

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

3 PGR2024-00009

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

5 - - - - -

6 BEIGENE USA, INC. AND BEIGENE, LTD.,
7 Petitioners,

8 v.

9 PHARMACYCLICS LLC

10 Patent Owner.

11 - - - - -

12

13 DEPOSITION OF MICHAEL J. ECK, M.D., PH.D., a
14 witness herein, pursuant to notice, the witness being duly
15 sworn by TERI C. GIBSON, Notary Public in and for the
16 State of Massachusetts, the witness physically located at
17 LATHAM & WATKINS LLP, 200 Clarendon Street, Boston, MA
18 02116, at 9:16 a.m., October 8, 2024, and the proceedings
19 taken down by Mechanical Stenography and computer-aided
20 transcription by TERI C. GIBSON, CSR, RPR, CRR.

21

22

23

24

25

Page 2			Page 4		
1	APPEARANCES:		1	E X H I B I T S (Retained)	
2	WEIL, GOTSHAL & MANGES LLP		2	NUMBER	DESCRIPTION PAGE
3	By: Anish Desai, Esq.		3	Exhibit 1001	HHS Public Access. Author 8
4	anish.desai@weil.com		4	manuscript. Re: Discovery of a	
5	By: Priyata Y. Patel, Esq.		5	BTK/MNK Dual Inhibitor for	
6	priyata.patel@weil.com		6	Lymphoma and Leukemia.	
7	By: Kathryn Leicht, Esq.		7	Exhibit 1060	Article entitled, "Discovery of 85
8	kathryn.leicht@weil.com		8	Selective Irreversible Inhibitors	
9	2001 M Street N.W., Suite 600		9	for Bruton's Tyrosine Kinase," by	
10	Washington, D.C. 20036		10	Zhengying Pan and others.	
11	(202)682-7000		11	Exhibit 2010	Declaration of Dr. Eck 7
12	Counsel for the Petitioner.		12	Exhibit 2011	CV of Michael J. Eck. 7
13	LATHAM & WATKINS LLP		13	Exhibit 2024	U.S. Patent 10,358,446 B2. Date 142
14	(By Brenda L. Danek, Esq.)		14	of Patent: Jul. 23, 20119.	
15	330 North Wabash Avenue, Suite 2800		15	Bruton's Tyrosine Kinase	
16	Chicago, IL 60611		16	Inhibitors. EX2024.0001 through	
17	(312)876-7646 E-mail: brenda.danek@lw.com		17	EX2024.0164.	
18	Counsel for the Patent Owner.		18	Exhibit 2028	Article entitled, 106
19	ALSO PRESENT:		19	"Kinase-targeted libraries: The	
20	Bob Giannini, Videographer		20	Design and synthesis of novel,	
21	*****		21	potent, and selective kinase	
22			22	inhibitors."	
23			23	Exhibit 2037	Glide 5.5 User Manual 118
24			24		
25			25		

Page 3			Page 5		
1	I-N-D-E-X		1	E X H I B I T S	
2	WITNESS	PAGE	2	NUMBER	DESCRIPTION PAGE
3	MICHAEL J. ECK, M.D., PH.D.		3	Exhibit 2046	Article entitled, "Discovery of 97
4	By Mr. Desai	7	4	TAK-659 an orally available	
5	By Ms. Danek	168	5	investigation inhibitor of Spleen	
6			6	Tyrosine Kinase (SYK).	
7	E X H I B I T S		7	Exhibit 2055	Article Re: Synthesis and SCAR. 96
8	NUMBER	DESCRIPTION PAGE	8	*****	
9	Exhibit 1	HHS Public Access. Author 24	9		
10	manuscript. Re: Discovery of a		10		
11	BTK/MNK Dual Inhibitor for		11		
12	Lymphoma and Leukemia.		12		
13	Exhibit 2	U.S. Patent 11,672,803 B2. Date 74	13		
14	of Patent: June 13, 2023. Use		14		
15	of Inhibitors of Brutons Tyrosine		15		
16	Kinase (BTK)		16		
17	Exhibit 3	Screenshot of a file. Maestro - 147	17		
18	Scratch Project (from Ex.		18		
19	2113.prjzip)		19		
20	Exhibit 4	Screenshot, Maestro - Scratch 148	20		
21	Project (from Ex. 2114.prjzip)		21		
22	Exhibit 5	Screenshot, Maestro - Scratch 150	22		
23	Project (from Ex. 2113.prjzip)		23		
24	Exhibit 6	Screenshot, Maestro - Eck_Ex2114 153	24		
25	(Attached to the transcript)		25		

1 P-R-O-C-E-E-D-I-N-G-S 2 VIDEOGRAPHER: Good morning. 3 We are on the record. This is the 4 videographer speaking, Bob Giannini, with court 5 reporter Teri Gibson with Trust Point.One. 6 Today's date is October 8, 2024. 7 The time is 9:16 a.m. Eastern time. 8 We are here with Latham & Watkins 9 located in Boston, Massachusetts, taking the 10 video deposition of Michael Eck in the matter of 11 BeiGene U.S.A., Inc., and BeiGene Limited versus 12 Pharmacyclics, LLC. 13 Will counsel please introduce 14 themselves for the record? 15 MR. DESAI: Anish Desai on behalf of 16 the petitioner. 17 MS. PATEL: Priyata Patel on behalf of 18 the petitioner. 19 MS. LEICHT: Kathryn Leicht on behalf 20 of the petitioner. 21 MS. DANEK: Brenda Danek with Latham & 22 Watkins on behalf of Pharmacyclics and the 23 witness. 24 VIDEOGRAPHER: Will the court reporter 25 please swear in the witness?	Page 6	1 A. I have that as well. 2 Q. That's Exhibit 2011. 3 A. Yes. 4 (Exhibit 1001 previously marked for 5 identification, an article. Re: 6 Discovery of a BTK/MNK Dual Inhibitor for 7 Lymphoma and Leukemia.) 8 Q. And you also should have a copy of the 9 patent at issue, the '803 patent, which is 10 Exhibit 1001. 11 Do you see that? 12 A. I do, yes. 13 Q. Okay. Have you ever been deposed before? 14 A. I have, yes. 15 Q. How many times? 16 A. I don't know an exact number. 17 Q. So more than a few times? 18 A. Six, seven, on the order of that. 19 Q. So you are a bit familiar with this 20 process? 21 A. It's been a while, but I have been through 22 it before. 23 Q. Okay. I guess a few simple ground rules 24 for today. The reporter is writing down everything we 25 are saying, so it's important that you and I wait for	Page 8
1 (Oath given to the witness.) 2 MICHAEL J. ECK, M.D., PH.D. 3 EXAMINATION 4 BY MR. DESAI: 5 Q. Could you state your full name for the 6 record? 7 A. Michael Joseph Eck. 8 Q. And it's Dr. Eck. 9 Do you understand that you are here today 10 for a deposition in the PGR 2024-0009? 11 A. I do, yes. 12 Q. And you have submitted an expert 13 declaration on behalf of Pharmacyclics, correct? 14 A. That's correct. 15 (Exhibit 2010 previously marked for 16 identification, Declaration of Dr. Eck.) 17 *** 18 (Exhibit 2011 previously marked for 19 identification, CV of Michael J. Eck.) 20 Q. You should have in front of you a copy of 21 your declaration which is Exhibit 2010; do you see 22 that? 23 A. I do, yes. 24 Q. And there should also be a copy of your CV; 25 do you see that?	Page 7	1 each other. I will wait for you to finish answering 2 before I ask the next question, and if you do your 3 best to wait until I am done asking the question and 4 start answering, that will make things go smoother. 5 Do you understand? 6 A. I do. 7 Q. If you don't understand a question, just 8 let me know, and I will do my best to ask a better 9 question if I can; is that okay? 10 A. Yes. 11 Q. And I usually try to take a break every 12 hour. If you want a break sooner, let me know, and I 13 will do that. 14 A. That works for me. 15 Q. Okay. Is there any reason you can't 16 provide accurate and truthful testimony today? 17 A. No. 18 Q. And you've been retained by Pharmacyclics 19 to provide testimony in this case. When did your firm 20 first learn about this case? 21 A. I don't remember precisely but last summer. 22 Probably first became aware of it early last summer. 23 By "last summer", I mean summer of 2023. 24 Q. Why don't we take a -- just pull up your 25 declaration, and you've confirmed that is your	Page 9

1 declaration, right? 2 A. Yes. 3 Q. Okay. Did you review this declaration 4 before signing it? 5 A. I did, yes. 6 Q. Okay. And when did you start preparing 7 this declaration? 8 A. Well, I don't remember precisely when I 9 started working on the document. I believe I was 10 formally retained by Pharmacyclics in August of 2023 11 and began working in earnest on the case as of around 12 that time. 13 Q. Okay. Can you estimate how much time 14 you've spent preparing this declaration that was 15 submitted on or signed on August 6, 2024? 16 A. In the hundreds of hours. Probably in the 17 neighborhood of 200 hours that I've tracked for 18 invoicing purposes but many hours that I've tracked 19 for invoicing purposes, and I'm sure many more hours 20 that I've spent thinking about it, laying in bed at 21 night or in the middle of the day, taking a few 22 minutes to do a literature search and going down a 23 rabbit hole that I -- you know -- neglected to write 24 down. 25 Q. Did you draft this declaration yourself?	Page 10	1 declaration, as far as I know, is included in the 2 table. 3 Q. What did you do to prepare for today's 4 deposition? 5 A. Met with counsel, reviewed materials 6 relevant to the case, reread my declaration, reviewed 7 the patent, reviewed Dr. Showalter's first 8 declaration, other materials relevant to the case. 9 Q. How many meetings did you have with lawyers 10 preparing for the deposition? 11 A. I believe three. 12 Q. How much time was spent preparing? 13 A. Roughly half a day for a couple days and 14 one full day. 15 Q. Okay. Among the materials you reviewed, 16 did you look over -- strike that. 17 Do you understand that you -- you provided 18 some native files with respect to the modeling you 19 did? 20 A. Yes. 21 Q. Okay. And in preparing for today's 22 deposition, did you look over any of those native 23 files? 24 A. I didn't, no, not -- you know -- not since 25 I provided them to counsel to provide to you.	Page 12
1 A. Drafted it together with counsel. 2 Q. Aside from counsel, did you have anyone -- 3 did you consult with anyone in preparing this 4 declaration? 5 A. No. 6 Q. Did you have any assistance from any 7 individuals in your lab when drafting this 8 declaration? 9 A. No. 10 Q. So it's fair to say you have not consulted 11 with anyone, other than your attorneys while drafting 12 this declaration? 13 A. That's correct. I've relied on materials 14 as I've cited in my report, but I haven't consulted 15 with anyone. 16 Q. If you go to pages 5 through 10 of your 17 declaration, there is a list of materials reviewed and 18 considered. 19 Do you see that? 20 (Witness reviewing the document.) 21 A. I do, yes. 22 Q. Is there anything that you feel as though 23 you had reviewed and considered that you did not 24 include in this table? 25 A. I think everything that is relevant to the	Page 11	1 Q. All right. And did you review your 2 declaration in preparing? 3 A. Yes. 4 Q. Have you identified any errors or mistakes 5 in your declaration that you would like to correct? 6 A. I haven't noticed anything that needs 7 correcting, no. 8 Q. Okay. Why don't we look at your CV in 9 Exhibit 2011. That is your CV, correct? 10 A. That's correct. 11 Q. Is this relatively up to date? 12 A. Usually, it has a date prepared or updated 13 on it, but it was up to date as of the time it was 14 provided a few months ago. 15 Q. You have a bachelor's degree in electrical 16 engineering from RICE? 17 A. I do, yes. 18 Q. And while you were at RICE, did you 19 study -- did you do any -- did you have particular 20 study with respect to computational chemistry? 21 A. I didn't study computational chemistry at 22 RICE. I did a course in organic chemistry and other 23 courses in chemistry but not -- not anything in 24 computational chemistry. 25 Q. Did you have any classes or receive any	Page 13

1 training with respect to ligand screening or docking 2 software? 3 A. As an undergraduate, no. 4 Q. (Nodding head up and down.) 5 A. No. 6 Q. You have an MD and a Ph.D. in biochemistry 7 from the University of Texas, Southwestern, right? 8 A. That's correct. 9 Q. And you completed, is it -- let's see -- 10 medical school and your Ph.D. in 1991, right? 11 A. Correct. 12 Q. Okay. Throughout any of that work, your MD 13 and Ph.D., did you study computational chemistry? 14 A. Learned aspects of it in courses in 15 graduate school and -- and, you know, in my training 16 as a Ph.D. student and tools that we use in 17 crystallography use aspects of computational chemistry 18 and molecular dynamics, simulated annealing 19 refinement. 20 Q. Did you take any classes or receive any 21 training in virtual ligand screening or docking 22 software? 23 A. I haven't taken any formal courses in 24 virtual ligand screening or docking. 25 Q. Did you receive any training with respect	Page 14 1 you were conducting virtual ligand screening and using 2 docking software? 3 A. I don't recall having done any virtual 4 ligand screening as a postdoc, no. 5 Q. During any of your coursework or during 6 your post-doctoral fellowship, did you study protein 7 kinesis? 8 A. Sorry. Can you repeat that? 9 Q. During any of your coursework or your 10 post-doctoral fellowship, did you study protein 11 kinesis? 12 A. Yes. 13 Q. Can you describe the study, what courses 14 you took or when was that? 15 A. So much of my post-doctoral research was in 16 the area of tyrosine kinases. One of the 17 contributions that I'm most proud of is having 18 determined the three dimensional structure of a kinase 19 called SARK, one of the first recognized 20 proto-oncogenes. This was a major landmark in the 21 field, or at least I like to think that it was, 22 understanding how it works and was regulated from a 23 structural perspective. 24 Q. Have you done any study with respect to 25 kinase inhibitors? Page 16
1 to those during your years in medical school to obtain 2 your Ph.D.? 3 A. Not that I recall. 4 Q. All right. And then you did your 5 post-doctoral fellowship, which was in structural 6 biology, is that right? 7 A. Yes. 8 Q. And you completed that in 1996? 9 A. Yes. 10 Q. Did that involve any study of computational 11 chemistry? 12 A. No formal classroom work in computational 13 chemistry. 14 Q. Was there any informal work? 15 A. Again, we use aspects of computational 16 chemistry in my research and, you know, and -- you 17 know, I'm sure read papers, although I don't recall 18 specific papers that I read in the field of 19 computational chemistry. 20 Q. Did you take any classes or receive any 21 training in virtual ligand screening or docking 22 software during your post-doctoral fellowship? 23 A. Not that I recall. Again, no formal 24 training but part of the world that I was embedded in. 25 Q. So during your post-doctoral fellowship,	Page 15 1 A. Yes. 2 Q. Can you describe that? 3 A. It's been a long-time interest throughout 4 my professional career studying, not just the 5 structure and regulation of protein kinases but also 6 how inhibitors bind to them and determining co-crystal 7 structures of inhibitors bound to kinases. 8 Q. Since 1991, you have held academic 9 appointments at Harvard Medical School, correct? 10 A. In 1991 as a post-doctoral fellow, yes. 11 Q. Is it correct that since 1991 you've 12 been -- 13 A. I have been affiliated with Harvard, yes, 14 in one capacity or another. 15 Q. In that time period, from 1991 to the 16 present, have you done any work in computational 17 chemistry? 18 A. It depends on what you mean by, "done work 19 in computational chemistry." My lab has used 20 computational chemistry tools over that period of time 21 on a number of projects. 22 Q. Okay. Sticking with that, your lab using 23 computational chemistry tools over that period of 24 time, was it you specifically that was using those 25 computational tools or was it someone else in your Page 17

1 lab? 2 A. It was most typically people that I 3 supervised using them. 4 Q. Can you -- is there -- are you able to 5 identify a time when you were the one that was 6 specifically using these computational tools? 7 A. I certainly engaged with my trainees and 8 used the tools myself at times to follow their work 9 and to learn more myself about how the tools work and 10 what they were powerful for. 11 Q. Can you identify some of these 12 computational tools that you've used in your lab? 13 A. So for virtual ligand screening it's been 14 primarily Schrödinger software, the Maestro, Glide 15 programs for virtual ligand screening and docking. We 16 have used molecular dynamics software and molecular 17 dynamics embedded within crystal graphic software 18 refinement packages for our structural biology and 19 x-ray crystallography work. 20 Q. Okay. And in your lab when you've been 21 talking about the use of this software for virtual 22 ligand screening, is it typically someone else in your 23 lab that's using the software, or is it typically you 24 that's using the software? 25 A. As I said, it's typically my trainees or	Page 18 1 where I see the whole thing at once? 2 Q. Okay. Were there multiple occasions where 3 you had to speak with Mister -- I'm trying to say the 4 name -- Guzgalas? 5 A. There were a few. 6 Q. Can you describe, aside from the one you've 7 just mentioned, that you were stuck in a mode, what 8 other questions you had of Mr. Guzgalas? 9 A. I'm trying to think. I think, if I'm 10 remembering right, we discussed, you know, other 11 options for software to use for docking. You know, he 12 mentioned a package called VinaDock or AutoDock. In 13 the end, you know, I thought that since I used 14 Schrödinger software and Maestro and Glide before, 15 that was the software -- the Schrödinger software, 16 Maestro, and Glide, these are the names of programs. 17 Since I'd used them previously, that that's what I 18 would use here. It's very common, standard software 19 across the industry and has been for quite some time, 20 including well before 2011. 21 Q. If you might just speak up a little bit 22 more. 23 A. Yes. 24 Q. What's Mr. Guzgalas' background? 25 A. He's a Ph.D. computational chemist. He is
1 staff scientists. 2 Q. But in this case for your declaration, you 3 did utilize some of this docking software? 4 A. Correct, hands on, me, myself. 5 Q. And you did not enlist the help of anyone 6 in your lab? 7 A. I did the docking myself. If I had 8 questions, I'd pop out and talk to my comp-chem expert 9 in the lab, computational chemistry post-doc, but I 10 did all of the work on this myself. 11 Q. So you did speak to your computational 12 chemistry post-doc with respect to the work you've 13 done in this case? 14 A. I asked questions of it. I didn't enlist 15 him to do the work for me, but if I had a question, I 16 would ask him. 17 Q. And what's -- can you just -- what's his 18 name or her name? 19 A. Demetrius Guzgalas (phonetic). 20 Q. Can you recall what questions you asked? 21 A. Let's see if I can think of a specific 22 example. 23 I was stuck in a mode that I couldn't 24 figure out how to get out of and so forth. You know, 25 how do you -- you know, how do I get back to the view	Page 19 1 a post-doctoral fellow. 2 Q. Would you say his expertise is more -- 3 strike that. 4 Would you say that he is more experienced 5 or less experienced than you in using these types of 6 docking software for virtual ligand screening? 7 A. He's, you know, a full-time computational 8 chemist. You know, I wouldn't want to try and sum up 9 my years of experience and perspective compared with 10 his, but I would consider him more expert in 11 computational chemistry as a discipline than I am. 12 He is a person who can write and modify 13 computational chemistry software. I'm not such a 14 person. I'm a tool user, not a toolmaker in that 15 respect. 16 Q. Okay. Why don't we take a look at 17 paragraph 6 of your declaration. Are you there? 18 A. Oh, sorry. I'm looking at Page 6 of my CV. 19 Q. Yeah, I'm sorry. The declaration. 20 (Witness complied.) 21 A. I'm there. 22 Q. Okay. Do you see where it says: 23 "Cancer drug discovery is a major focus 24 of my laboratory"? 25 A. Yes, I do.
	Page 20
	Page 21

