Q. So here, though, it was 11 cycles, right?</p> <p>3 A. It appears to be, yes.</p> <p>4 Q. And assuming that those cycles are run</p> <p>5 consecutively, that would be about 55 weeks, right?</p> <p>6 A. Yes.</p> <p>7 Q. And for each cycle after the first one,</p> <p>8 the patients would come in on days 1 and 15 for blood</p> <p>9 draws, right?</p> <p>10 A. Sorry. Say that again, please.</p> <p>11 Q. And for each cycle after cycle 1, the</p> <p>12 patients would come in for additional blood draws on</p> <p>13 days 1 and 15, right?</p> <p>14 A. On cycles 3, 5, 7 and 9.</p> <p>15 Q. Oh, on cycles 3, 5, 7 and 9 --</p> <p>16 A. And 11.</p> <p>17 Q. -- they would come -- right, and 11 --</p> <p>18 they would come in on days 1 and 15 for blood draws.</p> <p>19 And additional assays would be run, is that right?</p> <p>20 A. What additional assays? I'm sorry, I</p> <p>21 didn't catch that.</p> <p>22 Q. The same -- the biomarker assays we</p>                                                                                                                                            |
| <p>1 11 cycles?</p> <p>2 MS. DANEK: Objection, form.</p> <p>3 THE WITNESS: Not based on this. In the</p> <p>4 totality of the specification, I would recommend</p> <p>5 ongoing oral daily dosing based on the specification.</p> <p>6 BY MS. PATEL:</p> <p>7 Q. But if you wanted to determine the</p> <p>8 occupancy level, if you wanted to measure occupancy</p> <p>9 and inhibition in a future BTKI treatment, would you</p> <p>10 do that for only one cycle or would you do it for</p> <p>11 more than one cycle?</p> <p>12 MS. DANEK: Objection, form.</p> <p>13 THE WITNESS: Based on the specification,</p> <p>14 knowing what we know now because of the</p> <p>15 specification, I think one cycle would be adequate.</p> <p>16 BY MS. PATEL:</p> <p>17 Q. What about the specification gives you</p> <p>18 confidence that one cycle would be adequate?</p> <p>19 A. Because we know that the clinical activity</p> <p>20 of ibrutinib is very good with ongoing dosing and</p> <p>21 that you're inhibiting the target. So you don't need</p> <p>22 to continue to evaluate the occupancy if you know</p>                                                                                                                                       | <p>Page 155</p> <p>1 discussed earlier.</p> <p>2 A. Oh, yeah. On those --</p> <p>3 Q. Right, on those days.</p> <p>4 A. Yes.</p> <p>5 Q. Is it possible that the occupancy could</p> <p>6 change from cycle to cycle for a particular patient?</p> <p>7 A. So I think about taking that in the</p> <p>8 context of 2011, I would look at that still as</p> <p>9 therapeutic efficacy, is it therapeutically</p> <p>10 effective, yes or no. Or is it something that is</p> <p>11 therapeutically effective that over time becomes</p> <p>12 resistant to therapy like a lot of our therapeutics.</p> <p>13 Because if you're just talking about will</p> <p>14 it be therapeutically effective by hitting BTK, the</p> <p>15 answer is yes, and that's not going to change over</p> <p>16 time. However, if you start talking about, oh, these</p> <p>17 patients develop resistance at some point, which we</p> <p>18 know happens with BTK inhibitors, we have that</p> <p>19 knowledge over the last 10 years, if that happens,</p> <p>20 sure, BTK occupancy may -- may change. And the</p> <p>21 patient may progress.</p> <p>22 Q. The disease would progress in the patient,</p> |
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| <p>1 right?</p> <p>2 A. Yes.</p> <p>3 Q. And is that a reason to do multiple cycles</p> <p>4 rather than just one cycle?</p> <p>5 A. Again, it depends what you're trying to</p> <p>6 define. If you're trying to define therapeutic</p> <p>7 activity by an efficacy by inhibiting BTK, one cycle</p> <p>8 is fine.</p> <p>9 Q. Did you look at the occupancy data for</p> <p>10 each of these 11 cycles in example 7?</p> <p>11 A. I did not. I relied on the summary.</p> <p>12 Q. So you don't know if the occupancy data</p> <p>13 changed between blood draws for any particular</p> <p>14 patient, right?</p> <p>15 A. Where would I find that in the</p> <p>16 specifications?</p> <p>17 Q. Well, I don't think it's in the</p> <p>18 specification. You are not aware of whether any</p> <p>19 patients experienced a change in occupancy between</p> <p>20 cycles in example 7, right?</p> <p>21 A. Correct.</p> <p>22 Q. Is that something you would want to know</p>                                                                                                                                                                                                                       | Page 158 | <p>1 not a -- it's neither in that as -- I guess the</p> <p>2 answer is no as it relates to the therapeutic</p> <p>3 efficacy in the claims in the patent. One cycle is</p> <p>4 adequate.</p> <p>5 BY MS. PATEL:</p> <p>6 Q. Let me just ask that again so --</p> <p>7 A. Yeah.</p> <p>8 Q. -- I can be clear on what your answer is</p> <p>9 here. In order to determine a therapeutically</p> <p>10 effective amount, do you think a single cycle would</p> <p>11 be sufficient?</p> <p>12 A. Again, I know I'm splitting hairs, but</p> <p>13 when it comes to one cycle looking at how therapeutic</p> <p>14 efficacy is defined in the patents --</p> <p>15 Q. Sorry. Can I stop you there? I don't</p> <p>16 know what you mean by therapeutic efficacy. I want</p> <p>17 to know what the therapeutically effective amount</p> <p>18 would be.</p> <p>19 MS. DANEK: Counsel, he was answering your</p> <p>20 question and you interrupted him. Right now it's</p> <p>21 hopelessly confusing as to what the pending question</p> <p>22 is. So maybe you can start over and please don't</p>                                                                                                      | Page 160 |
| <p>1 when deciding whether or not additional cycles would</p> <p>2 be necessary to assess occupancy?</p> <p>3 A. The only reason I would want to know that</p> <p>4 when it comes to the clinic was if a patient was</p> <p>5 progressing and we saw signs of progression. That's</p> <p>6 the reason I would want to know. But at this time,</p> <p>7 no, because clinical context is these patients</p> <p>8 continue to respond for a long time on these drugs.</p> <p>9 Q. And when determining a therapeutically</p> <p>10 effective amount, do you think one cycle would be</p> <p>11 sufficient?</p> <p>12 A. Let me contextualize that again. As</p> <p>13 relates to the specifications in the patents, yes,</p> <p>14 one cycle is sufficient. As it relates to</p> <p>15 understanding maximum activity in a patient, that's</p> <p>16 not how we treat the patients. We treat them with</p> <p>17 ongoing therapy. But in my clinical practice, at the</p> <p>18 same time the drugs work very quickly of relieving a</p> <p>19 sign or symptom of CLL.</p> <p>20 Q. So is that a yes or a no?</p> <p>21 MS. DANEK: Objection, form.</p> <p>22 THE WITNESS: It's -- it's neither. It's</p> | Page 159 | <p>1 interrupt him when he's answering.</p> <p>2 BY MS. PATEL:</p> <p>3 Q. I'll ask the same question for the third</p> <p>4 time which I believe is clear. In order to determine</p> <p>5 what the therapeutically effective amount would be</p> <p>6 for a particular irreversible BTKI, is it your</p> <p>7 opinion that a single cycle would be sufficient?</p> <p>8 A. And by amount, do you mean dose?</p> <p>9 Q. Yes.</p> <p>10 A. My answer is the same in that as it</p> <p>11 relates to the definition of therapeutic efficacy in</p> <p>12 the claims, one dose is adequate. As it relates to</p> <p>13 what we've learned since 2011 based on the</p> <p>14 specifications and based on the confirmation from all</p> <p>15 the BTK inhibitors we have, we use continuous dosing</p> <p>16 because the patients continue to respond. And in</p> <p>17 that case, yes, it's therapeutically effective, so we</p> <p>18 know to continue it clinically for as long as the</p> <p>19 treatment is working.</p> <p>20 Q. So you're talking about the definition of</p> <p>21 therapeutic efficacy in the claims. Do you think the</p> <p>22 claims recite the term "therapeutic efficacy"?</p> | Page 161 |