Page 22 1 Q. And there is a reference to "EGFR", do you 2 see that? 3 A. I do. 4 Q. Does that refer to "epidermal growth factor 5 receptor"? 6 A. That's correct, yes. 7 Q. Is that a tyrosine kinase? 8 A. It is, yes. 9 Q. Are you familiar with the name -- I'm 10 trying to say it -- osimertinib? 11 A. Very much, yes. 12 Q. Did I say that right? 13 A. You did. Very good. 14 Q. Is that an inhibitor of EGFR? 15 A. It is, yes. 16 Q. And it's FDA-approved as Tagrisso? 17 A. Correct. 18 Q. Is that an AstraZeneca drug? 19 A. It is. 20 Q. And I will use the word "Tagrisso" because 21 that's easier to say. 22 A. You can call it "OC". That's what we call 23 it. 24 Q. Okay. Tagrisso forms covalent bond to a 25 cysteine residue of EGFR, correct?	Page 24 1 Okay. Why do you say, "no"? 2 A. I had no interactions with AstraZeneca. 3 This predated any, as far as we know, any work of 4 AstraZeneca along the lines of this particular 5 concept. 6 Q. Okay. So in this -- for this project with 7 respect to Tagrisso, it wasn't a situation where 8 AstraZeneca provided a series of potential inhibitors 9 to you? 10 A. No. 11 Q. Why don't we take a look at exhibit -- this 12 is exhibit -- we need to mark this. Sorry. We need a 13 sticker. 14 (Exhibit 1 marked for identification, an 15 article. Re: Discovery a BTK/MNK Dual 16 Inhibitor for Lymphoma and Leukemia.) 17 Q. I've handed you a paper that's been marked 18 as Eck 1, Eck Exhibit 1, and it's a January 2016 paper 19 entitled, "Discovery of a BTK/MNK Dual Inhibitor for 20 Lymphoma and Leukemia." 21 Do you see that? 22 A. I do, yes. 23 Q. Do you recognize this paper? 24 A. I do. 25 Q. And you are one of the co-authors?
Page 23 1 A. That's correct. 2 Q. And it targets the ATP-binding site? 3 A. It does. 4 Q. Is the Tagrisso project one the projects 5 you reference in this paragraph that involved 6 structure information -- informed development of 7 irreversible inhibitors that target a cysteine residue 8 near the active site? 9 A. Yes and no. AstraZeneca probably would say 10 "no," but I might say "maybe." 11 Q. Can you elaborate? 12 A. So my colleagues and I developed the first 13 so-called third generation EGFR inhibitor, a molecule 14 called WZ4002. We published it in a nature paper in 15 2009. The concept there was to develop a compound 16 that was a covalent inhibitor of EGFR, but that it was 17 selective for the mutant form over wild type EGFR. 18 And WZ4002 was more or less a roadmap for the 19 development of osimertinib, which came a few years 20 later from AstraZeneca as a similar structural 21 scaffold to osimertinib, Tagrisso. 22 Q. So was this project with respect to 23 Tagrisso, was it a collaboration with AstraZeneca? 24 A. No. 25 Q. No.	Page 25 1 A. I am, yes. 2 Q. If we take a look at the abstract. Would 3 you agree that the goal of this study that's being 4 described here is to discover an inhibitor that 5 inhibits both BTK and MNK? 6 A. That was the outcome of the study. I'm not 7 sure that that was the goal from the get-go. 8 Q. Okay. But that was the result? 9 A. That was the result. 10 Q. All right. Speaking of results, why don't 11 we go to the section on Page 7, entitled "Results." 12 (Witness complied.) 13 Q. The very first sentence confirms what we 14 were just talking about, that it was being envisioned 15 that there could be an inhibitor that could target -- 16 target two distinct cysteine residues ATP-binding 17 sites of both kinases, right? 18 A. Yes. 19 Q. And then if you go to the next paragraph, 20 it says: 21 "In order to explore this possibility, we 22 searched our kinase inhibitor database to 23 identify a scaffold that could provide a 24 suitable platform..." 25 Do you see that?

Page 26 1 A. Yes. 2 Q. So is it fair to say that in order to 3 identify a scaffold here, you and your co-authors 4 searched a kinase inhibitor database that contained 5 known structures? 6 A. That's what it says here. I don't have a 7 specific memory of this aspect of the project and how 8 it involved -- if I'm remembering right, this was a 9 project that my lab was fairly peripherally involved 10 in. 11 Q. If we take a look at -- sticking with that, 12 that paragraph, it mentions "Torin2" in the next 13 sentence? 14 A. Yes. 15 Q. It talks about that being a -- an excellent 16 inhibitor of mTOR but less potentially inhibits MNK2? 17 A. Correct. It says, "mTOR (IC50=250 pM)", 18 which is quite potent, but only 620 nanomolar against 19 MNK2. 20 Q. Okay. So I believe what was then described 21 is some potential changes to Torin2; is that right? 22 A. Yeah. Give me a minute, and I can read. 23 Q. Sure. And maybe you could also look at 24 Figure 1B on Page 15. That might help you. 25 (Witness reviewing Exhibit 1.)	Page 28 1 these experiments suggest that QL-X-138 2 is a non-covalent inhibitor of MNK1 and 2 3 kinases", correct? 4 A. Where are you reading now? 5 Q. It's at the top of Page 8. 6 A. "Collectively these experiments suggest 7 that QL-X-138 is a non-covalent inhibitor 8 of MNK1 and 2 kinases." 9 That's what it says, correct. 10 Q. Okay. Do you also understand that a 11 docking study of QL-X-138 was conducted with respect 12 to the MNK2 kinase structure? 13 A. Can you direct me to the figure or section 14 where that -- 15 Q. It would be the bottom of Page 8. 16 (Witness reviewing the document.) 17 A. Yes, that's correct. A modeling study was 18 done docking QL-X-138 and MNK. 19 Q. Okay. And if we go to page 16, are you 20 there? 21 A. Yes. 22 Q. Figure 2F is the, "Molecular modeling 23 demonstration of the designed 24 irreversible binding mode of QL-X-138 25 with MNK2 kinase", correct?
Page 27 1 A. Okay. 2 Q. Okay. So what you see in Figure 1B and 3 also described on page 7 is this structure that's 4 called, "QL-X-138"? 5 A. Yes. 6 Q. Okay. And that's a modification of Torin2, 7 right? 8 A. It would be fair to say that Torin2 was the 9 inspiration for QL-X-138 -- 10 Q. Okay. 11 A. -- or that QL-X-138 incorporates aspects of 12 the Torin2 structure. 13 Q. Right. 14 And then on Page 7, there is a description 15 of tests that were performed on QL-X-138, right? 16 The last paragraph. 17 (Witness reviewing the document.) 18 A. That's correct. 19 Q. Right. 20 So you had also described, if you turn to 21 the -- it's the bottom of Page 7 and the top of Page 22 8. Do you see that? Describing the assays that were 23 performed, right? 24 A. Yes. 25 Q. Okay. And it states that, "Collectively	Page 29 1 A. That's correct. 2 Q. Did you do this modeling? 3 A. I did not, no. 4 Q. Do you know who did? 5 A. Not for sure. It's possible that it was my 6 post-doctoral fellow Kai Hon Yun (phonetic), but it's 7 more likely that either one of Nathaniel Gray's 8 post-docs or Kin Song Lu (phonetic) or one of his 9 colleagues took the project with them to their new 10 position in China, would have done them, the molecular 11 modeling. The major role of my lab and this paper was 12 the crystallography work with the compound, and that 13 would have been Kai Hon Yun's work. 14 Q. Okay. Looking at this molecular modeling, 15 2F, this would suggest that the warhead would form a 16 covalent bond with the cysteine 225, correct? 17 A. So as it's modeled here, the -- well, to 18 back up a bit, the cysteine that's being targeted in 19 MNK1/2, the cysteine 225, is in a different position 20 than cysteine 481 in BTK, and you can see that in 21 Panel A of Figure 1. 22 And so I would describe this as a 23 relatively speculative docking exercise that maybe by 24 virtue of being able to bind in a different 25 confirmation to MNK that instead of binding -- well,

1 sorry, I shouldn't say that. 2 MNK doesn't have the same corresponding 3 cysteine. It's Cys481 and BTK. So the concept here 4 was that maybe with a different binding mode with the 5 inhibitor, you could hit this different cysteine. And 6 that's what the modeling suggested, that that was a 7 reasonable hypothesis in this case. But I want to 8 make clear that we would have regarded this as a much 9 more speculative hypothesis than -- than, you know, 10 for example, docking an [^]abrutinive-like molecule in 11 BTK. 12 Q. Okay. 13 A. So sort of a qualitatively different 14 docking exercise given a very different set of 15 structural facts and circumstances and relatedness to 16 known inhibitors. 17 Q. Okay. So then is it fair to say this 18 was -- you would characterize this as a fairly 19 speculative modeling demonstration of irreversible 20 binding of QL-X-138 with the MNK2 kinase? 21 A. I think in this particular case, it was a 22 bit of a reach. And, again, this is, you know, me 23 looking at what I'm seeing here now. I haven't, you 24 know, reviewed this paper recently. I haven't thought 25 deeply about it, but that's the -- that's what I'm	Page 30	1 Q. So one of the tests you performed was an IP 2 kinase assay with BTK measuring IC50 value? 3 A. That's correct. That's what it says here. 4 Q. Okay. And there is also demonstrated that 5 QL-X-138 might irreversibly inhibit BTK because it had 6 an IC value of 9.4 -- 7 (Reporter requested clarification.) 8 MR. DESAI: Slow down. I'm sorry. 9 Yeah, I will try again. 10 BY MR. DESAI: 11 Q. And the results demonstrated that QL-X-138 12 might irreversibly inhibit BTK because it had an IC50 13 value of 9.4 nanomolar, correct? 14 A. That's correct. That's the first half of 15 the sentence. 16 Q. And then if we go to Page 8, there was some 17 molecular modeling study done with the BTK kinase 18 x-ray structure, correct? 19 The very bottom of the page. 20 A. Yeah, I was just reading it. That's 21 correct. 22 Q. Okay. So after performing the assay to 23 measure the IC50 value, a docking study of this 24 structure was performed, right? 25 A. I have no idea what the sequence of events	Page 32
1 taking from it as we sit here today. 2 Q. All right. And then the assays that were 3 performed, the experimental results demonstrated that 4 QL-X-138 is a non-covalent inhibitor of MNK1/2, 5 correct? 6 A. I haven't read the whole paper but from the 7 paragraph that we just reviewed, the takeaway was that 8 it was likely binding to MNK in a non-covalent mode. 9 Although, the evidence for that was the ADP 10 competitive aspect and, you know, depending on 11 precisely how the experiment was performed, you might 12 or might not have been able to rely on that as a 13 readout of covalent versus non-covalent binding, but 14 my colleagues are careful scientists, and I assume 15 they did it right. 16 Q. Okay. Why don't we keep going. 17 If we look at Page 8 -- actually, I'm 18 sorry. Stay on Page 7. The second full paragraph. 19 Towards the middle, there is a discussion of 20 experiments with respect to the BTK kinase. 21 Do you see that? 22 A. Starting with, "An IP kinase assay" with 23 BTK kinase demonstrated? 24 Q. Yes. 25 A. Yes.	Page 31	1 in real-time was. 2 Q. Okay. So you don't know whether the 3 modeling was done first or the assay? 4 A. It would have only made sense to have, you 5 know, been thinking about the way in which the 6 molecules would bind, you know, before having made 7 them and tested them in an assay. 8 Q. So you think that it would only have made 9 sense to have done the molecular modeling study first 10 and then do the assays. Is that what you are saying? 11 A. So let me clarify a bit. I think when -- 12 you know -- when one is working to develop inhibitors 13 for a target, one is thinking about how the molecules 14 that one is making bind. And so it's not like, you 15 know, we do this and then move on and forget about it. 16 You know. We are constantly, you know, looking and 17 revisiting and thinking and, you know, one person 18 might have done some modeling very early on, and 19 another person might have gone back later and done a 20 more formal docking study. 21 I don't have a specific recollection or 22 even ever -- don't know that I ever had any specific 23 knowledge of exactly who did what at what point in 24 time in this particular study. But, typically, you 25 know, this is -- it's -- I would say, you know, we are	Page 33

1 immersed in the -- in the structure of the molecules 2 and visualization tools. Docking tools are things 3 that were used day in and day out to understand how 4 things work and to visualize the binding molecules. 5 Q. Okay. I want to clarify because you did 6 say that it would only have made sense to have been 7 thinking about the way in which the molecules would 8 bind before having made them and test them in an 9 assay. So I just want to understand what's your 10 testimony or opinion. 11 A. Before and after, yeah. So I didn't mean 12 by "before," exclusively before, but I would imagine 13 it would be hard for me to imagine that somebody who 14 is a part of this team wouldn't have been with 15 whatever tool of choice, you know, considering how the 16 molecule would bind and target kinases, you know, at 17 some point before modifying the structures. 18 Q. Okay. So then to be fair, you don't know 19 whether the modeling -- sorry -- the molecular 20 modeling study and the assays in this paper were 21 conducted, whether they were conducted or whether they 22 were done at the same time; is that right? 23 A. I've tried to make clear that I don't have 24 the specific knowledge of who did what and in what 25 order or when it was done, but that my experience with	Page 34	1 structure of EGFR with covalent inhibitors bound and 2 thought about ways of grafting acrylamide on to JAK 3 inhibitor scaffolds to make JAK3 inhibitors. So that 4 would be one example from many years ago. 5 Q. Did you publish a paper on this? 6 A. We have published on JAK3, yes. 7 Q. Presumably, that would be listed in your CV 8 somewhere? 9 A. I would expect so, yes. 10 Q. We have been going about an hour, and we 11 are probably at a good spot to switch topics, so I'll 12 take a break. 13 VIDEOGRAPHER: 10:09 off the record. 14 (Off the record at 10:09 a.m.) 15 (On the record at 10:21 a.m.) 16 VIDEOGRAPHER: One moment. 17 Time, 10:21. 18 We are back on the record. 19 BY MR. DESAI: 20 Q. Okay. We were talking about the -- like, 21 the order of modeling versus experimental assays when 22 evaluating potential inhibitors before we went to 23 break, right? 24 A. Yes. 25 Q. Now, would you agree that regardless of the	Page 36
1 this and other projects such that these are tools we 2 are using on a regular basis. And it's likely that -- 3 that the molecular docking visualizations were done 4 and revisited at multiple points in the course of the 5 study, and we began in the course of preparation in 6 the manuscript. 7 Q. Can you give me an example? 8 You said in "my experience with this and 9 other projects." 10 Can you give me an example of a project you 11 had where the order of sort of operations was to 12 perform the molecular modeling study first and then 13 confirm with assays? 14 A. I can think of many examples. 15 Q. Okay. Can you provide a few of them 16 just -- sure. 17 A. Sure. So one of the first projects, maybe 18 the first project I worked on with Nathaniel Gray, 19 interested in making inhibitors of a kinase called 20 JAK3. And, you know, had the notion of making 21 irreversible JAK3 inhibitors. JAK3 happens to be one 22 of the kinases that has a cysteine in the 23 corresponding position to Cys481 and BTK. And, you 24 know, superimposed structures of JAK3 with inhibitors 25 bound, reversible inhibitors with -- with the	Page 35	1 order or the one after the other or at the same time, 2 the experimental part is necessary and you would never 3 rely solely on modeling to confirm that a potential 4 inhibitor will irreversibly bind a kinase? 5 A. I wouldn't make that generalization that 6 one would never want to -- want to do that. 7 Typically, in the course of an inhibitor discovery 8 project, you want to know whether the inhibitor does 9 in fact inhibit. So it would be routine to proceed as 10 well with biochemical assays to measure inhibition of 11 the kinase of interest by the molecule of interest. 12 Q. Okay. At paragraph 6 of your declaration, 13 it talks about cancer drug discovery being a major 14 focus of your laboratory; is that correct? 15 A. That's correct. 16 Q. Have you ever identified a cancer drug 17 based solely on modeling? 18 A. I'm not sure that I've ever identified what 19 has turned out to be a cancer drug by any method, 20 although I hope that I will have -- 21 Q. Okay. 22 A. -- if by "cancer drug" you mean a molecule 23 that's administered to patients to treat their cancer. 24 Q. So you've never identified any cancer 25 drugs?	Page 37

Page 38 1 A. To this point in any career, a molecule 2 that has come from my lab has not advanced to human 3 clinical trials. 4 Q. Okay. Now, you talked about collaborators 5 in Paragraph 6, and I guess we established that 6 Tagrisso was not an example that involved 7 collaboration, right? 8 A. Tagrisso, per se, didn't come from my lab, 9 correct. 10 Q. Can you give me an example of a development 11 of an inhibitor that did involve collaboration? 12 A. We are working now on a molecule called 13 EAI-432 that's an allosteric EGFR inhibitor. So it 14 has a different mechanism of action from Tagrisso. It 15 binds in a different binding pocket. That's a project 16 that's involved quite a lot of collaboration over the 17 years. 18 Q. Who are you collaborating with? 19 A. We discovered the initial scaffold in a 20 collaboration with Novartis, and we've worked for a 21 number of years with colleagues at the Dana-Farber; 22 with Nathaniel Gray, a medicinal chemist; Posse Hanna 23 (phonetic), a thoracic oncologist who has a research 24 laboratory that does cellular pharmacology studies of 25 inhibitors on lung cancer cell lines and developed	Page 40 1 a Novartis division called GNF in La Jolla. So they 2 did the high-throughput screen and identified chemical 3 matter. Then we subsequently studied selective 4 compounds that came out of that high-throughput screen 5 and determined how they bound to EGFR, the mutant 6 EGFR, using x-ray crystallography and kind of took it 7 from there with further development in studying their 8 mechanism faction and making subsequently more potent 9 inhibitors. 10 Q. Let me go back to a previous answer that 11 you gave, which was that none of the -- none of your 12 work has actually led to a cancer drug being put into 13 the clinic; is that right? 14 A. No molecule that we have developed has gone 15 to the clinic. We've inspired molecules that have, 16 osimertinib being an example. Osimertinib or 17 Tagrisso. 18 Q. Do you know why any of the inhibitors that 19 you've identified have not advanced to clinic? 20 A. I think, typically, you know, our role as 21 academics has been to develop things for proof of 22 concept stage. We haven't been resourced to further 23 develop them to clinical application. WZ-4002, you 24 know, I think, again, was, you know, an academic 25 effort. It's my understanding, actually, that it was
Page 39 1 compounds called JBJ-125 for short and JBJ-63 that we 2 subsequently published on. 3 Then we had a collaboration for about 4 two years with Takeda in further developing this 5 concept toward -- toward the clinical application. 6 Ultimately developed a molecule call EAI-432 that we 7 think is -- we are working to advance to the clinic. 8 My colleague David Scott, who runs the medicinal 9 chemistry for Dana-Farber worked together with me on 10 that for a number of years now. So very collaborative 11 project. 12 Q. Right. 13 So when you say, "We discovered the initial 14 scaffold in collaboration with Novartis", what was 15 your role in that collaboration? 16 A. I conceived the screen. At that -- at that 17 time, EGFR inhibitors that were being used in lung 18 cancer had been developed against wild type EGFR. As 19 far as I know, nobody had bothered to think about "or 20 maybe we could make an inhibitor that inhibited the 21 mutant form of the kinase but didn't inhibit the 22 normal form." 23 So I devised a screen, proposed it to 24 Novartis. My laboratory made the mutant kinase for 25 the screen, and the screening work was carried out at	Page 41 1 sold on the black market in China for some period of 2 time. 3 And so I would say nothing that came from 4 my lab directly was used in an approved capacity. I'm 5 not sure that some of it hasn't been used in an 6 unapproved capacity. But, yeah, typically, our 7 efforts have stopped short of trying to advance these 8 to the clinic. 9 Q. You have a patent, the '803 patent. Why 10 don't we go to the back of Claim 1. 11 A. I'm there. 12 Q. Okay. And you understand that a 13 significant focus of this case and this PGR has to do 14 with the Z' aspect of this claim? 15 A. I do, yes. 16 Q. Okay. And the structure of the Z'-scaffold 17 is recited in the claim at Column 151, starting right 18 below the picture and going to Column 152 to about 19 Line 5. Do you see that? 20 I'm sorry. Line 2. 21 A. I do, yes. 22 Q. Okay. And I understand you disagree with 23 Dr. Showalter's opinion regarding the breadth of the 24 potential irreversible BTKI structures that fall 25 within the scope of this claim, right?

Page 42 1 A. I do, yes. 2 Q. Okay. Do you agree that there are billions 3 of possible structures that fall within the scope of 4 the claimed Z'-structure? 5 A. No, I don't agree with that. 6 Q. Okay. So just looking at the structure of 7 the Z' that's claimed, which is an optionally 8 substituted fused heterocyclic ring, consisting of a 9 5-membered ring and a 6-membered ring, each having at 10 least one nitrogen heteroatom. 11 Do you understand that? 12 A. Yes. 13 Q. Okay. Just looking at that, can you -- are 14 you following me? 15 We are just focusing on that aspect of the 16 claim right now. 17 A. Yes. 18 Q. How many possible structures fall within 19 the scope of that aspect of the claim? 20 A. I haven't done that calculation. 21 Q. Okay. Do you agree with Dr. Showalter that 22 it would be in the millions? 23 A. I think if you take Z' divorced from the 24 claim, put the claim aside for a moment, and just take 25 the question of having optionally substituted fused	Page 44 1 "... Dr. Showalter ignores the required 2 substituents on Z', namely the 3 linker-warhead and the phenoxyphenyl 4 group." 5 Correct? 6 A. Correct. 7 Q. Okay. And then towards the middle of the 8 paragraph, you say: 9 "... a POSA would have further understood 10 that these required substituents on Z' 11 and their orientations and the potential 12 steric hinderance that results from 13 adding the substituent, would limit the 14 scope of acceptable Z'-scaffolds." 15 Do you see that? 16 A. Yes. 17 Q. Okay. What is the size of the genus of 18 what you refer to as, "acceptable Z'-scaffolds"? 19 A. I have no idea. I haven't tried to do that 20 calculation. 21 Q. Sitting here right now, would it be in the 22 thousands? 23 A. Again, I -- you know, I haven't done that 24 analysis. I wouldn't -- I wouldn't want to put a 25 number on it.
Page 43 1 heterocyclic ring system, you know, with 2 to 4 2 nitrogen heteroatoms and with these further 3 limitations on optional substitutions, then I wouldn't 4 disagree that there could be on the order of billions 5 of compounds that could meet that description. 6 Q. Okay. 7 A. Again, you know, wholly divorced from the 8 claim. 9 Q. I understand. That was my question about 10 just the Z'-structure itself. 11 So to be fair and to be clear, just looking 12 at the Z'-structure itself, as described in that 13 claim, you would agree that that alone, by itself, 14 encompasses billions of possible structures? 15 A. Again, considering it aside from the claim, 16 I would agree that that could potentially encompass 17 billions of structures according to Dr. Showalter's 18 calculations. 19 Q. Okay. Now, if we go to your declaration 20 and we go to Page 181 -- sorry -- Page 132. 21 A. Page 132? 22 Q. Yes, paragraph 181. Are you there? 23 A. Yes. 24 Q. Okay. And you start this by -- by saying 25 that:	Page 45 1 Q. So sitting here today, you have no idea 2 whether it's in the thousands, millions, or billions? 3 A. I didn't say that. 4 Q. Then what's the answer? 5 A. The answer is I wouldn't put a number on 6 it. You know, I would say comfortably more than 7 hundreds but beyond that, you know, without -- yeah, 8 just not -- haven't done that analysis, haven't 9 thought about how I would do that analysis precisely, 10 and so I don't want to try to put a number on it. 11 Q. Okay. Well, based on your expertise, what 12 analysis would you have to do to determine the size of 13 the, "acceptable Z'-scaffold"? 14 A. Again, as I say, I haven't thought in 15 detail about how I would approach it. 16 Q. Are you able to explain to me today based 17 on your experience with drug discovery, what steps you 18 would do to assess the scope and the size of the 19 acceptable Z'-scaffold? 20 A. In my many years working in this area, 21 that's never something that's been a necessary part of 22 my work, and so I haven't thought about that kind of 23 calculation. 24 Q. Now, if we go to the top of Page 133, you 25 say:

1 Dr. Showalter does not account for 2 whether the Z'-scaffolds that he 3 identified would actually satisfy the 4 need for the H-bonds to the hinge and the 5 ability for the phenoxyphenyl to occupy 6 the hydrophobic back pocket and for the 7 linker-warhead to covalently bind to 8 cysteine 481. 9 Do you see that? 10 A. Yes. 11 Q. Okay. So we agreed that just looking at 12 the Z'-structure alone, the number of possible 13 structures is in the billions, right? 14 A. Yes. And let me further clarify that 15 that's the Z' detached from the other pieces that it's 16 attached to. I guess I'm strictly -- the definition 17 as claimed there with -- sorry -- not as claimed. 18 The sub-portion of the claim that refers to 19 the heterocyclic structure and its substitution is 20 divorced from everything else, including required 21 substituents. 22 Q. I'm not trying to trick you. I think we 23 are on the same page here; that we are talking about 24 just the Z'-structure. 25 A. Just want to be clear.	Page 46	1 that calculation. I've looked carefully at 2 Dr. Showalter's approach to the problem; and for the 3 reasons I've explained in my declaration, I think it's 4 fatally flawed, but I haven't undertaken the analysis 5 to try and reach a number myself. 6 Q. Okay. What are the structures that are 7 common to the species of Z'-scaffolds that would meet 8 those requirements that you specify here at the top of 9 Page 133 with respect to the need for H-bonds and the, 10 you know, the ability for the phenoxyphenyl to occupy 11 the hydrophobic back pocket and for the linker-warhead 12 to covalently bind? 13 A. Sorry. Can you repeat the question? 14 Q. Okay. Top of Page 133 I would say you've 15 identified some -- what I would call is requirements, 16 "the need for H-bonds to the hinge and the ability for 17 the phenoxyphenyl to occupy the hydrophobic back 18 pocket and for the linker-warhead to covalently bind." 19 Do you see that? 20 A. Yes. 21 Q. What are the common -- what are -- for 22 the -- strike it. 23 Can you identify structures that would be 24 common to all of the species of Z'-scaffolds that 25 would satisfy those requirements?	Page 48
1 Q. Yeah. Don't worry. We're clear on that. 2 Just the Z'-structure itself, what's listed 3 there, is in the billions, right? 4 A. I have no reason to doubt that aspect of 5 Dr. Showalter's calculation. That is not a 6 calculation that I've done myself. 7 Q. Now, of those potentially billions, you 8 would agree that not all of them will satisfy the need 9 for H-bonds to the hinge and the ability for the 10 phenoxyphenyl to occupy the hydrophobic back pocket 11 and for the linker-warhead to covalently bind to 12 cysteine 481, correct? 13 A. Not all of them would have the 14 phenoxyphenyl and not all of them would have the 15 linker-warhead and not all of them would have the 16 capacity to form the necessary hydrogen bonds to the 17 hinge. 18 Q. Okay. What is the size of the genus of 19 Z'-scaffolds that meet the requirements of the claim, 20 the structure in the claim that we went through, and 21 would satisfy the need for H-bonds to the hinge and 22 the ability for the phenoxyphenyl to occupy the 23 hydrophobic back pocket and for the linker-warhead to 24 covalently bind cysteine 481? 25 A. Yeah, I don't know. I haven't tried to do	Page 47	1 MS. DANEK: Objection to form. 2 A. So the claim species have many structural 3 features in common. So as I've laid out in the 4 declaration, it's very clear that there is a 5 phenoxyphenyl that's required. It's very clear that 6 there is a specific linker-warhead, the pepperidine 7 (phonetic) with the attached acrylamide that's 8 required. 9 With respect to the Z'-structure, it will 10 be required that it be able to appropriately position 11 the phenoxyphenyl to bind in the back pocket and 12 simultaneously appropriately position the 13 linker-warhead to react with Cys481. So Z's that are 14 within the claim will have that structural feature. 15 Additionally, they will have to sterically fit within 16 the ADP binding site and form from one to three 17 hydrogen bonds with the hinge. 18 Q. So you said with respect to the 19 Z'-structure, it will be required to bind in the -- I 20 guess my question is about what are the structures 21 that are common to the Z'-scaffolds that will meet 22 those requirements that you specified? 23 A. So, I think, you know, as we have 24 established, there are specific structural limitations 25 laid out in the claim that have to do with -- let's	Page 49

1 turn back to them. 2 Q. You are looking for Claim 1? Yeah. 3 A. So, "The optionally-substituted fused 4 heterocyclic ring system comprising two to four 5 nitrogen heteroatoms wherein the optionally 6 substituted fused heterocycle ring system consists of 7 a 5-membered ring comprising at least one nitrogen -- 8 " 9 Q. Slow down. You might want to slow down. 10 A. Paragraph 151, below the structure, 11 approximately line 63. 12 So "comprising at least one nitrogen 13 heteroatom fused to a 6-membered ring 14 comprising at least one nitrogen 15 heteroatom." 16 So those are very clear structural features 17 of Z'. In addition, as you can see in the diagram 18 above, the Z'-scaffold has to be -- those substituents 19 have to be attached, and the Z'-scaffold has to have a 20 structure that will appropriately position those for 21 back pocket binding with phenoxyphenyl and an 22 approximation with the cysteine for the warhead, the 23 linker-warhead substituent. 24 And then also, as is well-known in the art, 25 the Z' moiety will have to have hydrogen bond	Page 50	1 Q. Now I want you to assume that the Z' can be 2 any structure that falls within the scope of what's 3 listed in the claim, which is a fused 5-membered ring 4 and 6-membered ring and each has at least one nitrogen 5 heteroatom, okay? 6 A. Okay. 7 Q. Is it your opinion that every single 8 structure that falls within that scope, which is the 9 Z' attached to a phenoxyphenyl group, and the Michael 10 warhead acceptor, linker-warhead, would meet those 11 three requirements? 12 MS. DANEK: Objection, form. 13 A. I think it's clear that not every potential 14 Z'-structure -- so I think you only listed two of 15 those requirements but invoking the third, so if -- if 16 you have a molecule that positions phenoxyphenyl in 17 the back pocket, forms hydrogen bonds, to the hinge, 18 and when binding the BTK properly positions the 19 linker-warhead for reaction with Cys797, then, yes, I 20 would expect those molecules to inhibit BTK. 21 Q. So the answer to my question is, you're 22 saying that, yes, that every single Z' that meets 23 those requirements and has phenoxyphenyl group and the 24 Michael linker-warhead acceptor, would satisfy those 25 three requirements that we just specified?	Page 52
1 acceptors, donors, that can make hydrogen bonds to the 2 hinge. They are a known feature of ATP site kinase 3 inhibitors. 4 Q. Okay. Let's try to break this down, all 5 right. 6 I understand you to be specifying here at 7 page 133, we went through, can we call them the three 8 requirements because I don't want to repeat them every 9 time I ask a question. 10 Three requirements: The need for the 11 H-bonds to the hinge and the ability for the 12 phenoxyphenyl to occupy the hydrophobic back pocket, 13 and for the linker-warhead to covalently bind to 14 cysteine 481. 15 Can we call those the three requirements? 16 A. Yeah, we can. I understand what you mean 17 by "three requirements", yes. 18 Q. All right. So we are on the same page 19 there, okay. Now let's talk about the structure that 20 I'm interested in asking with respect to those three 21 requirements. I want you to assume that we are 22 talking about the inhibitor of BTK -- well, sorry -- a 23 molecule that has the phenoxyphenyl group and the 24 Michael warhead acceptor, linker-warhead, okay? 25 A. Okay.	Page 51	1 A. If when bound to BTK, it puts the 2 phenoxyphenyl in the back pocket and orients the 3 linker-warhead to the Cys481 and hydrogen bonds with 4 the hinge, then it would be a BTK inhibitor. 5 Q. So you're saying if the Z'-structure meets 6 those requirement, then it would meet those 7 requirements? 8 A. I'm just trying to answer the question I'm 9 asked. 10 Q. All right. I got you. All right. We'll 11 move on. 12 All right. You also describe here in 13 paragraph 133 that a POSA would use virtual docking to 14 predict which Z'-scaffolds would satisfy the need for 15 H-bonds to the hinge and the ability for the 16 phenoxyphenyl to occupy the back pocket and for the 17 linker-warhead to covalently bind, right? 18 A. Yes. 19 Q. How would a POSA use virtual docking to 20 identify all of the possible Z'-scaffolds that meet 21 the structural limitations of the claim and also 22 satisfy the need for H-bonds to the hinge, the ability 23 for the phenoxyphenyl to occupy the back pocket, and 24 for the linker-warhead to covalently bind? 25 A. I don't think I have said that a POSA would	Page 53

Page 54 1 be -- would use that to identify all. I can't imagine 2 that a POSA would want to set about figuring out all 3 of the possible ways to inhibit BTK with the molecule 4 of these claims. But I think for any particular 5 potential BTK inhibitor I think a POSA could very 6 readily do that analysis. 7 Q. Okay. Let's take a specific scaffold 8 structure, and let's use zanubrutinib as an example, 9 okay? 10 A. Sure. 11 Q. You are familiar with that scaffold 12 structure, correct? 13 A. I am, yes. 14 Q. As of June 2011, you would agree a POSA 15 would not know the structure of zanubrutinib, correct? 16 A. As far as I know, zanubrutinib was -- was 17 developed after 2011. 18 Q. So the answer is, yes, a POSA would not 19 know the structure of zanubrutinib as of June 2011, 20 correct? 21 A. Not certainly not as "zanubrutinib", as far 22 as I know. 23 Q. Okay. So sticking with what a POSA knows, 24 as of June 2011, what would lead a POSA to use virtual 25 docking to model the structure -- sorry -- to model	Page 56 1 A. Yes. 2 Q. Okay. What would lead a POSA to draw that 3 structure in June 2011, the scaffolding structure? 4 A. The scaffold structure, sure. 5 So this may take a bit of digging around to 6 find the relevant places in my declaration. but as an 7 example, I think I pointed out pre-priority structures 8 that have a carboxamide moiety to make the hydrogen 9 bonds to the hinge, and they have carboxamide moiety 10 attached to a heterocyclic ring structure. 11 The '803 specification specifies a 12 5-membered ring and a 6-membered ring. And although 13 the 6-membered ring of zanubrutinib is unsaturated, I 14 also pointed out in my declaration other kinase 15 inhibitors known in the art prior to 2011 that have 16 similarly unsaturated scaffolds. 17 And so grafting those things together, 18 looking at how B43 binds and having docked ibrutinib 19 and understanding how ibrutinib is going to bind, a 20 POSA who was interested to make something 21 ibrutinib-like, yet not ibrutinib itself, might have 22 taken those parts out of the parts kit of kinase 23 inhibitors and put them together to make a docked 24 ibrutinib. 25 Q. You do agree that a POSA would not be able
Page 55 1 the scaffold structure that is used in zanubrutinib? 2 A. Well, as I've explained in the declaration, 3 the approach of scaffold hopping or scaffold swapping 4 was well known in the art as of 2011 and widely 5 practiced by kinase drug discoverers. And a POSA 6 reading the specification of the '803 patent would 7 recognize the value of the phenoxyphenyl as a 8 specificity determinant. 9 They would recognize the value of the 10 linker-warhead as a specificity and potency 11 determinant, and they could, using approaches 12 straightforward in the art, draw any number of 13 structures and subject them to docking by swapping in 14 parts from other known structures and doing 15 readily-doable molecular modeling studies to create 16 zanubrutinib and any number of other molecules, 17 rutinib-like molecules of the claim. 18 Q. Okay. So let's try that again. 19 You have this specific structure of 20 zanubrutinib in mind, right? 21 Why don't you take -- 22 A. Let's look at it. 23 Q. -- a look in your -- just so you have it in 24 mind. I'm sure it's somewhere in your declaration. 25 Page 82.	Page 57 1 to find that scaffold structure for zanubrutinib 2 anywhere in the prior art as of June 2011, correct? 3 A. You mean the specific scaffold structure of 4 zanubrutinib? 5 Q. Yes. 6 A. That's correct. To my recollection, it's 7 not drawn anywhere in the '803 patent. 8 Q. It's not drawn in the '803 patent, and it's 9 not drawn anywhere in the prior art, right, that you 10 know of? 11 A. That's correct. As far as I know, it's not 12 drawn in the prior art. 13 Q. So in order to model that, that structure, 14 a POSA would have to envision that structure on their 15 own, right? 16 A. As I was just explaining, a POSA would take 17 the specification and recognize the specific 18 structural constraints of where the phenoxyphenyl 19 needed to be, where the linker-warhead needed to be, 20 and reach into the parts kit of kinase inhibitors and 21 using well-established scaffold swapping, scaffold 22 morphing approaches, arrive at zanubrutinib and dock 23 it as a potential BTK inhibitor of the claims. 24 Q. So a POSA would have to invent that 25 structure and then model it, right?