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| <p>Page 162</p> <p>1 A. In that context, I'm using it the same as<br/>2 what's in my declaration as therapeutically effective<br/>3 amount. It's from the specification.<br/>4 Q. So in your opinion, in order to determine<br/>5 the therapeutically effective amount of an<br/>6 irreversible BTKI, you would only need to dose a<br/>7 cohort of patients at a particular dose for one<br/>8 cycle, is that right?<br/>9 A. Yes.<br/>10 Q. In your experience, have you ever heard of<br/>11 a study like the one described in example 7 that used<br/>12 only a single cycle to determine the therapeutically<br/>13 effective amount?<br/>14 MS. DANEK: Objection, form.<br/>15 THE WITNESS: Typically, no. But again,<br/>16 it's different in treating the patients and -- and<br/>17 developing treatment paradigms ongoing for<br/>18 therapeutic clinical benefit in my patients than it<br/>19 is for the specification.<br/>20 So if we stick with the definition of<br/>21 therapeutically effective amount per the<br/>22 specification, that, as a quote, sufficient amount --</p>                                                                              | <p>Page 164</p> <p>1 BY MS. PATEL:<br/>2 Q. What would you do in that situation that<br/>3 you just described?<br/>4 A. If my patient -- I didn't feel like my<br/>5 patient was showing signs of response?<br/>6 Q. Yes.<br/>7 A. I would be thinking about alternate<br/>8 therapy.<br/>9 Q. You wouldn't increase the dose or anything<br/>10 like that?<br/>11 A. No. As long as I had them on a dose that<br/>12 I knew inhibited BTK, I would not increase the dose.<br/>13 Q. So there could be doses that inhibit BTK<br/>14 but don't elicit a response from the patient?<br/>15 A. So the reality is across populations, the<br/>16 drugs aren't perfect. They don't always work. In an<br/>17 individual, we make our best assessment and<br/>18 recommendation, but as we can see from the data, the<br/>19 drugs don't always work. But that's not what's here<br/>20 in the specification related to if something's<br/>21 therapeutically effective.<br/>22 Q. So if only one cycle is sufficient, why</p>                                                                                                                                     |
| <p>Page 163</p> <p>1 this is -- I'm looking at paragraph 72 in my<br/>2 declaration, the third line down. If we stick to<br/>3 therapeutically effective amount is a sufficient<br/>4 amount of an agent or a compound being administered<br/>5 which will relieve to some extent one or more of the<br/>6 symptoms of CLL/SLL, the result can be reduction<br/>7 and/or alleviation of the signs, symptoms or causes<br/>8 of CLL or any other desired alteration of a biologic<br/>9 system.<br/>10 So that's the definition I'm using in my<br/>11 analysis of the claims. And based on one cycle, I<br/>12 would see that. Of course if a patient is<br/>13 benefitting from that, I'm going to continue them on<br/>14 that treatment. And that's the benefit of continuing<br/>15 therapy and that's why these trials continue the<br/>16 drugs.<br/>17 To put another way, the converse of that<br/>18 is true. If a patient was treated with an<br/>19 irreversible BTK inhibitor and none of those things<br/>20 happened within the first month, I would be concerned<br/>21 that that would be the rare individual that this drug<br/>22 was not going to work.</p> | <p>Page 165</p> <p>1 does example 7 describe 11 cycles?<br/>2 MS. DANEK: Objection, form.<br/>3 THE WITNESS: Because we're not just<br/>4 thinking about the specifications and what's<br/>5 therapeutically effective in a specification. We're<br/>6 thinking about treating the patient and continuing<br/>7 the therapy as long as they're benefitting.<br/>8 Now, at the same time the claim does talk<br/>9 about continuous dosing through lymphocytosis and we<br/>10 start doing all of that. So the patients will be<br/>11 benefitting -- you're hoping the patients -- whenever<br/>12 you do an early trial, you're hoping they benefit and<br/>13 you continue the treatment.<br/>14 But as far as what's -- the lesson learned<br/>15 from ibrutinib in the specification is that it's<br/>16 therapeutically effective in the majority of<br/>17 patients. And as long as it's -- and that<br/>18 correlation relates to inhibiting BTK.<br/>19 BY MS. PATEL:<br/>20 Q. Back to column 136, it says if two DLTs<br/>21 are observed during cycle 1, then dosing at that dose<br/>22 and higher is suspended and the MTD is established as</p> |