Page 58 1 A. I wouldn't characterize it that way. 2 Q. So you wouldn't characterize developing 3 novel scaffold structures as "invention"? 4 A. Not -- in some cases, that would be true. 5 In this particular context, I wouldn't characterize it 6 that way. 7 Q. But you would agree that the inventors of 8 the '803 patent did not possess that specific 9 structure, correct? 10 A. That's correct. 11 Q. They didn't envision it, did they? 12 MS. DANEK: Objection, form. 13 A. I have no idea what they did or didn't 14 envision. 15 Q. Well, actually, you do. You have the 16 patent. 17 A. With respect to, you know, specifics of, 18 you know, the elaborations of their invention. 19 Q. Why don't we go to Page 32 of your 20 declaration. 21 A. (Witness complied.) 22 Q. And this is Paragraph 60, and you reference 23 Formula E in the '803 patent, right? 24 A. That's correct. 25 Q. And you describe Formula E as providing	Page 60 1 where you said that is a functional definition, that 2 provides a very "restrictive", I think was the word 3 you used, "structural constraint"? 4 A. Yes. 5 Q. Okay. Well, how many -- what's the scope 6 of how many structures would meet that function of 7 "binds to the active site of the kinase, including a 8 tyrosine kinase"? 9 A. I haven't tried to count. 10 Q. Then how do you know it's restrictive? 11 A. So I have many years of experience. 12 Q. Okay. 13 A. And in my experience, not every structure 14 will bind to the active site of a kinase. 15 Q. But sitting here, you couldn't say how many 16 do and how many don't? 17 A. As I said, I haven't tried to calculate 18 them. 19 Q. What are the structures that are common for 20 this orb, what are the structures that are common for 21 those that will bind? 22 A. So, typically, they will have one to three 23 hydrogen bond donors and acceptors. Typically, oxygen 24 and nitrogen atoms can form hydrogen bonds to the 25 hinge. They will have a structure that appropriately
Page 59 1 "a structure, represented as an orb that 2 binds to the active site of a kinase, 3 including a tyrosine kinase." 4 Correct? 5 A. That's correct. 6 Q. Now, the phrase, "binds to the active site 7 of a kinase," that's a function, right, not a 8 structure? 9 A. "Binds to," is definitely a function. 10 Q. Right. 11 So if an orb is defined as binding "to the 12 active site of a kinase, including a tyrosine kinase," 13 that would be a functional definition of the orb, 14 correct? 15 A. A functional definition that encompasses, 16 necessarily, very restricted structural constraints. 17 Q. Okay. Well, in this context of chemistry, 18 all functional definitions would encompass 19 substructure, right? 20 MS. DANEK: Objection, form. 21 Q. I mean, we are talking about structures 22 that perform the function; are we not? 23 A. We are talking about structures that 24 perform the function. 25 Q. Okay. So now going back to the question	Page 61 1 positions those hydrogen bond donors and acceptors to 2 interact with the hinge. They will sterically fit 3 within the ATP binding site. They will typically also 4 have some amount of shape complementarity to the ATP 5 binding site. 6 Q. Are you done? 7 A. Yes. 8 Q. You further describe in Paragraph 63 that: 9 "... Formula E is an element that makes 10 the appropriate H-bonds with the hinge 11 region while appropriately orienting the 12 fixed substituents." 13 Do you see that? 14 A. I'm sorry. Where are you reading? 15 Q. I'm at the bottom of Page 32 and top of 16 page 33. 17 A. Yes. 18 Q. Okay. So, again, "Formula E," the orb 19 "is an element that makes the appropriate 20 H-bonds with the hinge region while 21 appropriately orienting the fixed 22 substituents"? 23 A. Correct. 24 Q. That's another functional definition of the 25 orb, right?

1 A. You know, I think that this has very 2 specific structural implications, structural 3 requirements. You know, it's as if you said, you 4 know, the structure of ATP, you know, has the position 5 of a phosphate for phosphoryl transfer, that imposes 6 particular structural requirements on the ATP 7 molecules, right. It has to be a high-energy 8 phosphate ester bond that can be transferred and 9 cleaved. It has to be attached to the ribose 10 substituent of ATP in a way that it positions it into 11 the proper place of the active site with the kinase. 12 So you can't interpret -- you know, so 13 certainly as a word, "orienting" is a verb, you know, 14 and so that is functional. But in order to accomplish 15 that function, a POSA would recognize that in the 16 context of the structure of BTK and the way a 17 particular scaffold was binding to the hinge, that it 18 would limit the structures that could accomplish that 19 desired function and guide one to specific structures 20 for accomplishing that desired function. 21 Q. Okay. I'm going to try and paraphrase what 22 you just said, which is making appropriate H-bonds and 23 appropriately orienting fixed substituents are 24 functions, but your opinion is that there are a 25 limited number of structures that will accomplish	Page 62	1 that a functional definition or a structural 2 definition," what is your answer? 3 A. My answer is that if you parse the words, 4 that they are presented as a functional definition, 5 but a POSA in reading them, would apply in the context 6 of the known structure to specific structural 7 limitations. 8 Q. What are those specific structural 9 limitations? 10 A. As we've discussed, the ability to form one 11 to three H-bonds with the hinge, having chemical 12 substituents, nitrogens, oxygens, appropriately 13 positioned to make, you know, interactions with those 14 residues, you know, with the correct geometry, with 15 the correct relative positioning of hydrogen bonds and 16 having the geometry that would allow attachment of the 17 phenoxyphenyl in the correct place and the 18 linker-warhead in the correct place. 19 Q. Okay. 20 A. So as I explained previously when 21 discussing zanubrutinib as an example, one is applying 22 these requirements in a very structural context and, 23 you know -- yeah, how to say it? Not any structure 24 will do that. And so using techniques that are known 25 in the art: scaffold -- scaffold swapping, for	Page 64
1 those functions, correct? 2 A. I think what I said was that those -- 3 Q. It's a "yes" or "no" question. 4 MS. DANEK: He can answer. 5 Q. So you can try -- you can say "yes", "no", 6 or "I don't know"? 7 A. Yeah. I don't -- 8 Q. I don't need another paragraph answer. 9 A. I don't accept your paraphrasing of my 10 response. 11 Q. Okay. So then let's be clear for the 12 board, okay. 13 It's your opinion that makes the 14 appropriate H-bonds with the hinge region and 15 appropriately orienting the fixed substituents is a 16 structural definition, "yes" or "no" -- 17 MS. DANEK: Objection to form. 18 Q. -- or "I don't know"? 19 MS. DANEK: Objection to form. 20 A. Sorry. Ask that again. 21 Q. Okay. If one of the PTAB judges in this 22 case were to ask you: 23 "Dr. Eck, is it your opinion that makes the 24 appropriate H-bonds with the hinge region while 25 appropriately orienting the fixed substituents, is	Page 63	1 example, one can identify readily specific Z' 2 structures that will meet those limitations, and 3 thereby, visualize, recognize compounds that fall 4 within the claims. 5 MR. DESAI: Okay. Thank you. 6 Why don't we take another break. 7 VIDEOGRAPHER: 11:10. We are off the 8 record. 9 (Off the record at 11:10 a.m.) 10 (On the record at 11:26 a.m.) 11 VIDEOGRAPHER: One moment. 12 Time, 11:26. 13 We are back on the record. 14 BY MR. DESAI: 15 Q. We were talking about Formula E, and I want 16 to go to Column 62 in the patent. Are you at Column 17 62? 18 A. I am. 19 Q. And the specification here provides eight 20 examples of potential orb embodiments, right, at the 21 bottom of Column 62 and top of Column 63? 22 A. Yes, that's correct. 23 Q. And these eight illustrations are 24 illustrations of specific scaffold structures -- 25 sorry -- specific structures for the hinge binding	Page 65

1 scaffold, right? 2 A. That's correct. 3 Q. And all eight of these scaffold structures 4 fall within the scope of the claimed Z'-scaffold, 5 correct? 6 A. To the best of my understanding, that's 7 correct. 8 Q. And it's your opinion -- 9 A. Oh, let me -- let me correct myself. 10 Q. Sure. 11 A. They satisfy the structural limitations of 12 that part of the claim with respect to the description 13 of Z' as it's described below there -- with respect to 14 the structural aspects of that claim as described in 15 the -- you know, "wherein Z' is an optionally 16 substituted fused heterocycle ring system", et cetera, 17 that part of the structural description of the claim, 18 that's correct. 19 Q. Yeah. So I'll just ask my question again 20 because that's what I thought I asked, just so the 21 record is clear. 22 A. I was just clarifying that I wasn't -- 23 yeah. 24 Q. Yeah. Let me -- let me just ask the 25 question and try it again to make sure we are on the	Page 66	1 You say, "The specification's Formula E 2 recognizes that the substructures that 3 bind to the highly conserved hinge region 4 are fungible and predictable," right? 5 Did I read that correctly? 6 A. Yes, you read that correctly. 7 Q. So my next question is, when you say, 8 "Formula E recognizes that the substructures", you are 9 referring to the Z'-scaffold structure, right? 10 A. Yes. 11 Q. All right. So your opinion is that the 12 Z'-scaffold structures -- a person of ordinary skill 13 in the art would understand from Formula E that the 14 Z'-scaffolds that bind to the hinges are fungible and 15 predictable, correct? 16 A. The opinions that I have provided explain 17 that there is a tremendous wealth of knowledge in the 18 art about structures that combined to the hinge and 19 bind in the ATP site and satisfy those hydrogen 20 bonding requirements to the hinge. It's well-known in 21 the art that one can swap out scaffolds and graft 22 substituents from other scaffolds on to the scaffold 23 of interest, and in that sense, the scaffolds are 24 fungible; that's the sense in which I'm using that 25 word here.
1 same page. 2 These eight structures here do not 3 illustrate the phenoxyphenyl group or the Michael 4 acceptor linker-warhead, correct? 5 A. That's correct. 6 Q. But you would agree that these eight hinge 7 binding scaffold structures all fall within the scope 8 of the claimed Z'-scaffold? They meet the structural 9 requirements in the claim for Z'? 10 A. As defined, you know, as I was saying, in 11 the paragraph following the drawn chemical structure. 12 Q. In the claim, you mean? 13 A. Correct. 14 Q. Yes. I think we're on the same page. 15 And it is your opinion that a POSA would 16 have understood from Formula E that the Z'-scaffold 17 that bind to the hinge region are fungible and 18 predictable, correct? 19 A. You guys used the word "fungible" in at 20 least a few places in my declaration, not to refer to 21 the scaffold in general, but to the specific groups 22 that make the hydrogen bond interactions with the 23 hinge. 24 Q. Okay. If we look at Paragraph 103, Page 70 25 of your declaration.	Page 67	1 Q. Okay. And they would have been fungible 2 and predictable to the inventors, this '803 patent, 3 right? 4 A. I think the inventors of the '803 patent 5 would have been well aware of the techniques of 6 scaffold morphing and scaffold hopping in the art. 7 Q. Okay. And looking at those eight scaffold 8 structures, Column 62 and Column 63, a POSA reading 9 the '803 patent would understand that each of those 10 eight scaffold structures would make the appropriate 11 H-bonds with the hinge region, correct? 12 A. So the scaffold structures as they are 13 illustrated here are unsubstituted, although they 14 indicate particular locations at which they could be 15 substituted. So these structures per se, as drawn 16 here, wouldn't necessarily, you know, with the atoms 17 depicted in these illustrations, make hydrogen bonds 18 to the hinge. 19 Q. Would a POSA understand that, from the '803 20 patent, that these scaffold structures 62 and 63 are 21 all scaffold structures that would be used with the 22 fixed substituents, meaning the phenoxyphenyl group 23 and the linker-warhead? 24 A. I think a POSA would take away that they 25 were scaffolds that could be considered for use in

1 that role, in that position of Z'. 2 Q. Okay. And would a POSA understand, reading 3 that patent, that when used in that position with the 4 fixed substituents, that each of those eight scaffold 5 structure would make the appropriate H-bonds with the 6 hinge region? 7 A. I have not -- I haven't analyzed that 8 specific question, you know, whether all of these 9 embodiments would necessarily be operative. 10 Q. But you've opined that a POSA would be able 11 to readily understand and predict whether a scaffold 12 would make these appropriate H-bonds, right? 13 A. That's correct. I think one could take a 14 structure of interest and readily determine whether it 15 was expected to form the desired H-bonds to the hinge. 16 Q. And by including these in their patent, 17 aren't the inventors teaching that these are eight 18 structures that would form those appropriate H-bonds? 19 A. Well, again, these structures are 20 unelaborated. They're not substituted. And so just 21 as we sit here looking at these structures, I don't 22 think I can say that a POSA would necessarily take 23 that away from reading this. 24 Q. So a POSA wouldn't know reading this patent 25 whether or not any of these structures would form the	Page 70 1 that at least some of these structures would be able 2 to be used to make an ibrutinib-like BTK. A POSA 3 reading the patent would understand that at least some 4 of them, right, that's what you said? 5 A. Yes. 6 Q. Okay. So reading the patent, which of 7 those eight would they -- would be in the category of 8 at least some that would be able to be used to make an 9 ibrutinib-like BTK? 10 A. So as I said, as we sit here, I haven't 11 done that analysis. As we sit here today, I can't 12 answer that question, but I can tell you that as a 13 POSA or as a member of a POSA team, how I would 14 approach that, right. So, you know, taking, for 15 example, the structure in the lower left in Column 63, 16 that looks to me as a POSA, like a promising structure 17 for making a BTK-like inhibitor. I would propose an 18 amine substitution in the first position that's 19 indicated for, you know, for substitution. I would 20 propose the phenoxyphenyl in the second and the 21 linker-warhead of the claims in the third. 22 I would consult with my medicinal chemist 23 colleague for an opinion as to whether he agreed that 24 that would be good. I would carry out a docking 25 exercise to assess how well it fit within the active
1 appropriate H-bonds with the hinge region while also 2 appropriately orienting the fixed substituents, right? 3 MS. DANEK: Objection to form. 4 A. That's not correct at all. A POSA would be 5 very clear that at least some of these structures 6 would be able to be used to make an ibrutinib-like 7 BTK. 8 Q. So a POSA would read this patent, and you 9 said would understand -- that at least some of them 10 would be able to be used to make an ibrutinib-like BTK 11 inhibitor; which ones? 12 You read the patent. 13 A. I read the patent. I can take a minute to 14 remind myself, for example, which one is, you know, is 15 precisely ibrutinib. 16 Q. You don't need to do that because we know 17 that ibrutinib is ibrutinib. 18 A. I think we can agree that a POSA would well 19 understand that. 20 Q. What about the other ones that are not 21 ibrutinib? 22 A. As I said, I haven't -- I haven't gone 23 through them one by one and done that analysis. 24 Q. Okay. So, again, I'm going to ask it 25 again. You said that a POSA -- it would be very clear	Page 71 1 site of BTK. And, yeah, and will thereby have 2 visualized a new BTK inhibitor, ibrutinib-like. "New" 3 in the sense of one that, you know, has been invented 4 and described here, but probably not been synthesized 5 and tested previously. 6 Q. On the patent, would you mind drawing what 7 you just proposed there for that? I think you said 8 it's the bottom left illustration on the Column 63, 9 right? 10 A. Sure. 11 Q. And you can use some shorthand if you need 12 to, to -- if you don't -- you can simply just draw 13 where you propose. I believe you proposed where the 14 phenoxyphenyl group would go and where you propose the 15 linker-warhead would go, and I think you proposed an 16 amine group. 17 (Witness drawing.) 18 Q. Okay. 19 MS. DANEK: Counsel, can I see the 20 exhibit. 21 MR. DESAI: Yeah. Sure. 22 (Document tendered to counsel.) 23 MR. DESAI: We will mark this as 24 Exhibit 2. We will do that. 25 *****
	Page 72
	Page 73

1 (Exhibit 2 marked for identification, 2 Patent '803.) 3 MS. DANEK: I believe that none of that 4 -- Dr. Eck's commentary on his marking of what 5 has been marked as Exhibit 2 -- 6 MR. DESAI: I didn't really ask a 7 question, so I don't know if you want that on the 8 record, but it's fine if you want it. 9 MS. DANEK: Just that he offered to 10 mark another one and you said not to. 11 MR. DESAI: I didn't ask him to. You 12 can ask him when it's your turn if you want to. 13 I gave him a chance to mark one, and he chose 14 what he chose. 15 BY MR. DESAI: 16 Q. I mean, if you want to pick a -- Dr. Eck if 17 you have a different set of substitutions that you 18 want to draw, I'm happy to give you a shot at that and 19 then you can draw it, and then I can ask questions 20 about it. 21 A. Sure. 22 Q. It's fine with me. 23 A. Sorry. What column? 62? 24 Q. 62. 25 (Witness reviewing the document.)	Page 74 1 figure on the bottom right, do you see that one? 2 A. This one? (Pointing.) 3 Q. Yes. 4 Could you draw what a POSA would do with 5 respect to making an ibrutinib-like BTK using that 6 scaffold based on reading the '803 patent? 7 A. You know, off the cuff, I wouldn't -- 8 wouldn't draw something on this scaffold. 9 Q. Why? 10 A. I think, you know, sitting here today 11 looking at it, not having thought about it or analyzed 12 it previously, would have to apply tools to decide 13 where to substitute it to make it most likely to 14 adopt, you know, to properly position the 15 phenoxyphenyl and other groups. 16 Q. In order to figure out whether these 17 scaffolds that are in Column 62 and 63 -- sorry, 18 strike that. 19 Setting aside the one scaffold here that is 20 actually used in ibrutinib, can we set that to one 21 side? 22 A. Okay. 23 Q. Setting that one aside, for the other ones, 24 the other seven, in order to figure out whether that 25 scaffold could be used with the affixed substituents, Page 76
1 Q. So just to be clear, why don't we put a 2 number 1 just so that we know which one you drew 3 first. Put a "1" there, and then you can put a "2" 4 and draw your second one. 5 (Witness drawing.) 6 Q. So you chose -- just for the record, you 7 chose the one at the top right of Column 63? 8 A. That's correct, as marked there as 9 number 2. 10 THE COURT REPORTER: On Exhibit 2. 11 (Document tendered to counsel and witness.) 12 Q. Would a POSA understand that what you just 13 drew and marked as number 2, would make the 14 appropriate H-bonds with the hinge region while 15 appropriately orienting the fixed substituents? 16 A. As I explained, you know, as a next step 17 I'd consult with the medicinal chemist colleague. I 18 would dock it in the ibrutinib structure to reassure 19 myself that it made the expected hydrogen bonds. But 20 even just looking at it here, we see that it would 21 have an appropriately-positioned hydrogen bond donor 22 and a hydrogen bond acceptor to make the hydrogen 23 bonds with the gatekeeper plus 1 and gatekeeper plus 24 3. 25 Q. Flip to column 62. Right there. For the	Page 75 1 form the appropriate H-bonds, and then ultimately 2 irreversibly inhibit BTK, a POSA would have to figure 3 out where the substituents go and then conduct 4 modeling and testing in a sort of trial and error way 5 to figure out whether it would work, right? 6 MS. DANEK: Objection to form. 7 A. I wouldn't characterize it as "trial and 8 error." I think for some of them, it would be quite 9 obvious that, you know, as I've illustrated in the 10 number 2 example here, yeah. For others, I think I 11 would take more consideration and as I said, modeling 12 to have a sense of whether that was a particularly 13 desirable scaffold to use. 14 Q. And it's your opinion that modeling to 15 figure out whether a scaffold is of a particular 16 interest to you is something that would be ordinary 17 for a team for a POSA to do, right? 18 A. As I've explained in my report, you know, 19 structural modeling is very widely used in drug 20 discovery including kinase inhibitor discovery, in 21 fact, almost universally. 22 Q. Did you use a docking program to predict 23 the expected binding mode of any of these eight 24 scaffold structures in Column 62 and Column 63? 25 A. I used it for ibrutinib. Page 77

1 Q. Did you do it for any of the others? 2 A. I'd have to look at the structures from the 3 Zhang, et al., paper to see if any of them 4 corresponded to this. So if the Zhang 7 or 8 5 compounds correspond to one of these, and I also did 6 docking with that. 7 Q. Would you agree that by including these 8 eight specific scaffold structures for Formula E, the 9 inventors confidently and accurately predicted that a 10 molecule having any of these eight structures along 11 with the fixed substituents would irreversibly inhibit 12 the BTK -- 13 (Reporter requested clarification.) 14 MR. DESAI: I can ask it again. Let me 15 ask it again. I will start over. 16 Q. Would you agree by including these eight 17 specific scaffold structures for Formula E, that the 18 inventors confidently and accurately predicted that a 19 molecule having any of these eight structures along 20 with the fixed substituents of an oxyphenyl group and 21 the linker-warhead, would irreversibly inhibit BTK? 22 MS. DANEK: Objection, form. 23 A. No, I wouldn't say that. 24 Q. In order to assess whether a molecule 25 having one of these eight structures, along with the	Page 78 1 definition of "aryl"? 2 A. I think a POSA would agree that this was a 3 reasonable definition of "aryl". 4 Q. Now, at Column 62, the specification uses 5 the term "biaryl," correct? 6 Line 44. 7 A. Yes. 8 Q. Okay. You understand that "bi" means 9 "two," right? 10 A. Yes. 11 It says, "In some embodiments, orb is a 12 substituted fused biaryl moiety..." 13 Q. Right and "bi" means "two," right? 14 A. The common meaning of "bi" is "two." 15 Q. So you would agree that the meaning of 16 "biaryl" means a structure with two aromatic rings, 17 right? 18 A. I don't think a POSA reading this patent 19 would take that away as the inventor's intended 20 meaning or the drafter's intended meaning of "biaryl". 21 Q. What is their definition of "biaryl" then? 22 A. Well, I haven't been able to find a 23 specific definition of "biaryl" in the patent, but 24 they've defined "aryl" and their definition of "aryl", 25 as I've outlined in my declaration, speaks strictly
1 fixed substituents, would irreversibly inhibit BTK, 2 additional experimentation modeling would be required, 3 right? 4 MS. DANEK: Objection to form. 5 A. You haven't mentioned other substituents. 6 You've mentioned only these scaffolds and the fixed 7 substituents. 8 Q. Okay. A quick couple of questions about 9 the word "aryl". You understand that's defined in the 10 patent specification, right? Column 15. 11 A. Remind me. 15? 12 Q. 15. Top of 15, line 4. 13 A. Yes. 14 Q. "... 'Aryl' refers to an aromatic ring 15 wherein each of the atoms forming the 16 ring is a carbon atom", right? 17 A. Yes. That's correct. 18 Q. "Aryl rings can be formed by five, six, 19 seven, eight, nine, or more than nine carbon atoms", 20 right? 21 A. That's correct. 22 Q. "Aryl groups can be optionally 23 substituted", right? 24 A. That's correct. 25 Q. Is this a typical or sort of the standard	Page 79 1 about rings with carbon atoms in them. 2 And they've illustrated under the "biaryl" 3 section, ringed structures with nitrogen heteroatoms. 4 So it wouldn't make sense to take away from the 5 patent -- a POSA wouldn't take away from this that the 6 inventors and drafters had in mind some strict 7 definition of "biaryl". 8 Additionally, as I've outlined in my 9 declaration, there are other instances where they 10 refer to compounds as "aryl" that also have partially 11 saturated rings. 12 Q. Okay. Have you used or heard the word 13 "biaryl" outside of the context of this patent? 14 A. I'm sure that I must have. I don't recall 15 a specific instance. 16 Q. Okay. It's not a word that the inventors 17 invented, right? 18 A. I think that's fair to say. 19 Q. Okay. So what does it mean -- when you're 20 teaching your chemistry classes or at the university, 21 what does "biaryl" mean? 22 A. I don't teach organic chemistry. 23 Q. So you don't know then? 24 A. Well, as I've said, as a POSA reading the 25 patent --
	Page 80 Page 81

Page 82 1 Q. I asked you a different question, though. 2 What does "biaryl" mean to you outside of the context 3 of this patent? 4 A. So outside of the context of this patent, 5 you know, "biaryl", if you break it down literally, 6 suggests two aromatic rings. 7 Q. Okay. And your opinion is that this patent 8 is using the word differently. It doesn't mean that 9 in this patent, right? 10 A. I think, as is plain from reading the 11 specification, that they are using "biaryl" somewhat 12 loosely here. 13 Q. What do they use it to mean? 14 A. Well, you know, we see specific examples of 15 things that they regard as biaryl and, you know, seven 16 of eight of those examples are strictly-speaking, 17 biaryl. One example is partially saturated and 18 therefore not according to that, you know, sort of a 19 strict definition of "biaryl", you know, not biaryl. 20 So from that, I take away that the intended meaning 21 here, you know, refers to the structures and more 22 broadly, to, you know, to bicyclic structures that 23 also can contain nitrogens in addition to just having 24 carbons in the rings. 25 Q. All right. So it just would be really	Page 84 1 substituted fused biaryl moiety selected 2 from," and then there are eight 3 structures that are shown, right? 4 A. That's correct. 5 Q. Okay. And seven of those eight structures 6 would meet this strict definition of "biaryl", which 7 is two aromatic rings, correct? 8 A. I want to make it clear, I'm not offering a 9 definition of "biaryl." 10 Q. I think that was clear from my question 11 which is I posed the hypothetical. 12 A. Okay. Sorry. So you are asking me to 13 confirm that seven of eight of these confirm that 14 potential definition of "biaryl"? 15 Q. Yes. 16 A. That's correct to my understanding. 17 Q. And the one that would not meet that strict 18 definition of "biaryl" is which one? The bottom right 19 one on 62? 20 A. Yes, that's correct. This one. 21 (Pointing.) 22 Q. Okay. So if a POSA was selecting a 23 substituted fused biaryl from this group of eight and 24 was using that strict definition of "biaryl", a POSA 25 would not select E4, correct?
Page 83 1 helpful to understand, for the purposes of this case 2 and your analysis, what is your understanding as the 3 meaning of "biaryl" in this patent? 4 If the judges asked you that question, what 5 would you say? What's the meaning of "biaryl" in this 6 patent? 7 A. I think the meaning of "biaryl" is what the 8 drafters have laid out here in black and white. You 9 know, they've described their invention. They've 10 illustrated structures. I can't give you -- you know, 11 they've used "biaryl" loosely. For that reason, I 12 can't give you a specific definition of "biaryl." 13 As far as I know, there is no -- you know, 14 I've never read a generally-agreed upon field 15 definition of "biaryl" either. 16 Q. Okay. If we -- at some point you did say 17 that strictly-speaking or literally-speaking, "biaryl" 18 would mean two aromatic -- sorry. Let's take it one 19 step at a time, okay. I'm going to take that strict 20 definition that at one point you gave. Let's just 21 say, hypothetically, for my next set of questions, 22 "biaryl" means two aromatic rings, okay? 23 A. Okay. 24 Q. All right. At Column 62, Line 44, it says: 25 "In some embodiments, orb is a	Page 85 1 MS. DANEK: Objection to form. 2 A. I can't think of a particular reason that a 3 POSA wouldn't select this particular structure. 4 You've referred to it as "E4". You know, I haven't 5 formed an opinion as to whether or not it is or isn't, 6 you know, a preferred embodiment, you know, whether 7 inhibitors incorporating this would be preferred 8 embodiments or not. 9 Q. What does the patent specification teach a 10 POSA about that embodiment E4? 11 A. The patent specification teaches that it's 12 a potential embodiment, not that it's a preferred 13 embodiment and indicates positions at which it would 14 be substituted. 15 Q. Hold on one second. Why don't we grab -- 16 I'll hand you what's marked as 17 Exhibit 1060. I will give you mine. We have extra 18 copies. 19 (Exhibit 1060 previously marked for 20 identification, an article by Zhengying 21 Pan and others.) 22 Q. You have reviewed this article, a Pan 23 article, right? 24 A. Yes. 25 Q. Discussed at Paragraphs 70 to 80 of your

1 declaration, right? 2 78 to 80. 3 (Witness reviewing document.) 4 A. Yes, that's correct. 5 Q. This is an article that discusses the 6 discovery of ibrutinib, correct? 7 A. That's correct. 8 Q. The only Z'-scaffold structure this 9 discloses is the ibrutinib Z'-scaffolding structure, 10 correct? 11 MS. DANEK: Objection to form. 12 A. The scaffold that's disclosed is the 13 scaffold which is used in ibrutinib, but could also be 14 used in many other ibrutinib-like inhibitors. 15 Q. That wasn't the question I asked, but I 16 mean the question I asked -- 17 A. Sorry. Can you repeat the question? 18 Q. The only Z'-structure that it discloses, 19 scaffold structure, is the Z'-scaffold structure that 20 is actually used in ibrutinib, right. 21 Is there an alternate Z'-scaffold structure 22 that's disclosed in this article? 23 A. No. 24 Q. Okay. And do you understand that that 25 scaffold structure comes from a known reversible	Page 86	1 lead for Compound 1, Pan discloses synthesizing 2 various BTKs right? 3 A. That's correct. 4 Q. And these synthesized BTKs were subjected 5 to mass spectrometry to verify covalent binding, 6 right? 7 A. That is one of the tests that they used, 8 correct. 9 Q. They also subjected them to an IC50 assay, 10 right? 11 A. I believe that's correct. 12 Q. And then they subjected them to a 13 cellularizer, right? 14 A. Yes. 15 Q. Pan did not use modeling to select the new 16 scaffold for development of the new kinase drug, 17 correct? 18 A. As far as I know, they did not. I want to 19 read through the paper again to make sure, but I 20 believe as we've just discussed, they had identified 21 it in a screen and then subsequently did the modeling. 22 Q. Okay. Do you want to take a break and eat 23 lunch? 24 MS. DANEK: Sure. 25 VIDEOGRAPHER: Time is 12:10. We are	Page 88
1 compound? 2 A. Yes. 3 Q. Okay. So in other words for ibrutinib, the 4 scaffold structure that was adopted was a known, 5 existing scaffold structure, right? 6 A. Yes, that's correct. 7 Q. And we see that on Page 1, the right column 8 talks about scanning for known scaffolds, right? 9 A. Sorry. Where are you reading? 10 Q. The second column, "An initial campaign," 11 Exhibit 1060. 12 A. Yes, that's correct. 13 Q. At the time, it was typical for a POSA to 14 rely on known and existing scaffolds as leads in 15 developing new kinase structures, right? 16 A. I think it's fair to say that 17 pharmaceutical companies had libraries of compounds 18 developed in their kinase drug discovery campaigns, 19 that they would then screen against other kinase 20 targets of interest. So some libraries that they 21 screened, more focused than others focused, meaning 22 having been built and intended as kinase inhibitors at 23 some point in their history or having structural 24 resemblance to those. 25 Q. And after selecting this scaffold as the	Page 87	1 off the record. 2 (Off the record.) 3 ***** 4 5 A-F-T-E-R-N-O-O-N P-R-O-C-E-E-D-I-N-G-S 6 VIDEOGRAPHER: One moment. 7 The time is 1:01. 8 We are back on the record. 9 BY MR. DESAI: 10 Q. Ready? 11 Could we go to Paragraph 85 of your 12 declaration? 13 A. I am there. 14 Q. This is where you reference the '820 15 patent, right? 16 A. Correct. 17 Q. All right. And you reference it because 18 it, "describes a series of compounds as 19 kinase inhibitors that have the same 5:6 20 fused scaffold for hinge binding"? 21 A. Correct. 22 Q. Okay. And that is shown on Page 53? 23 A. Correct. 24 Q. And this scaffold is -- does not have two 25 aromatic rings, right?	Page 89

1 A. That's correct. 2 Q. Just quickly going back to Formula E in 3 your declaration, you had referenced, like, the 4 requirements of Formula E in terms of the orb, that 5 the element makes the appropriate H-bonds with the 6 hinge region while appropriately orienting the fixed 7 substituents. 8 Do you remember that? 9 A. Yes. 10 Q. Is your opinion that a POSA reading the 11 '803 patent would understand that the scaffold 12 structure you see on Page 53 of your declaration would 13 meet those requirements for the orb in Formula E? 14 A. Sorry. Can you repeat the second part of 15 that question? 16 Q. Yes. 17 Okay. So we have these requirements for 18 the orb in Formula E, making the appropriate H-bonds 19 with the hinge region while appropriately orienting 20 the fixed substituents; that's stated in your 21 declaration, right? 22 A. Correct. 23 Q. Now, looking at the scaffold structure that 24 we see from the 820 patent on Page 53 of your 25 declaration; you see that, right?	Page 90 1 useful for that. 2 Q. Okay. And with respect to that scaffold 3 structure you see on Page 53, where would a POSA 4 attach the phenoxyphenyl group? 5 A. As we've discussed before, I would, you 6 know, as we sit here today, I'm not equipped to do 7 that, but my approach to it would be to work with 8 other members of the POSA team, apply modeling tools. 9 Q. In order to model this, you would have to 10 figure out where to attach the phenoxyphenyl group, 11 right? 12 A. To model the final structure, obviously, 13 that's correct. 14 Q. And you would also need to know -- 15 A. One would start, for example -- apologies 16 if I'm interrupting, but I'd like to finish my answer. 17 Q. Sure. 18 A. One way a POSA might start is by, you know, 19 looking at the dock structure of ibrutinib in the 3GEN 20 crystal structure, and then taking this scaffold and 21 superimposing it on that structure and establishing 22 then how to position the phenoxyphenyl and the 23 linker-warhead structures such that the geometric 24 requirements would be met. So one would start the 25 process even without having elaborated the complete
1 A. Yes. 2 Q. Would a POSA reading the '803 patent, 3 equipped with the knowledge of the prior art as well, 4 would they understand that that scaffold structure 5 from the '820 patent would meet those requirements for 6 the orb in Formula E, which is that it would make 7 appropriate H-bonds with the hinge region while 8 appropriately orientating the fixed substituents? 9 A. So as an unsubstituted scaffold, as the raw 10 scaffold as it's drawn here, I don't think that a POSA 11 would, you know, immediately recognize it as fitting 12 that definition. On the other hand, a POSA equipped 13 with the standard tools of the trade, I think would 14 understand that it could, you know, potentially be 15 used in a way to meet the requirements of the orb in 16 Formula E. 17 Q. What do you mean "could potentially?" 18 Do you mean that it may, it may not, you'd 19 have to model or test it to figure that out; is that 20 what you mean? 21 A. I think, as I said, that the POSA would use 22 the standard tools of the trade and compose a 23 structure positioned hydrogen bond donors, acceptors, 24 model it in the structure of Marcotte, et al, and 25 would be able to readily determine whether it was	Page 91 1 structure. 2 Q. Okay. Now, I'm going to try my question, 3 okay. My question is this: in order to model this 4 scaffold, right, and whether it would serve these 5 purposes that you have stated are requirements for 6 Formula E, the orb, right? Okay? 7 A POSA would have to figure out where to 8 attach the phenoxyphenyl group, and where to attach 9 the Michael acceptor linker-warhead, correct? 10 A. Did you say in order to model it, one would 11 have to do that? 12 Q. Yes. 13 A. No. As I just explained, one could start 14 with the scaffold and use the structural information 15 to determine where to place those substituents. One 16 wouldn't have to apriori place those substituents in 17 order to start the modeling exercise, start a modeling 18 exercise with a scaffold or a fragment. 19 Q. And then play around with it to figure out 20 where to put those; is that right? 21 A. I wouldn't characterize it as "playing 22 around with it," but examine the structural 23 constraints and proceed as informed by the 24 specification in the '803 patent to achieve the 25 desired, predictable end.
	Page 92 Page 93

Page 94 1 Q. According to you, visualizing the docking 2 of a candidate BTKI could be accomplished in a matter 3 of minutes, right? 4 A. That's correct. 5 Q. So you could take that scaffold structure 6 and in a matter of minutes visualize whether it would 7 be a candidate BTKI, right? 8 A. We're talking about two different things. 9 So as I've -- the section of my declaration that 10 you're quoting from, I'm talking about taking a 11 fully-formed inhibitor and docking it. Here, we are 12 talking about taking a scaffold and elaborating it 13 into a fully-formed inhibitor. 14 Q. How long would that take? 15 A. I mean, if I were in my office, at my work 16 station, you know, I could in a matter of, you know, I 17 think less than an hour, have a clear sense of where I 18 would want to attach the phenoxyphenyl and the 19 linker-warhead and the other substitutions that I 20 might be interested in adding in order to achieve 21 hydrogen bonds with the hinge. 22 Others who are -- you know -- what am I 23 trying to say? 24 Yeah, I'm not particularly fast. I'm slow 25 and deliberate. Others could probably do it even	Page 96 1 didn't do any modeling -- 2 Q. Can we just stick to the question that's 3 asked? Let's stick to the question that was asked. 4 Did you do any modeling of that? 5 A. I didn't do any modeling of this isolated 6 scaffold. 7 (Exhibit 2055 marked for identification, 8 Article Re: Synthesis and SCAR.) 9 Q. Okay. All right. Why don't we go to 10 Page 121 of your declaration, and there is a structure 11 shown at the top from Exhibit 2055. 12 Do you see that? 13 A. Yes. 14 Q. Okay. And you described this as a 15 partially saturated hinge binding element? 16 A. That's correct. 17 Q. Could you just -- what are you referring to 18 in that structure as being a partially saturated hinge 19 binding element? 20 You can circle with the red pen. That's 21 fine. 22 A. Sure. (Witness complied.) 23 Q. Okay. It's the fused ringed structure on 24 the left? 25 A. Correct.
Page 95 1 faster. 2 Q. Do you think you are a POSA? 3 A. I'm confident that I'm a POSA, yes. 4 Q. You are not above the level of skill of a 5 POSA? 6 A. I think in the -- in the realm of a POSA as 7 it relates to the '803 patent, I don't necessarily 8 consider myself of -- above an ordinary level of 9 skill. In certain areas, I think I'm well above the 10 ordinary level of skill, but as a member of a POSA 11 team who is informing with respect to kinase 12 structure, kinase inhibitor structure function 13 relationships, I think I'm -- you know -- talented and 14 somewhere in the pack. I consider I'm pretty ordinary 15 and common. 16 Q. But you've never taken the time to figure 17 out where you would attach the phenoxyphenyl group in 18 a Michael acceptor linker-warhead for this 19 structure -- a scaffold structure in the '820 patent, 20 correct? 21 A. Correct. That's not an exercise that I 22 have done. 23 Q. And, therefore, you did not do any modeling 24 of that scaffold, correct? 25 A. So I did modeling of zanubrutinib but I	Page 97 1 Q. I'm assuming the answer is going to be the 2 same, but you have not taken the time to assess 3 where a POSA would attach the phenoxyphenyl group or 4 the Michael acceptor linker-warhead for this 5 particular scaffold? 6 A. That's correct. I haven't done that 7 exercise. 8 Q. And, therefore, you haven't done any 9 modeling of this either? 10 A. I believe I looked at the 2QD9 crystal 11 structure to understand the binding mode of that 12 compound, but I haven't done any modeling of that 13 structure or that specific scaffold. 14 (Exhibit 2046 marked for identification, an 15 article. Re: Discovery of TAK-659.) 16 Q. Why don't we go to Page 125, and in the 17 middle of the page, there is a structure from 18 Exhibit 2046, correct? 19 A. Correct. 20 Q. Okay. And this is, I think, another 21 example of what you are saying is a partially 22 saturated hinge binding scaffold? 23 A. That's correct. 24 Q. Okay. And again, same question, you have 25 not taken the time to assess where a POSA would attach