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| <p>1 the previous cohort, is that right?</p> <p>2 A. Yes.</p> <p>3 Q. So you basically keep going and advancing</p> <p>4 through cohorts until greater than two DLTs are</p> <p>5 observed, right?</p> <p>6 A. Yes.</p> <p>7 Q. And approximately how many cohorts did it</p> <p>8 take until the MTD was identified for Imbruvica? So</p> <p>9 if you look at 138, line 26, it says that 49 patients</p> <p>10 were enrolled in cohorts 1 through 4, right?</p> <p>11 A. I'm sorry, I'm looking here, but I don't</p> <p>12 see the number. I see on line 27 --</p> <p>13 Q. Twenty-seven.</p> <p>14 A. -- I see 29 patients.</p> <p>15 Q. Oh, did I not say -- yeah, 29 patients.</p> <p>16 Oh, 29 patients, right, were enrolled in cohorts 1</p> <p>17 through 4, is that right?</p> <p>18 A. Yes.</p> <p>19 Q. And so there was no escalation to cohort</p> <p>20 5, right?</p> <p>21 MS. DANEK: Objection, form.</p> <p>22 THE WITNESS: They don't report on</p>                                                                                                                        | <p>Page 166</p> <p>1 cycles, right?</p> <p>2 A. It would, yes. I guess my understanding</p> <p>3 is that those patients -- you could have enrolled --</p> <p>4 you could have been at 15 weeks and been enrolling</p> <p>5 cycle 4 without having those other patients have gone</p> <p>6 to 11 months. So I may have misunderstood your</p> <p>7 question.</p> <p>8 Q. Sure. Yeah, I'm not saying it's 11, you</p> <p>9 know, weeks back-to-back.</p> <p>10 A. Okay.</p> <p>11 Q. Or 11 months back-to-back.</p> <p>12 A. Okay.</p> <p>13 Q. Yeah, yeah. No. So -- so then I guess</p> <p>14 the question is how many -- how many cycles total</p> <p>15 would that be? That would be 11 cycles each for</p> <p>16 cohorts 1 through 3 and at least one cycle for cohort</p> <p>17 4, right?</p> <p>18 MS. DANEK: Objection, form.</p> <p>19 THE WITNESS: It also depends because we</p> <p>20 only -- so we have 29 patients, 12 follicular, four</p> <p>21 large cell lymphoma, four with mantle cell lymphoma</p> <p>22 and two marginal zone lymphoma, which I know is</p>                                                                      |
| <p>1 additional patients. That is true. I don't know if</p> <p>2 they had enrolled those patients or not, but --</p> <p>3 BY MS. PATEL:</p> <p>4 Q. Okay.</p> <p>5 A. -- here we have, yes, to report on 29</p> <p>6 patients.</p> <p>7 Q. So we know that they had cohorts 1 through</p> <p>8 4. They went through cohorts 1 through 4, right?</p> <p>9 A. Right.</p> <p>10 Q. So that would have been 11 cycles for</p> <p>11 cohorts 1 through 3, right, at least?</p> <p>12 A. No, that's not my understanding. It would</p> <p>13 have been they all completed one cycle.</p> <p>14 Q. So we just discussed how cohort 1 would go</p> <p>15 through cycle 1 and if there were one or zero DLTs,</p> <p>16 then enrollment would begin for cohort 2, but cycle 1</p> <p>17 would still continue through 11 cycles.</p> <p>18 A. Correct.</p> <p>19 Q. And then, you know, we discussed how</p> <p>20 cohort 2 would begin cycle 1 and if there were no</p> <p>21 DLTs or only one DLT, then enrollment would begin for</p> <p>22 cohort 3, and cohort 2 would then proceed through 11</p> | <p>Page 167</p> <p>1 outside of the scope of the claims. But also to put</p> <p>2 that in context, you know, you have to factor into</p> <p>3 some patients might be progressing, things like that,</p> <p>4 so -- in coming off study.</p> <p>5 So it's hard to know exactly -- it's hard</p> <p>6 to deduce without them telling us how long the study</p> <p>7 would take or how many cycles patients got or things</p> <p>8 like that. So I can't really speculate on that.</p> <p>9 BY MS. PATEL:</p> <p>10 Q. Okay. Let's say that under this protocol,</p> <p>11 what would be the minimum amount it would take?</p> <p>12 Let's assume that the MTD is a dose that's</p> <p>13 administered to the first cohort, right? In that</p> <p>14 case, it would have taken 55 weeks total, right?</p> <p>15 MS. DANEK: Objection, form.</p> <p>16 THE WITNESS: So it wouldn't take -- are</p> <p>17 you saying it would have taken 55 weeks to</p> <p>18 potentially treat the first -- the first cohort of</p> <p>19 patients?</p> <p>20 BY MS. PATEL:</p> <p>21 Q. No, I'm saying if --</p> <p>22 A. If it was limited to one cohort, is that</p> |
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| <p>1 what you're asking?</p> <p>2 Q. Yeah. If the first cohort defined the</p> <p>3 MTD, then under this protocol, there would have been</p> <p>4 11 cycles, assuming they were run consecutively, it</p> <p>5 would have taken about 55 weeks, is that right?</p> <p>6 MS. DANEK: Objection to form. Well,</p> <p>7 objection, form.</p> <p>8 THE WITNESS: No, I don't think we can</p> <p>9 speculate for the same reason I said before, because</p> <p>10 you have some patients that may complete two cycles,</p> <p>11 may complete one, may complete three, may complete</p> <p>12 five. And then often in an early phase trial, the</p> <p>13 way it's designed is you're looking for the first</p> <p>14 primary endpoint is DLTs so -- after cycle 1.</p> <p>15 So you often will report out your outcome</p> <p>16 of DLTs prior to these patients going on study. As</p> <p>17 an example, we have some trials that, you know,</p> <p>18 patients that have been long reported out, but</p> <p>19 patients are still on the Phase 1 drug five years</p> <p>20 later.</p> <p>21 BY MS. PATEL:</p> <p>22 Q. So you're saying it could be longer than</p> | <p>Page 170</p> <p>1 A. I don't know because, again, that would</p> <p>2 all be hypothetical and speculative because these are</p> <p>3 different populations, you don't know how they're</p> <p>4 going to respond, you don't know how long they're</p> <p>5 going to respond. So you could have a readout very</p> <p>6 quickly. And also the primary endpoint of this</p> <p>7 study, Phase 1 is DLT and so you would know if -- at</p> <p>8 five weeks, you would have meaningful information</p> <p>9 about the primary endpoint which would be -- one of</p> <p>10 the primary endpoints which would be safety.</p> <p>11 So my point is there are patients that</p> <p>12 continue on treatment, but you've gotten the</p> <p>13 information you need from the study.</p> <p>14 Q. But example 7 describes 11 cycles, right?</p> <p>15 A. Right.</p> <p>16 Q. And you agree that in example 7, each</p> <p>17 cohort continued on for 11 cycles if there was one or</p> <p>18 less DLTs observed, right?</p> <p>19 MS. DANEK: Objection, form.</p> <p>20 THE WITNESS: I agree in principle that</p> <p>21 that's the design of the study, but I don't know how</p> <p>22 long patients would have stayed on an individual</p> |
| <p>1 that?</p> <p>2 A. No, that's not what I'm saying.</p> <p>3 Q. Could it be shorter than that?</p> <p>4 MS. DANEK: Objection, form. Than what?</p> <p>5 What is your -- what are we talking about?</p> <p>6 MS. PATEL: Counsel, let the witness ask</p> <p>7 the questions.</p> <p>8 BY MS. PATEL:</p> <p>9 Q. If you would like me to -- Dr. Spurgeon,</p> <p>10 if you want me to clarify my question, I'm happy to.</p> <p>11 A. No. I guess -- I guess -- if you could</p> <p>12 clarify your question, please.</p> <p>13 Q. I asked you if the MTD is defined in the</p> <p>14 first cohort, then what is the minimum amount of time</p> <p>15 that would take?</p> <p>16 MS. DANEK: Objection, form.</p> <p>17 THE WITNESS: When you say "that would</p> <p>18 take," what do you mean by that?</p> <p>19 BY MS. PATEL:</p> <p>20 Q. How long would it take cohort 1 to go</p> <p>21 through the cycles that are defined in the protocol</p> <p>22 in example 7?</p>                                                                                                                                                                                     | <p>Page 171</p> <p>1 patient level. Because if someone had a DLT at week</p> <p>2 1, they're off the study. They're not doing 11 more</p> <p>3 months of treatment.</p> <p>4 BY MS. PATEL:</p> <p>5 Q. What about at the level of the cohort?</p> <p>6 A. That's what I'm referring to, level of the</p> <p>7 cohort. So if someone didn't respond at week 1 or</p> <p>8 they had toxicity, that patient is no longer on the</p> <p>9 study or -- as an example, not here -- but just as an</p> <p>10 example, if you had six patients on a study and they</p> <p>11 all progressed at month 2, it's not going to take 55</p> <p>12 weeks. So that's why I can't even speculate or</p> <p>13 really effectively answer the question.</p> <p>14 Q. Where in example 7 does it say do 11</p> <p>15 cycles, but if a patient shows progression at cycle</p> <p>16 2, don't do 11 cycles?</p> <p>17 MS. DANEK: Objection, form.</p> <p>18 THE WITNESS: I'm trying to find specific</p> <p>19 language in example 7. It doesn't include that</p> <p>20 language. But in oncology trials, we take all</p> <p>21 patients off a therapy when they're progressing.</p> <p>22 BY MS. PATEL:</p>                                               |
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| <p>Page 174</p> <p>1 Q. In the last paragraph of example 7, do you<br/>2 see where it states that 29 patients, 12 follicular,<br/>3 seven CLL/SLL, four DLBCL and four mantle, two<br/>4 marginal with a median of three prior therapies have<br/>5 been enrolled in cohorts 1 through 4?<br/>6 A. Yes.<br/>7 Q. This indicates that only seven CLL/SLL<br/>8 patients were enrolled in this trial across cohorts 1<br/>9 through 4, right?<br/>10 A. Yes.<br/>11 Q. Do you know how many CLL/SLL patients were<br/>12 in each cohort?<br/>13 A. I don't see it listed here, no.<br/>14 Q. So there could have been one to two<br/>15 CLL/SLL patients in each cohort, right?<br/>16 MS. DANEK: Objection, form.<br/>17 THE WITNESS: There could have been CLL<br/>18 patients in different cohorts, multiple cohorts,<br/>19 yeah. But just seven of them, yes.<br/>20 BY MS. PATEL:<br/>21 Q. Or there could have been cohorts that had<br/>22 no CLL/SLL patients at all, right?</p> | <p>Page 176</p> <p>1 MS. DANEK: Objection, form.<br/>2 THE WITNESS: I think to answer that<br/>3 question, I view in the totality of the whole<br/>4 specification which includes other CLL studies.<br/>5 So again, it's kind of a hypothetical<br/>6 situation that I don't have a great answer for. What<br/>7 I can tell you is that those patients would -- if<br/>8 it's effective at inhibiting BTK irreversibly, then<br/>9 across a population, it's likely to be effective<br/>10 treating the disease.<br/>11 But when it comes to the claims and<br/>12 everything I considered, I think about it in the<br/>13 totality of the treatment, but that this was -- this<br/>14 contributed to that, especially given the BTK<br/>15 occupancy assay.<br/>16 BY MS. PATEL:<br/>17 Q. So in your view, occupancy data from seven<br/>18 CLL/SLL patients would be sufficient in the context<br/>19 of the specification?<br/>20 MS. DANEK: Objection, form.<br/>21 BY MS. PATEL:<br/>22 Q. To determine the therapeutically effective</p> |
| <p>Page 175</p> <p>1 A. That's also a possibility, yes.<br/>2 Q. And there could have even been a single<br/>3 cohort that had all seven CLL/SLL patients, right?<br/>4 A. Yes.<br/>5 Q. Okay. So let's assume that all seven<br/>6 CLL/SLL patients were in cohort 2.<br/>7 MS. DANEK: Objection, form.<br/>8 BY MS. PATEL:<br/>9 Q. If seven patients showed sufficient<br/>10 occupancy at the cohort 2 dosage amount, would that<br/>11 be enough data on which to determine the<br/>12 therapeutically effective dose for Imbruvica in<br/>13 CLL/SLL patients?<br/>14 MS. DANEK: Objection, form.<br/>15 THE WITNESS: Can you ask the question<br/>16 again, please?<br/>17 BY MS. PATEL:<br/>18 Q. If all seven CLL/SLL patients in cohort 2<br/>19 showed sufficient occupancy at that dosage, would<br/>20 that be enough data on which to determine the<br/>21 therapeutically effective dose for Imbruvica and<br/>22 CLL/SLL patients?</p>                                  | <p>Page 177</p> <p>1 amount for Imbruvica in CLL/SLL patients.<br/>2 MS. DANEK: Objection, form.<br/>3 THE WITNESS: In my opinion, the<br/>4 specifications included -- or the results included in<br/>5 the entirety of the specification related to CLL/SLL<br/>6 would help inform that, informs my opinion.<br/>7 BY MS. PATEL:<br/>8 Q. What if you only had occupancy data from<br/>9 four CLL/SLL patients. Would that be sufficient?<br/>10 MS. DANEK: Objection, form.<br/>11 THE WITNESS: Sufficient for what?<br/>12 BY MS. PATEL:<br/>13 Q. Determining the therapeutically effective<br/>14 amount for Imbruvica to treat CLL/SLL.<br/>15 MS. DANEK: Same objection.<br/>16 BY MS. PATEL:<br/>17 Q. Dr. Spurgeon, you've been quiet for a bit.<br/>18 Do you need me to repeat the question?<br/>19 A. No, I think I understand the question.<br/>20 Again, my opinion would be based on the totality of<br/>21 the specification. I would think that also based on<br/>22 the specification that, in taking everything</p>         |