1 the phenoxyphenyl group or the Michael acceptor 2 linker-warhead, correct? 3 A. That's correct. I wasn't asked to do that 4 and haven't done that. 5 Q. Okay. You did not -- you did not model 6 this scaffold either, correct? 7 A. That's correct. To my recollection, I 8 haven't modeled that scaffold. I did look at the 9 crystal structure that's referenced here, the 5TR6 PDB 10 deposition. 11 Q. Okay. I want to go back to your opinions 12 about scaffold swapping. I think it starts at 13 Paragraph 103 of your declaration. 14 A. (Witness complied.) 15 I am there. 16 Q. Okay. And one example of scaffold swapping 17 that you provide is using a hinge-binding structure 18 from a known ligand in a different kinase, correct? 19 A. Which specific example are you referring 20 to? 21 Q. Well, I think I'm saying more generally one 22 example of scaffold swapping that you provide is 23 that using -- you would be using a hinge-binding 24 structure from a known ligand in a different kinase, 25 correct?	Page 98 1 led a POSA to the specific Z-scaffold structure used 2 in zanubrutinib, correct? 3 A. If you limit the scaffold swapping to 4 taking the entirety of the hinge binding element and 5 the associated ring structures that present the hinge 6 binding element, then that would be true, but in 7 general and in the field, scaffold swapping, scaffold 8 hopping, scaffold wharfing, is not limited to that 9 kind of an exercise. Substructures can also be moved 10 and reconnected and re-assorted. 11 Q. Okay. But, again, in this context of the 12 question, I was talking about the context of using 13 known structures, right? 14 We will get to the modifying of structures 15 and creating new structures, but let's focus on this 16 aspect, which you have in your declaration at 104 of 17 using a known structure, okay? 18 A. Okay. 19 Q. All right. If a POSA reading the '803 20 patent was to scaffold swap based on using a known 21 hinge binding element as of June 2, 2011, that would 22 not have led a POSA to the specific Z-scaffold 23 structure used in a zanubrutinib, correct? 24 MS. DANEK: Objection to form. 25 A. I'm trying to be very clear that the Page 100
1 A. That's fair. 2 Q. That's, for example, discussed in 3 Paragraph 104 where you say: 4 "... a POSA in 2011 would have understood 5 that a hinge-binding substructure from a 6 known ligand is likely to make similar 7 interactions with the highly conserved 8 hinge in a different kind kinase." 9 A. That's correct. 10 Q. Okay. All right. And in Paragraph 104, 11 you say that a POSA would have been aware of numerous 12 kinase ligand structures to allow for swapping of 13 scaffolds, right? 14 A. That's correct. 15 Q. Okay. And then you -- you referenced some 16 protein data bank and publicly available kinase 17 structures and known scaffolds, right? 18 A. Correct. 19 Q. And among these known structures and known 20 scaffolds you would agree in June 2011, none of them 21 are zanubrutinib scaffold structure, right? 22 A. To my knowledge, that's correct. 23 Q. So if a POSA reading the '803 patent was to 24 scaffold swap based on known hinge binding elements of 25 kinase inhibitor as of June 2011, that would not have	Page 99 1 Z'-structure of zanubrutinib itself was not known in 2 the art, although a POSA could have readily arrived at 3 it from the '803 specification and other structures 4 that were known in the art. 5 Q. So is it your view that it would have been 6 obvious to a POSA to come up with that structure based 7 on what's in the '803 patent and other information in 8 the art? 9 MS. DANEK: Objection to form. 10 A. I think with the information in the patent 11 and with -- with the knowledge in the art of a POSA, 12 the tools that were readily available to a POSA, that 13 a POSA could have recognized, visualized that 14 structure as a hinge-binding element suitable for 15 application in making an ibrutinib-like BTK inhibitor. 16 Q. And in the patent, what specifically are 17 you relying on that would have led a POSA to that 18 structure; is it Formula E or something else? 19 A. Formula E, you know, evokes the scaffold 20 swapping approach, but in addition to Formula E, we 21 have the other structural constraints in the 22 specification requirements with a very specific 23 phenoxyphenyl substituent and a linker-warhead 24 substituent and where and how those have to be 25 located. Those are additional factors that would Page 101

1 guide the POSA. 2 Q. Is the phenoxyphenyl group and the 3 linker-warhead, weren't those known in the art before 4 this patent as well? Is that a contribution that was 5 made by this patent? 6 A. The specific introduction of those 7 substituents in a particular way to make an 8 inhibitor -- first of all, to back up for a moment, 9 this is a use patent, and so the subject matter of 10 this patent is about using BTK-like inhibitors as 11 outlined and claimed here for treatment of a disease. 12 Q. You didn't answer the question, you 13 answered something else. 14 A. I want to answer your question, so if you 15 will pose it again, I will refocus and try to be 16 clearer. I want -- you know -- obviously, want to be 17 responsive. 18 Q. All right. So aside from Formula E, okay, 19 which we've covered, I think exhaustively, is there 20 anything else in this patent that would have lead a 21 POSA to the Z-scaffold structure in zanubrutinib? 22 A. Yes, I think so. 23 Q. Okay. Point me to where, column and line 24 number. 25 A. So --	Page 102	1 how ibrutinib binds in BTK. 2 They would read from the specification that 3 5:6 fused heterocycles were useful for conjoining and 4 presenting in the desired orientation the 5 phenoxyphenyl and the linker-warhead. 6 They would learn from the specification 7 that it was possible to have variability in the 8 orientation of attachment of the linker-warhead. So 9 there are very rich teachings that a POSA familiar 10 with the art of kinase inhibitor design and the rich 11 structural information already available in the 12 literature for BTK could have brought to bear in 13 elaborating the structure of zanubrutinib. 14 Q. Do you have a column and line number for me 15 anywhere in there beside Formula E? 16 A. So the structure of ibrutinib is at 17 Column 65, roughly lines 10 through 25. 18 Q. Okay. 19 A. And in other places, there are 20 linker-warhead structures depicted that show 21 variability. So, for example, in Column 53, roughly 22 lines 5 through 10. And while the scaffold ibrutinib 23 per se is not exemplified -- 24 Q. I think you meant "zanubrutinib." You said 25 "ibrutinib."
1 Q. If you could just grab the patent formula 2 column number, and then I'll ask a question. 3 MS. DANEK: Counsel, he can take 4 whatever effort he needs to answer your question. 5 Don't direct him or limit him. 6 MR. DESAI: I didn't -- but I didn't -- 7 I asked him to point me to the column, and that 8 was my question. Point me to the column and line 9 number. If you have a specific question for him 10 later, you can do it on redirect. 11 MS. DANEK: My instruction to you is 12 not limit how he is able to respond to your 13 questions. 14 BY MR. DESAI: 15 Q. Well, my question is point me to the column 16 and line number. I think you have another copy? 17 It's right there. 18 A. Right here. Sorry. So throughout the 19 patent, in looking to the specification and in taking 20 into consideration what's known in the art, one can 21 learn how to prepare inhibitors of the claims. So as 22 specific examples, we have the example of ibrutinib 23 itself that's present in many locations in the patent. 24 I'm sure you can find it faster than I can, but a POSA 25 would be able to understand how ibrutinib, precisely	Page 103	1 A. Sorry. The scaffold of zanubrutinib per se 2 is not exemplified in columns 62 and 63. The 3 embodiments presented there show that there is 4 variability in the 5:6 heterocycles that can be used 5 in some embodiments of the claim. Again, the 6 disclosure in the specification interpreted in light 7 of the rich knowledge in the art and the powerful 8 structural information is enabling in my opinion. 9 Q. If we go to Paragraph 105 of your 10 declaration, you state that in -- sorry -- 11 Paragraph 105 of your declaration. 12 A. Sorry. 13 Q. "... a POSA could generate additional 14 inhibitors from ibrutinib, whose 15 structure the '803 patent taught resulted 16 in potent inhibition of BTK in patients." 17 Do you see that? 18 A. Yes. 19 Q. When you say, "a POSA could generated 20 additional inhibitors" are you referring to, for 21 example, creating a new Z'-scaffold structure that's 22 not expressly found in the art as of June 2011? 23 A. Yes. As I've explained -- 24 Q. That was kind of a "yes" or "no" question 25 but if you want to keep going, that's fine.

1 A. Well, I will be very brief. 2 Q. Okay. Go ahead. 3 A. But, you know, as we have been through 4 before, part of the rich knowledge in the art is in 5 addition to scaffold swapping, scaffold morphing, 6 adding of substituents, closing of rings, et cetera 7 that were well-known. And, yes, as using part of that 8 toolkit, a POSA could generate additional inhibitors, 9 including inhibitors where that specific fully 10 elaborated Z'-structure had not been previously seen 11 in the art. 12 Q. That's referred to in this paragraph. You 13 refer to that or you refer to an article that would 14 call that as a "novel scaffold", right? 15 A. Just let me read what I have here to make 16 sure I'm oriented. 17 Q. Sure. 18 A. Yes, I'm quoting from the GOEZ reference 19 or -- no. Sorry. 20 Reference 2028. 21 "... binding element of a given kinase 22 lead is replaced, based on structural 23 information, with the novel scaffold." 24 Q. Here is that article. It's Exhibit 2028. 25 (Exhibit 2028 previously marked for	1 scaffold." Do you see that? 2 A. Yes. 3 Q. Okay. And one example of this is in 4 Figure 5, right? 5 A. That's correct. 6 Q. And Figure 5 is discussed in Paragraph 106 7 of your declaration, right? 8 Go to the next page and you will see it. 9 A. Yes. 10 Q. And this was -- this is depicting designing 11 a new scaffold by modifying a known scaffold; is that 12 right? 13 A. Let me just remind myself. That's not how 14 I would describe it, no. 15 Q. Okay. How would you describe it? 16 A. I would describe it as taking a scaffold 17 from a known inhibitor and incorporating a new 18 substituent to create a new inhibitor based on the 19 known scaffold. 20 Q. Right. This article does refer to that as 21 using a "novel scaffold", though, right? 22 A. I think they are referring in the paragraph 23 that has the bold heading, "Swapping fragments" to 24 fragments identified above. I would have to read 25 again more carefully to orient myself.
1 identification, an article, 2 Kinase-targeted libraries.) 3 Q. All right. You specifically rely on this 4 article for the proposition that one way of coming up 5 with a new type of inhibitor is to develop a novel 6 scaffold, right? 7 A. That's correct. This is one reference that 8 I have cited in support of that. 9 Q. Okay. And you also -- you specifically 10 rely on Page 4, it's the section that starts -- it's 11 labeled, "Swapping fragments." 12 Do you see that? 13 A. I do. 14 Q. And the second sentence, I think you quote 15 that: "A powerful approach for the 16 utilization of these novel kinase 17 scaffolds is in lead modification and 18 optimization," right? 19 A. Let me just read the paragraph to myself. 20 Q. Sure. 21 A. I'm here. 22 Q. Okay. So this strategy is described as, 23 "the hinge-binding element of a given 24 kinase lead is replaced, based on 25 structural information, with the novel	1 Q. All right. We already went through that 2 part of the section that describes it as using "novel 3 scaffolds." We don't need to do that again. 4 Figure 5 also shows that whether the new or 5 this novel structure, binds the hinge region was 6 confirmed by x-ray crystallography, right? 7 A. That's correct. 8 Q. Now, if we go to Page 3 -- are you on 9 Page 3? 10 A. Yes. 11 Q. In the second column, there is a sentence 12 that says, "The synthesis of molecules unknown in the 13 literature." 14 Do you see that? 15 A. I'm sorry. Where are we, on Page 3? 16 Q. Page 3, second column. "The synthesis of 17 molecules unknown in the literature." Do you see 18 that? 19 A. Yes. 20 Q. So that paragraph says, I will read, "The 21 synthesis of molecules unknown in the literature 22 carries many difficulties, such as large upfront 23 synthetic methodology development, unexpected and 24 sometimes undesirable physicochemical properties and 25 possible instability issues."

1 Do you see that? 2 A. Yes. 3 Q. Okay. And then it goes on at the end of 4 this column to say, "To this end, 5 extensive validation of the candidate 6 scaffolds is performed through activity 7 measurements, X-ray structural analysis, 8 and synthetic modification." 9 Do you see that? 10 A. Yes. 11 Q. In June 2011, the specific molecule of 12 zanubrutinib, including its Z-scaffold structure would 13 fall into the bucket of a molecule unknown in the 14 literature, correct? 15 MS. DANEK: Objection to form. 16 A. I'm sorry. Can you repeat the question. 17 Q. The scaffolds, the specific structure of 18 zanubrutinib, including its scaffold structure, would 19 fall into the bucket of a molecule unknown in the 20 literature, correct? 21 A. Zanubrutinib would fall in the category of 22 a molecule unknown in the literature, that's correct. 23 Q. Okay. All right, let's go to Paragraph 115 24 of your declaration. 25 A. Sorry. I would like to correct myself	Page 110 1 using Glide docking within the Maestro Schrödinger 2 modeling environment, right? 3 A. Schrödinger Maestro modeling environment, 4 correct. 5 Q. What version number did you use for Glide 6 and Schrödinger? 7 A. I don't remember off the top of my head. I 8 think it's a current version. I think that 9 information probably would be -- that specific answer 10 is probably in the native files that I've provided to 11 you. 12 Q. It's not a version that was available in 13 2011, correct? 14 A. That's correct. 15 Q. You do mention that in Paragraph 118 that, 16 "The functionality of the Maestro/Glide 17 software that I used for docking was 18 available in 2011." 19 Okay. Right? 20 A. That's correct. 21 Q. What do you mean by "the functionality"? 22 Like, just to the ability to dock the ligand? I 23 don't -- 24 A. Well, certainly the ability to dock the 25 ligand. The specific steps in the docking because Page 112
1 about Figure 5. 2 Q. Sure. 3 A. I think I misspoke before. So they have, 4 as I was describing before, made modifications to the 5 scaffold. So you could consider part of this to be a 6 new scaffold. I have no idea whether this scaffold 7 was known prior in the literature before or not, but 8 it wasn't, as I was understanding when I answered 9 previously, just an exercise of taking the existing 10 scaffold and grafting on another substituent. I just 11 wanted to make that clarification. 12 Q. Subject to you not knowing whether the 13 ultimately final scaffold was actually found somewhere 14 in the art, this could be a novel scaffold? 15 A. That's possible, yes. 16 Q. Gotcha. All right. If we go to 17 Paragraph 115 of the declaration. You refer here 18 to "a POSA" being "aware of computational tools for 19 the docking of ligands into target protein 20 structures," right? 21 A. Yes. 22 Q. Okay. And Glide is the only computational 23 tool that you discuss in your declaration, right? 24 A. That's correct. 25 Q. And you perform modeling on some compounds	Page 111 1 I've outlined here the protein preparation step, the 2 ligand preparation step, various options for degree of 3 precision in docking standard precision, XP, extra 4 precision or extended precision as they call it. 5 Q. You say that the software has been further 6 developed since June 2011. Right? 7 A. Correct. 8 Q. How has it been further developed? 9 A. I don't have specific knowledge of the 10 precise changes in the software. 11 Q. So you are not able to explain what changes 12 or improvements to Glide have been made, to 13 Glide/Maestro since 2011 compared to the version you 14 used for this declaration, right? 15 A. I don't have the knowledge to discuss the 16 technical details of changes. I understand that force 17 fields have evolved in the intervening years. There 18 may be differences in the force fields, and I'm sure 19 that there are probably differences in the specifics 20 of the user interface. But the basic functionality of 21 being able to prepare a receptor, prepare a ligand, 22 dock them, were certainly there in 2011 and being used 23 in my lab and around the world then and before then, 24 and as I've cited in any report, you know, used to 25 obtain similarly precise results as those that I have Page 113

1 seen here when comparing dock structures with x-ray 2 structures. 3 Q. So you're offering an opinion, and it 4 sounds like to me right now that you believe that the 5 software version from 2011 and the software version 6 from today that you used, would provide you the same 7 precision; is that right? 8 A. I think in a qualitative sense, that's 9 correct. So, in fact, you know, even by manual 10 docking without the aid of computational docking, one 11 would have a very clear picture of ibrutinib or 12 zanubrutinib binds to BTK and, you know, whether 13 something is, you know, a small fraction of an onstrum 14 (phonetic) to the left or right in one docking model 15 versus another, is frankly not a level of precision 16 that's important for the kind of computational 17 modeling that -- that we do or the a POSA would do for 18 these kinds of purposes. 19 Q. Is the accuracy of docking software and its 20 ability to predict improved since 2011? 21 A. I think that the answer to that is almost 22 certainly yes, but I haven't -- you know, I can't cite 23 you specific literature, specific papers to that 24 effect, but it's obviously an area of very active 25 development and interest. Over the last couple of	Page 114 1 Q. And then you also docked Compound 7 and 8 2 from Zhang. Zhang 2020 reference? 3 A. That's correct. 4 Q. Did you do any docking of any other 5 compounds besides the ones that we've just listed? 6 A. I remember at least one other compound. 7 Q. What was that other one? 8 A. It's the S-stereoisomer of ruthenium. 9 Q. Did you produce that? Did you provide that 10 native file? 11 A. If I was asked to, I'm sure I provided it. 12 MS. DANEK: You didn't ask for that 13 one. 14 MR. DESAI: Okay. 15 THE WITNESS: It's possible that it was 16 inadvertently in the file, if not asked for. I 17 can't say for sure, but I certainly didn't 18 intentionally include it if it wasn't asked for. 19 MS. DANEK: Okay. 20 BY MR. DESAI: 21 Q. Did you use, like, did you basically use 22 the same process -- so in Paragraph 116, you talk 23 about your process for docking ibrutinib. Did you use 24 that same process for those other compounds? 25 A. The same general process, yes. Whether I Page 116
1 years, obviously, machine learning approaches have 2 become a big push in this field as well, but that's 3 not a toolset that I was bringing to bear here. I was 4 using the simpler, older physics-based docking tools. 5 Q. I'm going to go to Paragraph 116. 6 A. I am there. 7 Q. Here you state that you dock ibrutinib 8 using Glide docking in the Maestro Schrödinger 9 modeling environment, right? 10 A. Correct. 11 Q. And you state that the, "docking was 12 carried out in standard precision, SP 13 mode, with ibrutinib, prepared using the 14 LigPrep functionality in Maestro", right? 15 A. That's correct. 16 Q. And did anyone assist you with this 17 modeling of ibrutinib? 18 A. I did that myself. 19 Q. Okay. And as I understand it, you also 20 docked zanubrutinib, right? 21 A. That's correct. 22 Q. And if we skip ahead to Paragraphs 184 and 23 185, you've docked five additional compounds: 24 compounds 20, 30, and 122 of the '446 patent, right? 25 A. 30, 20, and 122 of -- yes, that's correct. Page 115	1 did it in precisely the same way, I couldn't say for 2 sure. 3 Q. For the stereoisomer of ibrutinib that you 4 say you modeled, why didn't you discuss that in your 5 declaration? 6 A. I didn't see a specific need to. 7 Q. What did you model it for? What was the 8 point of doing that? 9 A. I was curious to see the impact of the 10 inversion of the stereocenter on the confirmation of 11 the compound and its ability to juxtapose the warhead 12 with cysteine 481 of BTK. 13 Q. And what was the impact? 14 A. I was struck by how similarly it could 15 position the warhead in spite of the inversion of the 16 stereochemistry. You know, one zigged and zagged and 17 the other zagged and zigged and ended up in very 18 similar positions in superimposing RNS isomers. 19 Q. I guess I'm trying to understand. 20 You were struck by the similarity, so this 21 was something that was important for your opinions or 22 not important? 23 A. Well, we know from Pan and we know from -- 24 yeah, we know from Pan that both R and S are potent 25 for inhibition. So I relied on that in reaching Page 117