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| <p>1 collectively, what we know about ibrutinib or</p> <p>2 ibrutinib-like treatments, that the like of it would</p> <p>3 be that if it was inhibiting BTK, that it would be</p> <p>4 active or therapeutically active and that it would</p> <p>5 relieve symptoms. But I can't opine further unless I</p> <p>6 consider the totality of the specification, because</p> <p>7 that's what we have to go off of. The other parts</p> <p>8 are just hypotheticals.</p> <p>9 Q. But when you discussed the portions of the</p> <p>10 specification that inform a POSA as to identifying</p> <p>11 the therapeutically effective amount, you only rely</p> <p>12 on example 7, right?</p> <p>13 MS. DANEK: Objection, form.</p> <p>14 THE WITNESS: I think as stated in my</p> <p>15 declaration on page 78, there's many examples I</p> <p>16 discuss that are -- that discuss the impacts of using</p> <p>17 ibrutinib or ibrutinib-like compounds.</p> <p>18 BY MS. PATEL:</p> <p>19 Q. Are you referring to paragraph 78 of your</p> <p>20 declaration?</p> <p>21 A. I'm sorry, yes, paragraph 78.</p> <p>22 Q. And that paragraph is contained in the</p> | <p>Page 178</p> <p>1 A. Yes.</p> <p>2 Q. Do you see any other citation other than</p> <p>3 the citation to Exhibit 1001, column 136, lines 22</p> <p>4 through 45 and column 137, line 9 through 26?</p> <p>5 A. No. I see example 7, yes.</p> <p>6 Q. And you're not -- there's no citation</p> <p>7 there to the totality of the specification, right?</p> <p>8 MS. DANEK: Objection, form.</p> <p>9 THE WITNESS: That is correct. I think,</p> <p>10 that being said, it's -- all these things go</p> <p>11 together. So even though I cite it there, in that</p> <p>12 example that the BTK occupancy assay, that needs to</p> <p>13 be considered in conjunction with all the other</p> <p>14 things in the specification.</p> <p>15 So that is the specifics about the</p> <p>16 on-target effects and the ability to inhibit BTK as</p> <p>17 it relates to different doses and different activity,</p> <p>18 highlighting that, even at lower doses, extensive BTK</p> <p>19 occupancy could be seen. And this was very different</p> <p>20 than what was done at the time with cytotoxic</p> <p>21 chemotherapy.</p> <p>22 BY MS. PATEL:</p> <p>Page 180</p> |
| <p>1 section titled the specification describes</p> <p>2 irreversibly inhibiting BTK treats CLL and SLL</p> <p>3 patients?</p> <p>4 A. Correct.</p> <p>5 Q. And then when you go to paragraph 119 of</p> <p>6 your declaration, are you there?</p> <p>7 A. Yes. I'm there, I'm there, yes. I'm</p> <p>8 looking at the specification, yes.</p> <p>9 Q. So that's the paragraph where you talk</p> <p>10 about how the specification teaches identifying</p> <p>11 therapeutically effective doses, by measuring the</p> <p>12 occupancy of BTK using a specific assay, right?</p> <p>13 A. Right.</p> <p>14 Q. And there you rely on column 136, lines 22</p> <p>15 to 45 and column 137, lines 9 through 26, right?</p> <p>16 A. Yes.</p> <p>17 Q. That's example 7, right?</p> <p>18 A. Yes, agreed.</p> <p>19 Q. Okay. And that's the only thing you cite</p> <p>20 there to support that statement, right? Just to</p> <p>21 clarify, Dr. Spurgeon, you're looking at paragraph</p> <p>22 119, right?</p>                                                                                                                                             | <p>Page 179</p> <p>1 Q. Okay. Can you turn back to the last</p> <p>2 paragraph in example 7, please.</p> <p>3 A. Yes.</p> <p>4 Q. Do you see where it says 19 of 22 patients</p> <p>5 from cohorts 1 through 3 or evaluable?</p> <p>6 A. Yes.</p> <p>7 Q. Is 19 evaluable patients enough to confirm</p> <p>8 efficacy?</p> <p>9 MS. DANEK: Objection, form.</p> <p>10 THE WITNESS: It depends -- again, it</p> <p>11 depends on context. This is very similar to what we</p> <p>12 were talking about with my paper. So this is a trial</p> <p>13 that included, very similar to the other paper that</p> <p>14 we already discussed, that multiple different</p> <p>15 histologies.</p> <p>16 BY MS. PATEL:</p> <p>17 Q. Does example 7 cover multiple different</p> <p>18 histologies?</p> <p>19 A. Yes.</p> <p>20 Q. Just like your paper?</p> <p>21 A. Yes. Yes. I said yes. I don't know if</p> <p>22 you could hear.</p> <p>Page 181</p>                                                                                                                                                                                                                       |

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| <p>1 Q. So in this context, would 17 evaluable<br/>2 patients be enough?<br/>3 MS. DANEK: Objection, form.<br/>4 BY MS. PATEL:<br/>5 Q. Strike that. I'll withdraw the question.<br/>6 So in this context, is 19 evaluable<br/>7 patients enough to confirm efficacy?<br/>8 MS. DANEK: Objection, form.<br/>9 THE WITNESS: Again, I think it's about<br/>10 context and, in this context, it's where you have a<br/>11 mixture of patients in particular. It's going to be<br/>12 different contexts for different studies. So what I<br/>13 get out of this is this is an early phase study that<br/>14 showed antitumor activity and used an assay that<br/>15 showed on-target effects.<br/>16 MS. DANEK: Counsel, I don't know if<br/>17 you're at a -- excuse me, Counsel. I don't know if<br/>18 you have much more. We've been going for quite a<br/>19 while, if you could get to a point where we could<br/>20 take a break.<br/>21 MS. PATEL: Sure. Let me just ask a<br/>22 couple more questions and then we can take a break.</p>                                                                                                                       | <p>Page 182</p> <p>1 was not done.<br/>2 Q. Okay. But what you would not take away<br/>3 from this study with 19 evaluable patients is that<br/>4 it's enough to confirm efficacy, right?<br/>5 A. Again, it depends how you're defining<br/>6 efficacy. Are you defining it for the patient<br/>7 population and FDA approval and counseling your<br/>8 patients or based on the specifications in the -- in<br/>9 the patent?<br/>10 Q. I want to know if a POSA, a clinical<br/>11 member of a POSA would look at data from 19 evaluable<br/>12 patients representing a range of histologies and<br/>13 conclude that that is sufficient to confirm efficacy.<br/>14 MS. DANEK: Objection, form.<br/>15 THE WITNESS: And I guess my answer is the<br/>16 same. It's impossible to make any of those<br/>17 conclusions off of -- you know, in this hypothetical<br/>18 when we have the whole specification at our disposal<br/>19 to inform our current thoughts.<br/>20 MS. DANEK: Counsel, is now a good time<br/>21 for a break?<br/>22 MS. PATEL: No, just one more question.</p> <p>Page 184</p> |
| <p>1 BY MS. PATEL:<br/>2 Q. So what you would get out of this study is<br/>3 that it's an early phase study that showed antitumor<br/>4 activity and used an assay that showed on-target<br/>5 effects, right?<br/>6 A. Can you repeat the question?<br/>7 Q. Sure. I was just repeating what you said<br/>8 in your last answer. So your testimony is that what<br/>9 you would get out of this study is that it is an<br/>10 early phase study that showed antitumor activity and<br/>11 used an assay that showed on-target effects, is that<br/>12 right?<br/>13 A. I would qualify that a little more. So I<br/>14 would say that this is a study using an irreversible<br/>15 BTK inhibitor, in this case ibrutinib, that showed<br/>16 antitumor activity in percentage of patients with<br/>17 multiple different histologies and that the BTK<br/>18 occupancy assay and cellular processes or the assay<br/>19 to evaluate the BTK-related cellular processes tell<br/>20 us about potential doses in a novel way, where before<br/>21 trials would be using cytotoxic chemotherapy in dose<br/>22 escalating to maximum tolerated dose. But here that</p> | <p>Page 183</p> <p>1 BY MS. PATEL:<br/>2 Q. A clinical -- would a clinical member of<br/>3 the POSA team, in the context of the specification in<br/>4 2011, look at data from 19 evaluable patients<br/>5 representing a range of histologies and feel that<br/>6 that is enough to confirm efficacy of Imbruvica?<br/>7 MS. DANEK: Objection, form.<br/>8 THE WITNESS: To confirm therapeutic<br/>9 efficacy of Imbruvica, is that what you're asking?<br/>10 BY MS. PATEL:<br/>11 Q. Sure.<br/>12 A. I'm going to say I don't know again<br/>13 because this is seven -- or 19 patients with<br/>14 different histologies. It's seven. I don't know if<br/>15 all those seven -- of CLL. I don't know if all those<br/>16 seven were on the lowest dose cohort, the highest<br/>17 dose cohort. I just -- I don't have enough<br/>18 information. So it's not an absolute number for the<br/>19 number of patients that can inform my answer.<br/>20 MS. PATEL: Okay. We can take a break.<br/>21 THE VIDEOGRAPHER: Off the record at 2:59<br/>22 p.m.</p> <p>Page 185</p>                             |