1 opinions that have anything to do with flexibility or 2 potential variability in the positioning of the 3 warhead. So that additional docking was more or less 4 superfluous and told us what we knew from -- by 5 chemical experiments. 6 Q. Just some quick questions about this, it's 7 Exhibit 2037. 8 (Exhibit 2037 marked for identification, 9 Glide 5.5 User Manual.) 10 Q. If we go to Page 028, yes. Are you there? 11 A. Yes. 12 Q. This is the manual for Glide, and we are 13 looking at the page which describes the process for 14 using LigPrep for ligand preparation, right? 15 A. Correct. 16 Q. And there's a series of steps, 1 through 13 17 on the next page? 18 A. Correct. 19 Q. When you prepared the compounds and modeled 20 in LigPrep, you had to go through each of these steps? 21 A. Well, as it says here, "Many of the steps 22 are optional and are controlled by 23 selecting options in the LigPrep panel or 24 specifying command-line options." 25 But in general, you know, as of Glide 5.5,	Page 118	1 cannot be performed until the receptor 2 grids have been generated," okay? 3 A. Correct. 4 Q. Did you have to go do that? 5 A. Yes. So I imported a 3GEN crystal 6 structure. I ran the protein prep functionality, you 7 know, after having removed the ligand. I 8 reincorporated the ligand for purposes of defining the 9 receptor grid in the box. I used default values for 10 box dimensions, at least as far as I know they were 11 default values. They looked reasonable to me, given 12 the size of the B43 ligand and the size of the 13 ibrutinib and zanubrutinib that I was docking. I 14 covered the relevant regions of the receptor, the 15 receptor being the 3GEN BTK crystal structure. 16 Q. Okay. Then if we go to Section 5.1, Ligand 17 Docking. You had to go through these tabs for ligand 18 docking as well, right? 19 A. So one -- one likely change between this 20 version and the version I was using, at least as far 21 as I know, it didn't exist as a version 5.5. There's 22 a panel called "one step docking", so a change in the 23 graphical user interface that streamlined the 24 application of the tool. 25 Q. Right, but you don't remember off the top	Page 120
1 these were the steps. 2 Q. Okay. And then if we go to Page 33, 033, 3 there is a section here on "Receptor Grid Generation 4 Panel"? 5 A. Correct. 6 Q. And you had to go through these steps, 7 right, to generate a receptor grid for BTK? 8 A. What steps are you referring to? 9 You mean setting a box length in X, Y, and 10 Z as indicated in Figure 4.5? 11 Q. 4.1 -- it's the overview, but there are 12 subsections describing the more specific steps. Did 13 you have to go through these steps? 14 A. So let me read what we are talking about 15 here so I understand what steps you are referring to. 16 (Witness reviewing the document.) 17 Q. All right. How about this, on Page 33, it 18 says, "The options in each tab of the 19 Receptor Grid Generation panel allow you 20 to define the receptor structure by 21 excluding any cocrystallized ligand that 22 may be present, determine the position 23 and size of the active site as it will be 24 represented by receptor grids, and set up 25 Glide constraints. Ligand docking jobs	Page 119	1 of your head what version you used? 2 A. If I'm remembering right, it's called -- 3 2024-2 or 2024. Yeah, I just -- don't quote me on 4 that. It was an up-to-date version. I vaguely recall 5 having seen a "2024" in the version number. 6 Q. Okay. I want to ask you -- I want to go 7 back to your comment about visualizing using docking 8 within a matter of minutes, Paragraph 209. 9 A. (Witness complied.) 10 Q. You said, "... a POSA would have routinely 11 identified and excluded structures that 12 were plainly not operable, i.e., 13 structure that would not be accommodated 14 within the known structural conformation 15 of BTK bound to a BTK inhibitor with 16 ibrutinib-like binding. Visualizing the 17 docking of a candidate BTKI could be 18 accomplished in a matter of minutes"? 19 A. I'm still looking for -- you said 209? 20 Q. Yes. 21 A. Oh, Page 209? 22 Q. Paragraph 209. 23 A. Yes, that's what I've written. 24 Q. All right. What could be done in a matter 25 of minutes is not clear to me. Can you explain? What	Page 121

1 are you saying could be accomplished in a matter of 2 minutes? 3 A. So as an example, you know, if I thought I 4 would, you know, redock ibrutinib this weekend, and I 5 think within 30 minutes of starting from scratch of 6 pulling up, you know, a new instance of Maestro, I was 7 able to proceed through all of these steps and dock 8 ibrutinib. So that's a matter of minutes. But 9 really, half an hour is not what I was referring to 10 "in a matter of minutes." 11 I think once one had that environment 12 established and had the protein preparation steps run, 13 then it would be trivial to take a large number of 14 structures and dock them and accomplish, you know, a 15 very large number of dockings in a very short space of 16 time. 17 We do virtual ligand docking and, you know, 18 as of 2011 or even before then, we were doing a screen 19 of -- I don't remember exactly how many million 20 compounds and I don't remember precisely how long it 21 all took, but once it's queued up, it's a matter of, 22 you know, CPU time and resources. 23 But certainly, you know, it can be done in 24 a parallelized workflow as of 2011 and, you know, 25 seconds per compound is my recollection.	Page 122 1 small, another 15 minutes, half an hour at the most, 2 and could have added -- and then once that, you know, 3 workflow was in place, could have even achieved higher 4 efficiencies. 5 And somebody who's a full-time 6 computational chemist, you know, scripting these 7 things, breaking them out across multiple servers and 8 CPUs, could achieve even higher throughputs if that 9 was felt to be necessary. 10 Q. Okay. So staying with this line of 11 thinking, you do understand that Dr. Showalters 12 explained that there are billions of structures that 13 fall within the literal scope of the Z'-structure 14 limitation at the time. We've been through that this 15 morning, right? 16 A. Yes. I understand that you -- 17 Q. How long would it take to evaluate which of 18 those Z'-structures and put them in the buckets of 19 ones that will be operable and ones that will not be 20 operable? 21 A. You are suggesting a false premise here. 22 There aren't billions of structures that a POSA would 23 screen. 24 Q. How many would they screen? 25 A. As we've discussed this morning -- Page 124
1 Q. Are you talking about the time that it 2 would take for the computer to compute it when it's 3 all -- once it's all queued up? 4 I mean, are you suggesting -- I just want 5 to be clear -- are you suggesting that you could 6 screen millions of compounds in a matter of minutes? 7 A. No. No, not at all, no. That's not what I 8 said. 9 Q. Perhaps you want to clarify. What do you 10 mean by you were able to screen millions of compounds 11 with just minimal CPU time? 12 A. I didn't say, "minimal CPU time." 13 I said how long it would take would be a 14 function of the resources in the number of CPUs that 15 you wanted to devote to it but -- so we could make a 16 distinction between human time and computer time here. 17 It sounds like that's what you are asking for; am I 18 correct? 19 Q. Yes. Cool. 20 A. So I think in a matter of minutes, and as I 21 gave an example, you know, myself, docking ibrutinib 22 is one compound, you know, in approximately 23 30 minutes, could start from scratch with no context 24 and do that. The incremental time to have docked, you 25 know, five more compounds, would have been relatively Page 123	1 Q. So you don't know? 2 A. -- I haven't tried to calculate that. 3 Q. All right. Okay. Let's just say that 4 there were a million, how long would it take? 5 A. Again, that would depend on the 6 computational resources that one wanted to bring to 7 bear on the problem but, you know, as of -- 8 Q. Forget the computer time. How long would 9 it take to set up to evaluate a million of those, to 10 actually prepare and dock a million of those? 11 A. Yeah, I haven't tried to estimate that. 12 Q. It would take a really long time, right? 13 A. I'm not sure what you mean by "a really 14 long time." 15 Q. It wouldn't be a matter of minutes, would 16 it? 17 A. I think it's fair to say that, you know, 18 starting from scratch, you couldn't do that in a 19 matter of minutes. 20 Q. In your experience -- I think you did say 21 that you've had the experience of evaluating millions, 22 right? 23 A. Yes, we've done virtual ligand screens. 24 Q. How long did that take? 25 A. I don't recall precisely. Page 125

Page 126 1 Q. Was it days? 2 A. I think it was -- was weeks or on the order 3 of two or three months. 4 Q. What project was this? 5 A. This was an effort to identify glue-type 6 molecules that would bind to -- that would lock two 7 Ras molecules together in a way that would keep them 8 from interacting with their downstream effectors. 9 Q. Do you have a paper associated with this? 10 A. Alas, we never published on this. 11 Q. And how did you go about evaluating or 12 screening these millions of possibilities? 13 A. With virtual ligand screenings. We had 14 determined the crystal structure of Ras that showed 15 how -- where in the asymmetric unit there were, if I'm 16 remembering correctly, two molecules of Ras, a dimer 17 of Ras. And they were using their effector binding 18 interfaces to make beta strand-like interactions that 19 looked like they stabilized this dimer and those were 20 the -- it's the same interaction surface that Ras uses 21 to engage the so-called "Ras binding domain" that's in 22 various downstream effectors that Ras will activate, 23 so things like raf family kinases. 24 So, anyway, it occurred to us that if two 25 Ras were busy interacting with each other in that	Page 128 1 A. Well, that's correct in that they were in 2 this database. 3 Q. Okay. You understand that the Z' that's 4 claimed in the patent, the '803 patent, encompasses 5 both known as well as scaffold structures that are yet 6 to be discovered, correct? 7 A. I wouldn't characterize it as, "yet to be 8 discovered", but I would say it's fair to say that Z' 9 could encompass scaffolds that had been previously 10 seen in the literature and scaffolds that hadn't been 11 previously seen in the literature as we discussed 12 before. 13 Q. So if you wanted to evaluate all of the 14 possible Z's, and whether they are operable or not 15 operable for this particular patent and this claim, it 16 would involve evaluating known structures as well as 17 structures that were not previously described, right? 18 A. I think that's fair to say. 19 Q. And you would agree that that would take a 20 different amount of time than the project you just 21 described, which involved evaluating structures that 22 are already described in the database, right? 23 A. There would be a step there in elaborating, 24 drawing out the structures to be docked that we didn't 25 have to contend with in our docking work.
Page 127 1 manner, that they couldn't interact with Ras and you 2 could -- raf. So that in that way, you could 3 neutralize a Ras. And we noticed a small pocket in 4 that interface, actually two symmetric pockets, that 5 we thought if we could find a small molecule would 6 bind in there might stabilize that dimer. So we were 7 doing virtual ligand screening focused on that pocket 8 and using what's call the ZINC database of ligand 9 structures. 10 Q. So you were evaluating known ligand 11 structures in that database? 12 A. Yeah, ligands that, you know, the ligands 13 that already had been elaborated and available in this 14 database for the purposes of making them available for 15 screening. 16 Q. Okay. So you were pulling known ligands 17 from a database and virtually screening them, correct? 18 A. Correct. 19 Q. And when was this project? 20 A. I don't remember exactly, but definitely 21 before 2012, so I think it would have been going on in 22 2011, 2010. 23 Q. So you were not evaluating in that context 24 structures that were not previously described, ligands 25 that were not previously described?	Page 129 1 Q. And that could be a very significant 2 undertaking, correct? 3 A. I can't imagine why a POSA would want to 4 undertake an exercise of trying to elaborate all 5 possible possibilities, but I would agree with you 6 that that would take a significant amount of time. 7 Q. Okay. 8 A. But, again, a completely doable thing given 9 the tools available in the art. 10 Q. A completely doable thing to do what? 11 Elaborate all of the possibles? 12 A. In my opinion, yes. 13 Q. And how long would that take? 14 A. Oh, as I have -- as we've talked about, I 15 haven't tried to estimate that. I haven't thought in 16 detail about how one would go about that. 17 Q. But you know it's possible, even though you 18 haven't thought about how someone could do that, 19 right? 20 MS. DANEK: Objection, form. 21 A. There is absolutely nothing about that that 22 strikes me as being impossible. 23 Q. Then elaborate on how they would do it 24 since you've already -- I feel like you are saying 25 that you know how they would do it, but when I ask,

1 you say, "I haven't thought about that." 2 A. I have expressly said that I haven't 3 thought in detail about how to execute on that. 4 Q. All right. So you're really just 5 speculating as to whether someone could actually 6 accomplish that? 7 MS. DANEK: Objection, form. 8 A. Yeah, as I've said, I am not sure why 9 anyone would want to do that in the first place. If 10 one was motivated, you know, and had the financial 11 wherewithal and thought that it would make -- the 12 financial reward would be there, I would expect that 13 one would work to make a plan and, you know, to devise 14 steps to elaborate all possible likely to work 15 Z'-structures. But, again, I haven't sat down to try 16 to think about how to approach that myself. And, 17 again, as I said, I don't know why anyone would want 18 to do that. 19 MR. DESAI: Okay. Why don't we take a 20 break? 21 VIDEOGRAPHER: Time is 2:16. We are 22 off the record. 23 (Off the record at 2:16 p.m.) 24 (On the record at 2:37 p.m.) 25 VIDEOGRAPHER: One moment.	Page 130 1 scores along with POSAs -- that the POSA would see, 2 you know, upon having done the docking, yes, would 3 lead the POSA to recognize that those were unlikely to 4 productively bind to BTK and inhibit it or potentially 5 productively bind. 6 Q. So to be clear, you said, "Therefore, a 7 POSA would have recognized that Compounds 8 30 and 122 were unlikely to productively 9 bind to BTK to irreversibly inhibit it." 10 Do you see that? 11 A. Yes. 12 Q. Are you saying it's therefore because of 13 the docking score or because of the docking score plus 14 the pose that you could see that's not actually shown 15 here in your declaration? 16 A. Let me just make sure I'm not -- yes, I 17 think I discussed above the POSAs and considerations 18 around that, and certainly a POSA wouldn't have been 19 solely looking at numerical scores, they would have 20 been examining the docking poses as well. 21 Q. Okay. What does a docking score mean then? 22 A. A docking score is a -- calculated, you 23 know, based on a formula to give a measure of 24 the quote, unquote "quality" of the docking -- a 25 substitute for an energetic favorability of a Page 132
1 Time is 2:37. We are back on the 2 record. 3 BY MR. DESAI: 4 Q. Could we go to Page 136 of your 5 declaration? 6 A. (Witness complied.) 7 I am there. 8 Q. Okay. We are looking at a paragraph here 9 that discusses the '446 patent and the docking scores 10 you've computed or had received for compounds 20, 30, 11 and 122, right? 12 A. Correct. 13 Q. Okay. And you reported a docking score of 14 minus 6.3 for Compound 122? 15 A. That's correct. 16 Q. And minus 5.5 for Compound 30? 17 It's on the next page. 18 A. Yes, that's correct. 19 Q. Based on these docking scores you state 20 that, "a POSA would have recognized that 21 Compounds 30 and 122 are unlikely to 22 productively bind to BTK to irreversibly 23 inhibit it", right? 24 A. I don't think I said based on those docking 25 scores, specifically, but certainly it was docking Page 131	1 particular pose. 2 Q. Okay. And you report a docking score of 3 minus 8.2 for Compound 20, right? 4 A. Yes. 5 Q. Okay. Well, what does the -- does the 6 docking score and the pose for doc -- the Compound 20 7 indicate that Compound 20 is likely to productively 8 bind to BTK to irreversibly inhibit it? 9 A. I wouldn't look at the docking score in 10 isolation, as I said, we would look at the pose as 11 well. But I think in looking at the pose and the 12 docking score and comparing that docking score with 13 structurally similar molecules that, you know, bind 14 and inhibit, would be confident that it would bind and 15 inhibit. 16 Q. Okay. So that brings up a point which is, 17 is it important to have a reference for these -- for 18 your analysis in terms of modeling and determining 19 whether what you see and the score you get will 20 predict that it would bind or not bind? 21 MS. DANEK: Objection to form. 22 Q. You brought up a reference right now, 23 right? 24 A. I think a reference is helpful. I haven't 25 opined on whether a reference is essential. Page 133

Page 134 1 Q. Okay. You did use a point of reference in 2 your analysis here, though, correct? 3 A. Yes. That's fair. 4 Q. And your point of reference was ibrutinib, 5 right? 6 A. Yes. 7 Q. And your reference was the docking score of 8 minus 8.8, right? 9 A. In this particular exercise. 10 Q. Okay. Well, with that reference of minus 11 8.8 and then you have these other docking scores that 12 you've calculated for Compound 20, 30, and 122, what 13 docking score would you need to indicate that the 14 compounds are likely to productively bind to BTK to 15 irreversibly inhibit it? 16 A. As I said, I wouldn't rely solely on a 17 docking score so I -- yeah. 18 Q. I believe you offered the opinion that 19 modeling would allow a POSA to predict, correct? 20 A. That's correct. 21 Q. Okay. So what are you using to predict 22 whether this compound that you've modeled is likely to 23 protectively bind or unlikely to protectively bind to 24 BTK to universally inhibit it? 25 A. As I've explained in the declaration,	Page 136 1 A. I didn't draw a line. 2 Q. Well, then how would a POSA draw a line if 3 you couldn't? 4 A. I think as I did here, a POSA would see, as 5 was obvious in this case, you know, what worked and 6 what didn't. So, you know, did the docking poses look 7 reasonable, were the hydrogen bonds made, were things 8 where they were supposed to be? 9 The score per se, as I've said, is just one 10 thing that a POSA would look at. Here there was a 11 clear divide between scores for things that looked 12 reasonable and things that didn't. So we have things 13 in the 8 range for things that look reasonable, 14 including for ibrutinib, which we know worked and 15 things in the 6 range and below for things that 16 didn't. So no ambiguity in this particular exercise 17 as to what looked like a promising structure to pursue 18 and what didn't look like a promising structure to 19 pursue. 20 Q. I think I understand what you are saying. 21 There was no real close call on this one? 22 A. Fair enough, yes. 23 Q. And, again, the reference score is 24 particularly important for that, right? 25 The point of reference is very important in
Page 135 1 the POSA would be looking at the binding pose, does it 2 put the phenoxyphenyl in the back pocket? 3 Does it position the Z' scaffold to make 4 the desired hydrogen bonds to the hinge? 5 Does it juxtapose the linker-warhead with 6 cysteine 481, and does it do so without introducing 7 steric clashes? 8 So if it docks, if the software will put it 9 there, then probably it's not creating intolerable 10 steric clashes; that said, not everything that can go 11 there and fit will have an ideal fit, and so might 12 have a poor docking score. And so that docking score 13 is an additional indicator in addition to the docking 14 pose of how favorable or unfavorable that -- that pose 15 is, and so a POSA would use that in addition to the 16 docking pose to predict whether a specific compound 17 was expected to be a BTK inhibitor. 18 Q. Okay. Now, for this example, you have got 19 several numbers here with a reference of minus 8.8, 20 right? 21 A. That's correct. 22 Q. Okay. So for this particular example, did 23 you draw a line or is there any line you can draw with 24 respect to the docking score that gives you an 25 indicator of favorable or unfavorable?	Page 137 1 terms of determining whether you have close calls or 2 not, right? 3 A. I think we can't really ascribe the 4 significance to the reference score that you seem to 5 want to ascribe to it. It's important. It tells you 6 where you are, it tells you, you know, one thing that 7 works has that value in that particular docking run or 8 exercise but -- and in a relative way for these 9 related ligands, I do think that it's very informative 10 but it's, as I've tried to explain, not the be-all and 11 the end-all. 12 Q. Sure. 13 Is it important to get the reference score 14 correct? 15 A. Without presuming where you are going with 16 this, I think I -- I can first, you know, reiterate 17 that there is not one particular reference score or 18 some bright line. 19 Second, in a particular docking run, there 20 could be differences in score that depend on the 21 specifics of how the experiment was -- how the docking 22 exercise was done and in two separate docking runs, 23 would not necessarily expect to come up with the same 24 value. And so I would -- you know, I think it's 25 important to compare apples to apples, oranges to