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| <p>1 (Recess.)</p> <p>2 THE VIDEOGRAPHER: Back on the record at</p> <p>3 3:08 p.m.</p> <p>4 BY MS. PATEL:</p> <p>5 Q. Okay. Dr. Spurgeon, could you turn to</p> <p>6 paragraph 125 of your declaration.</p> <p>7 A. Okay.</p> <p>8 Q. You state here at this paragraph that</p> <p>9 practicing the claimed methods would require only</p> <p>10 reasonable experimentation, right?</p> <p>11 A. I'm sorry, I'm on the right page. I don't</p> <p>12 know exactly which -- where exactly -- you're at</p> <p>13 paragraph 125?</p> <p>14 Q. Uh-huh. So do you see where you say, "As</p> <p>15 discussed above, the specification further teaches a</p> <p>16 novel and straightforward method for identifying a</p> <p>17 therapeutic dose of an irreversible BTK inhibitor</p> <p>18 within the claims by monitoring BTK occupancy in</p> <p>19 patient blood samples. Because of this teaching,</p> <p>20 practicing the claimed methods would require only</p> <p>21 reasonable experimentation"?</p> <p>22 A. Yes.</p>                                                                                                                 | <p>Page 186</p> <p>1 reasonable experimentation?</p> <p>2 MS. DANEK: Objection, form.</p> <p>3 THE WITNESS: I would consider -- I can't</p> <p>4 comment on the number of years of what's reasonable</p> <p>5 or not because what's reasonable to one person may</p> <p>6 not be reasonable to another depending on the</p> <p>7 context. But what I can say is that the</p> <p>8 experimentation required is the experimentation that</p> <p>9 is required by the FDA to get a drug approved. So</p> <p>10 that is a process that takes as long as it takes and</p> <p>11 that is reasonable.</p> <p>12 I think that being said, I think if</p> <p>13 anything, the specification, given its teachings,</p> <p>14 gives a real blueprint for doing these studies and</p> <p>15 potentially shortening the time that would be needed.</p> <p>16 So I don't think it's extensive, nor do I think it's</p> <p>17 unreasonable.</p> <p>18 BY MS. PATEL:</p> <p>19 Q. Okay. Let me ask this again because I</p> <p>20 think we might be speaking past each other a little</p> <p>21 bit. So let's assume that it would take a few years</p> <p>22 to practice the claimed methods. Would you, as a</p> |
| <p>1 Q. Assume that in order to practice the</p> <p>2 claimed methods, you would need to perform tests that</p> <p>3 would take a few years to conduct. Would you still</p> <p>4 consider that reasonable experimentation?</p> <p>5 MS. DANEK: Objection, form.</p> <p>6 THE WITNESS: I think, again, it depends</p> <p>7 on the context there. If you're talking about</p> <p>8 satisfying FDA regulatory pathways, that's one</p> <p>9 context. Another context would be doing a study that</p> <p>10 satisfied the claims in the specification. Those are</p> <p>11 two different --</p> <p>12 BY MS. PATEL:</p> <p>13 Q. Yeah, so let me clarify. I'm not asking</p> <p>14 you about satisfying FDA regulatory pathways. I'm</p> <p>15 saying that in order to practice the claimed methods,</p> <p>16 right -- do you understand what I mean by claimed</p> <p>17 methods?</p> <p>18 A. Yes.</p> <p>19 Q. So in order to practice the claimed</p> <p>20 methods, you would necessarily need to perform tests</p> <p>21 that would conduct a few years -- that would take a</p> <p>22 few years to conduct, would you consider that</p> | <p>Page 187</p> <p>1 clinical member of the POSA team, consider that to be</p> <p>2 a reasonable amount of experimentation?</p> <p>3 MS. DANEK: Objection, form.</p> <p>4 THE WITNESS: Again, I'm not going to</p> <p>5 speculate on the number of years. I think it would</p> <p>6 be -- I think the requirements outlined based on</p> <p>7 what's available, it's a blueprint, would not be</p> <p>8 excessive.</p> <p>9 BY MS. PATEL:</p> <p>10 Q. What is your understanding of excessive</p> <p>11 experimentation?</p> <p>12 A. So it's -- my understanding is, as far as</p> <p>13 the legal standard, what's been told to me on</p> <p>14 paragraph 34, as far as the Wands factors.</p> <p>15 Q. And your opinion from the perspective of a</p> <p>16 POSA is that, based on the Wands factors, practicing</p> <p>17 the full scope of the claimed methods would only</p> <p>18 require a reasonable amount of experimentation, is</p> <p>19 that right?</p> <p>20 A. Yes.</p> <p>21 Q. Would your opinion change if it were true</p> <p>22 that in order to practice the full scope of the</p>                                                                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <p>Page 188</p> <p>Page 189</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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| <p>1 claimed methods, you would have to conduct</p> <p>2 experiments that would take a decade to complete?</p> <p>3 MS. DANEK: Objection, form.</p> <p>4 THE WITNESS: I can't relate to that</p> <p>5 hypothetical because that would never happen.</p> <p>6 BY MS. PATEL:</p> <p>7 Q. Have you considered how long it would take</p> <p>8 to practice the full scope of the claimed methods in</p> <p>9 this case?</p> <p>10 A. Yes, in the context of whether it would</p> <p>11 require undue experimentation or not.</p> <p>12 Q. So how long in your opinion would it take</p> <p>13 to practice the full scope of the claims?</p> <p>14 A. There -- that's -- I can't answer that</p> <p>15 question, what's too long or how long, because</p> <p>16 there's too many variables that go into it. So</p> <p>17 someone could have stuff that's not excessive at all,</p> <p>18 at all, but maybe there's a drug formulation problem</p> <p>19 or maybe -- you know, there's a lot of variables that</p> <p>20 go into that that don't involve undue</p> <p>21 experimentation. Maybe there's not -- you know,</p> <p>22 maybe there's not enough money to perform the study.</p>                | <p>Page 190</p> | <p>1 the specification, that the development of other</p> <p>2 irreversible ibrutinib-like BTK inhibitors have the</p> <p>3 benefit of the specification and it would not require</p> <p>4 undue experimentation.</p> <p>5 BY MS. PATEL:</p> <p>6 Q. But that's not the question I asked. I</p> <p>7 asked you in this context, it's your position that</p> <p>8 you cannot estimate the amount of time it would take</p> <p>9 to practice the full scope of the claims, right?</p> <p>10 MS. DANEK: Objection, form.</p> <p>11 THE WITNESS: So in the -- so can you</p> <p>12 clarify the question or provide more detail?</p> <p>13 BY MS. PATEL:</p> <p>14 Q. I want to know if, when forming your</p> <p>15 opinions in this case, you had in mind an estimate of</p> <p>16 how long it would take to practice the full scope of</p> <p>17 the claims.</p> <p>18 A. I cannot accurately give an estimate</p> <p>19 because I've been doing this enough to understand</p> <p>20 that the estimates often are not sound of what -- of</p> <p>21 the reality of what's involved. That's why I would</p> <p>22 go back to my original answer, which I know you want</p>                                  | <p>Page 192</p> |
| <p>1 Maybe there's not -- maybe there's competing studies</p> <p>2 in the marketplace that patients can't go on the</p> <p>3 study. So that is a hypothetical that I think has</p> <p>4 too many variables to effectively address -- to put</p> <p>5 an actual timeline on it.</p> <p>6 Q. So you did not consider how long it would</p> <p>7 take to practice the full scope of the inventions in</p> <p>8 forming your opinions in this case, right?</p> <p>9 MS. DANEK: Objection, form.</p> <p>10 THE WITNESS: Yes, one would consider</p> <p>11 that. But what I'm saying is that it has to be in</p> <p>12 the context of all the factors. So there's not</p> <p>13 necessarily one right answer of what -- in my opinion</p> <p>14 of what equals a timeline for undue experimentation</p> <p>15 versus not. So there's not -- you know, there's --</p> <p>16 there is not a fixed time for that.</p> <p>17 BY MS. PATEL:</p> <p>18 Q. So you're saying in this context, you</p> <p>19 cannot estimate the amount of time it would take to</p> <p>20 practice the full scope of the claims, right?</p> <p>21 MS. DANEK: Objection, form.</p> <p>22 THE WITNESS: What I'm saying is, given</p> | <p>Page 191</p> | <p>1 that specific answer, but I cannot give my answer</p> <p>2 without contextualizing it. Because there are times</p> <p>3 when there would be totally -- there would not be</p> <p>4 excessive experimentation required, then it could</p> <p>5 take forever. There are other times where excessive</p> <p>6 experimentation could be required and it takes -- it</p> <p>7 would take less than you think.</p> <p>8 So that's why it's impossible to put -- so</p> <p>9 even, yes, I would think about milestones and things</p> <p>10 that, yes, this is where we need to go, this is</p> <p>11 what's needed, these are the requirements and of</p> <p>12 course we would do a timeline out as POSA. But it's</p> <p>13 easy to look back and say what the timelines could be</p> <p>14 or should be, but there are so many variables that go</p> <p>15 into that that it's impossible to make a definitive</p> <p>16 prediction.</p> <p>17 BY MS. PATEL:</p> <p>18 Q. And what are some of these variables that</p> <p>19 impact how long it would take to test a single BTKI,</p> <p>20 for example?</p> <p>21 MS. DANEK: Objection, form.</p> <p>22 THE WITNESS: So there are variables that</p> | <p>Page 193</p> |

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| <p>1 I alluded to in development of any drug. But also to</p> <p>2 be more specific, when we're talking about things</p> <p>3 that might affect the development of an irreversible</p> <p>4 ibrutinib-like BTK inhibitor that already has the</p> <p>5 benefit of the specification, that's different than</p> <p>6 another drug that doesn't have that specification</p> <p>7 already.</p> <p>8 At the same time, there are unforeseen</p> <p>9 things like I mentioned, right? The number of</p> <p>10 patients out there. There's too many other competing</p> <p>11 studies. Those trials are enrolling slowly. Or you</p> <p>12 open up a study at my institution and from a</p> <p>13 regulatory standpoint, it takes nine months -- or</p> <p>14 contractual negotiations take nine months, so the</p> <p>15 study doesn't open.</p> <p>16 Or there's funding -- the funding source</p> <p>17 for the trial is diminished and so there has to be a</p> <p>18 pause. Or you're doing a study and you see some sort</p> <p>19 of thing you didn't expect and, you know, like I</p> <p>20 said, the formulation -- you can't get the</p> <p>21 formulation you need, supply chain issues. I think</p> <p>22 you get the point. These aren't an exhaustive list</p> | <p>Page 194</p> <p>1 Q. Right. And in order to get a formulation</p> <p>2 of a drug, you would need to synthesize the active</p> <p>3 ingredient, right?</p> <p>4 A. Correct.</p> <p>5 Q. And who would do that?</p> <p>6 A. The chemistry team or the structural</p> <p>7 biologists or medicinal chemists would do that.</p> <p>8 Q. And then once they have -- once they've</p> <p>9 synthesized the BTKI, they would need to formulate it</p> <p>10 into a stable formulation, right?</p> <p>11 A. Right. And that is routine, yes.</p> <p>12 Q. Okay. And do you think that would be</p> <p>13 routine, to formulate an active ingredient of a drug?</p> <p>14 A. I think in this context, in what we're</p> <p>15 talking -- again, there's the broader question of</p> <p>16 cancer care and drug development. But then there's</p> <p>17 what we're talking about here, which is having a</p> <p>18 class of ibrutinib-like drugs, and zanubrutinib is</p> <p>19 one, so having that knowledge of what a BTK inhibitor</p> <p>20 could be, that changes what that process looks like.</p> <p>21 Q. Do you formulate drugs? Do you have</p> <p>22 experience formulating drugs?</p> |
| <p>1 by any means, but this just shows the challenges of</p> <p>2 using time as a fixed number -- exact fixed number as</p> <p>3 well.</p> <p>4 BY MS. PATEL:</p> <p>5 Q. So one of the issues you mentioned was you</p> <p>6 can't get the formulation you need. Can you</p> <p>7 elaborate on that?</p> <p>8 A. Well, you know, an example might be that</p> <p>9 there's the plant that's making -- again, I'm just --</p> <p>10 this is just all speculation. But, for example,</p> <p>11 let's say, you know, that the plant that makes the</p> <p>12 drug of interest is hit by a hurricane. I mean,</p> <p>13 these are -- I know that seems like an extreme</p> <p>14 example, but these things do happen where drug</p> <p>15 producers have a problem with their formulation of</p> <p>16 drug because they may not have access to the raw</p> <p>17 materials or things like that. That's just one</p> <p>18 example.</p> <p>19 But my point is it's just -- there are</p> <p>20 many things that factor into that timeline that</p> <p>21 aren't undue, they aren't excessive. It's just the</p> <p>22 nature of clinical research.</p>                                                                                                                    | <p>Page 195</p> <p>1 A. No.</p> <p>2 Q. And you agree, even with the</p> <p>3 specification, you would still need to administer a</p> <p>4 candidate BTKI to a live human being, right?</p> <p>5 A. Yes.</p> <p>6 Q. So in order to do that, you would have to</p> <p>7 synthesize it, you'd have to make it stable in</p> <p>8 formulation, right?</p> <p>9 A. Yes. But I don't think that qualifies as</p> <p>10 excessive because that's very routine.</p> <p>11 Q. What if you had to do that for a thousand</p> <p>12 BTKI candidates?</p> <p>13 A. I can't speak to a hypothetical thousand</p> <p>14 BTKI candidates.</p> <p>15 Q. Is it your understanding that</p> <p>16 experimentation is not excessive as long as the tests</p> <p>17 you need to conduct are routine?</p> <p>18 MS. DANEK: Objection, form.</p> <p>19 THE WITNESS: Can you ask that again,</p> <p>20 please?</p> <p>21 BY MS. PATEL:</p> <p>22 Q. Is it your understanding that</p>                                                                                                                                                                                                                           |

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| <p>1 experimentation is not excessive as long as the tests</p> <p>2 that you need to conduct are routine?</p> <p>3 A. So my understanding from a legal standard</p> <p>4 is what's described in that declaration at 35 that</p> <p>5 has been shared with me. And this was the framework</p> <p>6 that I was operating off of in paragraph 35, which</p> <p>7 says, "I also understand that the question of undue</p> <p>8 experimentation is a matter of degree, and that it</p> <p>9 does not require unduly extensive trial-and-error</p> <p>10 experimentation. I understand that the focus is not</p> <p>11 merely quantitative since a considerable amount of</p> <p>12 experimentation is permissible, if it is merely</p> <p>13 routine (e.g., involving repetition of known or</p> <p>14 commonly used techniques), or if the specification</p> <p>15 provides a reasonable amount of guidance."</p> <p>16 Q. Okay. And so I want to understand, from</p> <p>17 that, what you consider to be excessive</p> <p>18 experimentation and what you consider to be</p> <p>19 reasonable experimentation. So if, in order to</p> <p>20 practice the claimed methods, you needed to perform</p> <p>21 tests on hundreds of patients, would you find that to</p> <p>22 be excessive?</p> | <p>Page 198</p> <p>1 structural standpoint or the best one or two</p> <p>2 inhibitors. And that's a very different evaluation</p> <p>3 than testing all thousand in patients. We would</p> <p>4 never do that. But I can't speak to what those</p> <p>5 compounds are, what's one better than the other. I</p> <p>6 don't know the answer to that.</p> <p>7 Q. Yeah. And I'm not asking you which ones</p> <p>8 are better than the other. But do you understand</p> <p>9 that in order to practice the claimed methods, you</p> <p>10 would need to confirm that each and every one of</p> <p>11 those thousands would be effective at treating BTK --</p> <p>12 sorry, would be effective at treating CLL or SLL at a</p> <p>13 therapeutically effective amount?</p> <p>14 MS. DANEK: Objection, form.</p> <p>15 THE WITNESS: I understand that if you</p> <p>16 want to define if every one of those was effective --</p> <p>17 if you wanted to use every one of those and develop</p> <p>18 every one of those, then yes, I understand that. But</p> <p>19 the reality is no one would try to develop all 1,000.</p> <p>20 That's why this hypothetical is difficult</p> <p>21 to wrap my head around because that's not how things</p> <p>22 would work. And again, as a clinical person and a</p> |
| <p>1 MS. DANEK: Objection, form.</p> <p>2 THE WITNESS: Again, I would say that's a</p> <p>3 hypothetical that is not applicable here.</p> <p>4 BY MS. PATEL:</p> <p>5 Q. You don't think you would need to perform</p> <p>6 tests on hundreds of patients in order to practice</p> <p>7 the claimed methods here?</p> <p>8 A. I can't give you an actual number. But,</p> <p>9 again, the numbers you're quoting here are more in</p> <p>10 line with something like FDA approval pathways than</p> <p>11 they are practicing the scope of the claims.</p> <p>12 Q. Okay. Say Dr. Eck told you that there --</p> <p>13 he identified a thousand BTKIs that irreversibly bind</p> <p>14 cysteine 481, okay? Would you need to test each of</p> <p>15 those -- strike that.</p> <p>16 You agree that you would need to take each</p> <p>17 one of those BTKI candidates, administer it to a</p> <p>18 patient and draw their blood, right?</p> <p>19 A. No. No, because I wouldn't try and</p> <p>20 develop a thousand BTKI inhibitors -- irreversible</p> <p>21 BTK inhibitors. I would ask Dr. Eck, in your</p> <p>22 opinion, which is the best inhibitor from a</p>                                                                                                                    | <p>Page 199</p> <p>1 POSA, I would say, Dr. Eck, what's your top</p> <p>2 candidate? And that's the one I would put in</p> <p>3 patients. So the other 999 would be cast aside.</p> <p>4 BY MS. PATEL:</p> <p>5 Q. So what does it mean to you to practice</p> <p>6 the full scope of the claimed methods?</p> <p>7 A. Again, not being -- since I'm not an</p> <p>8 attorney, I can't -- may not give the appropriate</p> <p>9 language here from a technical standpoint, but it's</p> <p>10 really -- in this case, the claims of 1 and 8, that</p> <p>11 those could be practiced, along with the dependent</p> <p>12 claims, which my understanding is -- that we're not</p> <p>13 discussing at the moment.</p> <p>14 Q. Okay. So if Dr. Eck gave you candidate A</p> <p>15 and said this is a BTKI, it has the same structure as</p> <p>16 claimed in claims 1 and 8, and it's an irreversible</p> <p>17 inhibitor, right? You agree that you would take</p> <p>18 that -- you agree that in order to identify the</p> <p>19 therapeutically effective amount for candidate A, you</p> <p>20 would administer it to a patient and draw their blood</p> <p>21 and run occupancy tests as you discuss in your</p> <p>22 declaration, right?</p>                                                       |
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| <p>1 A. Yes, because there could be a possibility<br/>2 you're giving them a dose that is too low to bind BTK<br/>3 and irreversibly inhibit it.<br/>4 Q. And what if Dr. Eck told you that, in his<br/>5 view, there are a thousand different candidates in<br/>6 addition to candidate A that fall within the scope of<br/>7 claim 1 in that they satisfy the structural<br/>8 limitations of the claims and they irreversibly bind,<br/>9 covalently bind to cysteine 481, how would you<br/>10 identify the therapeutically effective amounts for<br/>11 each of those other candidates?<br/>12 A. I wouldn't. Again, I would say let's pick<br/>13 one or two and let's go with it, especially if there<br/>14 was no benefit of one -- known benefit of one<br/>15 compound over another from Dr. Eck.<br/>16 MS. PATEL: Why don't we take a break and<br/>17 I'll see how much more I have left, if anything.<br/>18 MS. DANEK: Okay.<br/>19 THE VIDEOGRAPHER: Off the record at 3:38<br/>20 p.m.<br/>21 (Recess.)<br/>22 THE VIDEOGRAPHER: Back on the record at</p> | Page 202 | <p>1 optimal scenario if you were going to develop a drug,<br/>2 that you would engage in that high-throughput assay.<br/>3 At the same time, the bare minimum would be making<br/>4 sure obviously it -- that structurally or otherwise<br/>5 from talking to Dr. Eck or other members of, you<br/>6 know, biology or chemistry team, that it irreversibly<br/>7 inhibited BTK. That would be the -- that would be<br/>8 the critical component.<br/>9 You wouldn't have to do the<br/>10 high-throughput screening to understand off-target<br/>11 effects to still practice the scope of the claim<br/>12 which would say that inhibiting BTK is<br/>13 therapeutically effective for CLL and SLL.<br/>14 MS. PATEL: Okay. I pass the witness.<br/>15 MS. DANEK: No questions.<br/>16 MS. PATEL: Okay.<br/>17 THE VIDEOGRAPHER: Anything else we need<br/>18 on the record, Counsel, before I read us off?<br/>19 MS. PATEL: No.<br/>20 MS. DANEK: No.<br/>21 THE VIDEOGRAPHER: Going off the record at<br/>22 3:50 p.m.</p> | Page 204 |
| <p>1 3:47 p.m.<br/>2 BY MS. PATEL:<br/>3 Q. Dr. Spurgeon, could you turn to paragraph<br/>4 131 of your declaration, please.<br/>5 A. 131?<br/>6 Q. Yes.<br/>7 A. Yes.<br/>8 Q. Do you see halfway down the paragraph<br/>9 where you say, "Notably, a POSA reading the '803<br/>10 patent to identify additional BTK inhibitors with<br/>11 ibrutinib's structural features for use in the<br/>12 claimed method would have understood how to measure<br/>13 kinase selectivity and potency against a given kinase<br/>14 using standard assays, including with commercially<br/>15 available high-throughput screening and kinase<br/>16 profiling"?<br/>17 A. Yes.<br/>18 Q. Do you agree -- so you agree that a POSA<br/>19 would need to test a candidate BTKI to measure kinase<br/>20 selectivity and potency, right?<br/>21 MS. DANEK: Objection, form.<br/>22 THE WITNESS: I agree that would be the</p>                                                                                                                                                            | Page 203 | <p>1 (Whereupon, at 3:50 p.m., the taking of<br/>2 the instant deposition ceased.)<br/>3<br/>4<br/>5<br/>6<br/>7<br/>8<br/>9<br/>10<br/>11<br/>12<br/>13<br/>14<br/>15<br/>16<br/>17<br/>18<br/>19<br/>20<br/>21<br/>22</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Page 205 |

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|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| <div>1 CERTIFICATE OF REPORTER</div> <div>2 UNITED STATES OF AMERICA ) ss:</div> <div>3 DISTRICT OF COLUMBIA )</div> <div>4 I, MARY GRACE CASTLEBERRY, RPR, the officer</div> <div>5 before whom the foregoing proceedings were taken, do</div> <div>6 hereby certify that the foregoing transcript is a</div> <div>7 true and correct record of the proceedings; that said</div> <div>8 proceedings were taken by me stenographically to the</div> <div>9 best of my ability and thereafter reduced to</div> <div>10 typewriting under my supervision; and that I am</div> <div>11 neither counsel for, related to, nor employed by any</div> <div>12 parties to this case and have no interest, financial</div> <div>13 or otherwise, in its outcome.</div> <div>14</div> <div>15</div> <div>16</div> <div>17 Notary Public in and for</div> <div>18 The District of Columbia</div> <div>19</div> <div>20</div> <div>21 My commission expires: 7/14/2026</div> <div>22</div> | <div>Page 206</div> |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                     |

Notice Date: Tuesday, 10. September 2024

Attention: Stephen E. Spurgeon, M.D.

Re:BeiGene USA, Inc. and BeiGene, LTD. v. Pharmacyclics LLC  
Deposition of Stephen E. Spurgeon, M.D. (9/6/2024)

NOTICE REGARDING SIGNING DEPOSITION TRANSCRIPT

The above referenced transcript is available for review. Within 30 days, or the applicable timeframe of your legal jurisdiction, the witness may read the testimony to verify its accuracy. Any changes can be noted on the following errata page.

Once the transcript has been reviewed, the witness should sign and date the certificate of deponent page. The signed certificate, errata, and original transcript (if provided) must be returned to TP.One per the rules of civil procedure.

If the transcript and errata are not returned within the allotted time, the unsigned transcript may be used as if signed by the witness.

Thank you,

TP.One Production Department  
Production@tp.one



Deponent Errata Page

Notice Date: 09/10/2024

Deposition Date: 9/6/2024

Deponent: Stephen E. Spurgeon, M.D.

Case Name: BeiGene USA, Inc. and BeiGene, LTD.  
v. Pharmacyclics LLC

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CERTIFICATE OF DEPONENT

I hereby certify that I have read and examined the foregoing transcript, and the same is a true and accurate record of the testimony given by me. Any additions or corrections that I feel are necessary, I will attach on a separate sheet of paper to the original transcript.

\_\_\_\_\_  
Signature of Deponent

I hereby certify that the individual representing himself/herself to be the above-named individual, appeared before me this \_\_\_\_ day of \_\_\_\_\_, 20\_\_, and executed the above certificate in my presence.

\_\_\_\_\_  
NOTARY PUBLIC IN AND FOR

\_\_\_\_\_  
County Name

MY COMMISSION EXPIRES:

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