1 oranges, and so that's what I've tried to do here by 2 docking ibrutinib in the same run with these other 3 compounds. 4 Q. Okay. And for compounds 20, 30, and 122 in 5 the '466 patent, you also had knowledge of the 6 experimental results for those based on what's in the 7 patent, right? 8 In other words, you had the IC50 values 9 that already told you whether they were potent or not 10 potent inhibitors? 11 A. That's correct. 12 Q. In particular, Compound 20 you reported as 13 having a 10 to 100 nanomolar IC50 value, right? 14 MS. DANEK: Objection to form. 15 Q. Or that's what you put in your declaration. 16 Page 135. 17 A. Page 135. 18 Q. If I'm wrong about that, you let me know. 19 A. Sorry. For which compound? 20 Q. Compound 20. It says the '446 patent 21 reports that it has the IC50 range of 10 to 100 22 nanomolar? 23 A. Yes, patent reports ranges and for Compound 24 20, it was in the 10 to 100 nanomolar range. 25 Q. And based on that, you said that Compound	Page 138 1 dock and are expected to work and those that don't and 2 that can be reflected also, experimentally. 3 And in general, you know, things in the 10 4 micromolar range aren't -- aren't, to put it lightly, 5 aren't highly-valued in the art, in this particular 6 art. 7 Q. So if a compound has an IC50 value greater 8 than a thousand nanomolars, what would that indicate 9 to you? 10 A. Well, that it wasn't a very potent 11 inhibitor. 12 Q. And that's, for example, Compound 7 Zhang 13 2020 identifies as having an IC50 value greater than 14 1,000 nanomolars, right? 15 A. That's correct. 16 Q. Now, based on your docking results for 17 Compounds 30 and 122, you say, "a POSA 18 would have deprioritized these compounds 19 for synthesis and further consideration, 20 appropriately, as it turned out." 21 Do you see that? 22 Page 137. 23 A. Yes. 24 Q. Okay. But the inventors of the '446 patent 25 did actually synthesize and run assays on Compounds 38 Page 140
1 20 was a potent inhibitor of BTK, right? 2 A. Yes, I'd consider in the 10s of nanomolar 3 to be potent. 4 Q. Okay. What IC50 value would indicate to 5 you that a compound is not productively binding to BTK 6 to irreversibly inhibit it? 7 A. I think in the art, kinase inhibitor design 8 a particular, you know, irreversible kinase inhibitor 9 design, you know, the person of skill is typically, 10 you know, looking for something in the nanomolar 11 range, not the 10,000 nanomolar or 10 micromolar 12 range. 13 So I don't want to say that something that, 14 you know, that had a detectable inhibition in 10 15 micromolar might not possibly be binding and 16 inhibiting, but at that kind of value, you know, one 17 couldn't even be certain that it was inhibiting in the 18 assay because it was binding in -- in the 19 structurally-expected way, especially for an 20 irreversible inhibitor, you would expect a more potent 21 binding than that anyway. 22 So perhaps I've used productively -- 23 perhaps I haven't been specific enough there, but I 24 think, you know, what I'm trying to explain here is 25 that there's a clear difference between things that Page 139	Page 141 1 and 122, correct? 2 A. Yes. 3 Q. And that's how they've obtained, for 4 example, IC50 values for those compounds, right? 5 A. That's correct. 6 Q. So they didn't, you know, deprioritize 7 those compounds for synthesis, right? 8 A. I can't speak to whether they did docking 9 or not. 10 Q. But in your world, at least what you've 11 explained, docking is something that can take a matter 12 of minutes and would allow someone to deprioritize 13 spending time on synthesis for further consideration 14 of the compounds, right? 15 A. Well, I'm talking about working from the 16 '803 patent to make BTK inhibitors, and I think that's 17 something that one would obviously employ. I can't 18 speak to whether -- you could remind me of when the 19 '466 patent published, whether those inventors would 20 have been able to avail themselves of this knowledge 21 or not. But I haven't been through the specification 22 of the '446 patent in the kind of detail that it would 23 take to know whether they did or didn't apply docking. 24 Q. Right, but this is the patent that was 25 filed from a provisional application in 2015; do you

1 see that? 2 And it was issued 2019. 3 A. Well, I see it issued in 2019. 4 Q. In the left column, you will see the 5 provisional and the related U.S. application data 6 towards the bottom left column. 7 A. Sorry. Left column, yes. I see that. 8 October 14 of 2015. 9 MR. DESAI: This is Exhibit 2024. 10 (Exhibit 2024 marked for identification, 11 Excerpt of Patent '446. Bruton's Tyrosine 12 Kinase Inhibitors.) 13 Q. So you would agree that in this timeframe, 14 the inventors of this '446 patent certainly would have 15 had access to the modeling, the computer software that 16 you have discussed today? 17 A. Yes. 18 Q. Okay. But even though they would have had 19 access to that, just like all persons of ordinary 20 skill in the art would, they didn't deprioritize 21 Compounds 30 and 122 for synthesis. They actually did 22 synthesize them, and they did actually obtain 23 experimental results, correct? 24 A. I have no idea what their priorities were, 25 but certainly they did synthesize them and measure	Page 142 1 say you would not -- you would not expect to see the 2 modeling be inconsistent with experimental test data 3 or vice versa? 4 A. So the modeling that I did, the docking 5 that I did with BTK and BTK inhibitors, I would say, 6 you know, it was completely consistent with the 7 available experimental data. And this is a case where 8 I think -- I don't know if the expression, "Shooting 9 fish in a barrel," means anything to you. 10 Q. Yeah. 11 A. But, you know, a very well-defined, 12 trackable, easy case, and that's because you have a 13 high resolution crystal structure with a similar 14 ligand bound that's providing the relevant 15 confirmation for binding of this class of compounds, 16 you know, as the receptor in the docking exercise. 17 And that provides, you know, very powerful constraints 18 on the docking and on the interpretation of the 19 docking results. So make it a very straightforward 20 exercise. 21 Q. Okay. Now, for Zhang 2020 you say here 22 that you report a docking score that was markedly 23 better for Compound 8 as compared with Compound 7, 24 right? 25 A. Yes. Page 144
1 IC50 values. I also can't speak to their motivations 2 in doing that. It's possible that they didn't expect 3 them to work well and made them nevertheless. 4 Q. Okay. 5 A. Certainly in my collaborations with 6 industry chemists, there would be things that we tell 7 them, "That's not going to bind. Don't even bother 8 making it," and they nevertheless, make it. 9 Q. Okay. 10 A. Chemists pride themselves on the numbers of 11 molecules they can make. You know, they often make 12 things -- in my experience, I have seen them make 13 things because they can make them and even if having 14 been told that there is a low probability of it 15 being -- of it working or of it being an improvement 16 over what's already been made. 17 Q. Have you ever seen modeling and 18 experimental results contradict each other? 19 A. I've seen that in my own experience. We 20 make compounds we expect to bind in a particular way 21 and later find that maybe even though they inhibit, 22 bind in a different way, but that's in a specific 23 case. It's not what we're talking about here with 24 BTK. 25 Q. Okay. So in the context of BTK, you would	Page 143 1 Q. Okay. And you say, "Accordingly, a POSA 2 would have prioritized Compound 8 over 3 Compound 7 for synthesis and further 4 testing", right? 5 A. Correct. 6 Q. But the author, Zhang, actually synthesized 7 and empirically-tested both Compound 7 and 8, right? 8 A. That's correct. 9 Q. So that's another example that sort of 10 contradicts your proposition that people wouldn't 11 spend time synthesizing and empirically-testing these 12 because they could just do the modeling. 13 MS. DANEK: Objection, form. 14 A. I don't see a contradiction, you know, the 15 tools being available and -- and a particular group 16 choosing to employ them or not. And, again, without 17 revisiting Zhang, I don't know to what extent they did 18 or didn't use computational docking but certainly 19 could have. 20 And I don't know, again, you know, what 21 their motivation for making that compound would have 22 been. You know, in looking at it, and without even 23 doing any docking, one would recognize that it's, you 24 know, missing a hydrogen bond partner that you would 25 expect would be important for binding of this class of Page 145

1 compounds. 2 Q. All right. I'm going to hand you what's 3 marked as -- 4 MR. DESAI: We will call this Eck 3. 5 Q. Okay. Do you see at the top of the -- this 6 is a screenshot. This is from Exhibit 2113. Do you 7 see that? 8 A. Yes. 9 Q. Okay. This is -- I will represent to you, 10 this is a screenshot from that file that you've 11 provided to us, okay? 12 A. Okay. 13 Q. And you see on the panel on the left side, 14 that's Structure3? 15 Sorry. Wait a minute. 16 MS. DANEK: Which side are we on? 17 MR. DESAI: Hold on one second. I'm 18 sorry. Give me a second. 19 BY MR. DESAI: 20 Q. Okay. Do you see on the left side, I'm on 21 the side of this that is -- the color is green, okay? 22 One side is green and the other side has like a 23 pinkish color? 24 A. Okay. Yes. 25 Q. On the green side. All right.	Page 146	1 you called ibrutinib "Structure3"? 2 A. Yes, in this particular file, mainly. 3 Q. And do you agree that this matches the 4 docking pose for ibrutinib that you illustrated on 5 Page 81 of your declaration? 6 A. It looks like it. 7 Q. Do you want to just confirm that? Are you 8 good? 9 A. I'm comfortable with it. I've looked at 10 this enough. 11 Q. And the Glide score for this compound, 12 ibrutinib, is minus 11.049, right? 13 A. That's correct. 14 Q. Okay. That is not the Glide score for 15 ibrutinib that you've reported in your declaration as 16 the reference point, Footnote 14, that we were looking 17 at earlier, right? 18 A. That's correct. 19 As I was telling you before, that was a 20 separate docking run, completely separate exercise. 21 Q. Okay. So let's see if we can try and 22 figure out where you got that minus 8.8 from. I'm 23 going to hand you -- we will mark this as Eck 24 Exhibit 4. 25 (Exhibit 4 marked for identification, a	Page 148
1 A. I was thinking right and left, not 2 retroverso, but I'm there, yes. Green side. 3 Q. And -- 4 MS. PATEL: You have the wrong tab. 5 MR. DESAI: I have the wrong tab? Let 6 me take that back because I think I gave you the 7 wrong one. We'll mark another exhibit as 8 Exhibit 3. 9 (Exhibit 3 marked for identification, a 10 screenshot, Maestro - Scratch Project.) 11 MS. DANEK: This is side one, the side 12 with green. 13 MR. DESAI: Yes. 14 BY MR. DESAI: 15 Q. So we've got Exhibit 2113 at the top, in 16 the menu bar, at the top, right? 17 A. That's correct. 18 Q. Okay. And then on the left-hand side of 19 the panel, you can see that Row 9 is highlighted and 20 it's called "Structure3"? 21 A. That's correct. 22 Q. And you would agree that the compound being 23 modeled here is ibrutinib, right? 24 A. That's right. 25 Q. In your files, I think as we understand it,	Page 147	1 screenshot, Maestro - Scratch Project.) 2 Q. Before you go to 4, just stick with 3 for a 3 second. One last question, you can see in the left 4 panel, there are, I think, three other rows that are 5 labeled, "Structure3", right? 6 A. That's correct. 7 Q. And none of those have a Glide score of 8 minus 8.8, right? 9 A. That's correct. 10 Q. Okay. All right. So now we can go to Eck 11 Exhibit 4. 12 All right. And this one, you've got a 13 project, and it's got at the top, again, it's 14 "Exhibit 2114." 15 Do you see that? 16 A. Yes. 17 Q. Okay. We have in the panel on the left, we 18 have, "Structure3." Row 4 highlighted. 19 Do you see that? 20 A. Yes. 21 Q. Okay. And this is the only "Structure3" 22 that we are able to find that would correlate with a 23 minus 8.8? 24 A. That's correct. This is the same docking 25 run that, as I'm sure you appreciate below, also	Page 149

1 docked the examples 20, 30, 122, and Compounds 7 and 8 2 from Zhang, et al. 3 Q. Is that ibrutinib that we see in Exhibit 4? 4 A. Unless I've mis-selected a Cairo center, 5 it's ibrutinib, but I think I'm -- I think it's 6 ibrutinib. 7 Q. You can see the phenoxyphenyl group and the 8 hinge scaffold match ibrutinib, right, but the 9 linker-warhead does not? 10 A. In this particular run, it looks like I 11 might have neglected to introduce the double bond and 12 the acrylamide. 13 Q. This is not ibrutinib, correct? 14 A. It's not ibrutinib. It's a reversible 15 analog of ibrutinib. 16 Q. Okay. Okay. All right. Let's just keep 17 going. I just have a couple more things that I want 18 to -- this was supposed to be -- yeah. I will just 19 give this one. 20 All right. Can I hand this back to you, 21 another -- because we're going to go back to the one 22 that I originally gave to you. We're going to make 23 this one as Eck Exhibit 5 now. That will be 5. 24 (Exhibit 5 marked for identification, 25 screenshot, Maestro - Scratch Project.)	Page 150 1 A. I believe that's correct, yes. 2 Q. And -- but if we go back to the other side, 3 Row 13, Structure8, that does not show the same 4 docking pose, right? 5 A. That's correct. 6 Q. Okay. Why do you have two different 7 docking poses for zanubrutinib? 8 A. So this highlights why I asked for the top 9 five docking poses. An important part of the docking 10 exercise is understanding where a potential 11 variability can come in. And here the results, I 12 think, were very much in line with what I would have 13 expected in that the phenoxyphenyl and central 14 scaffold were very reproducibly positioned in this 15 way, and then there was variability in the orientation 16 of the linker-warhead. So those are rotatable bonds. 17 The compound itself is not rigid. They are not 18 specifically constrained by the protein structure. 19 There's not one particular confirmation 20 that has a much more favorable position than the 21 other. And so understanding that variability and, as 22 I've discussed at some length in my report, also the 23 variability in the side chain rotamer, the cysteine 24 that that's going to react with, that, you know, this 25 docking exercise basically shows that A can get to B, Page 152
1 Q. Okay. I need to see which page you are 2 looking at because there are two sides to it. 3 Okay. Got you. 4 So focusing on Eck 5, this is the project 5 files that's labeled at the top Exhibit 1 -- 2113, 6 right? 7 A. That's correct. 8 Q. Okay. And then now the row that's 9 highlighted is structure 8 with the Glide value of 10 minus 9.575, right? 11 A. Yes. 12 Q. And this is zanubrutinib; is that right? 13 A. Yes. 14 Q. Then if we flip over, we have a different 15 row, also labeled "Structure8" with a docking score of 16 minus 9.062, right? 17 A. That's correct. 18 Q. And this is also zanubrutinib, right? 19 A. That's correct. 20 Q. Okay. And this dock structure corresponds 21 to the zanubrutinib dock structure shown on Page 82 of 22 your declaration, right? 23 A. That's correct. 24 Q. When I say "this", I'm referring to the 25 Row 16, Structure8? Page 151	1 that you can get the electrophile to the nucleophilic 2 cysteine. 3 Q. Okay. Let's go to Tab 24. We will mark 4 this as Exhibit 6. 5 (Exhibit 6 marked for identification, 6 screenshot, Maestro - Eck_Ex2114.) 7 Q. All right. Again, we are looking at the 8 top here, the file is Exhibit 2114, right? 9 A. Yes, that's correct. 10 Q. And the row we have highlighted is Compound 11 7, Row 50? 12 A. That's correct. 13 Q. Okay. And this has a Glide score of minus 14 6.48. I think that's 3. 15 A. Yeah, close enough. 16 Q. I agree. And this, I think, corresponds to 17 Compound 7 from Zhang 2020 and a docking score of 18 minus 6.5 that you reported in your declaration? 19 A. That's correct. 20 Q. Based on the docking score and the pose 21 here, you, I think, stated that "a POSA 22 would have recognized" that this is 23 "unlikely to productively bind to BTK to 24 irreversibly inhibit it," correct? 25 A. Let me look back to my declaration and see Page 153

1 exactly what I said. 2 MS. DANEK: Doctor, please tell me what 3 paragraph you are looking at. 4 A. Paragraph 185. I said docking of these 5 compounds, referring to Compounds 7 and 8 6 into the Marcotte structure, indicates 7 that both can be accommodated in the 8 active site with the phenoxyphenyl 9 positioned in the back pocket and the 10 linker-warhead approaching Cys481. 11 However, the docking score was markedly 12 better for 8 as compared with 7, minus 13 9.3 as compared with minus 6.5. A POSA 14 would have prioritized 8 over 7 for 15 synthesis and further testing. 16 I go on to talk about the measured 17 biochemical activities in Zhang, et al. 18 Q. So for Compound 20 in the '446 patent, you 19 get minus 6.3. For Compound 7, the Zhang reference, 20 you get minus 6.5; is that right? 21 It's in your declaration. 22 A. Yeah. I'm just looking here. Sorry. 23 Compound -- which two compounds are we comparing? 24 Q. Compound 122 minus 6.3, right? 25 A. Yes.	Page 154 1 not positioned to make even one hydrogen 2 bond to the hinge, resulting in a docking 3 score that was markedly worse for 122 as 4 compared with 20." 5 Q. Okay. That's fair. 6 A. So the lack of the hydrogen bond to the 7 hinge as well as the docking score, you know, or the 8 dings against that compound. 9 Q. So then for going to X6, for Compound 7, 10 can you explain why you get this docking score in the 11 same ballpark for Compound 7, minus 6.5? 12 What are the dings that you would say, 13 looking at this? 14 A. I'm not understanding your question. 15 Q. Okay. Let's try it a different way. If we 16 look at the docking pose for Compound 7, do you agree 17 that it forms two hydrogen bonds, the kind you see in 18 the region of BTK? 19 A. Yes. 20 Q. And is the linker-warhead at Compound 7 21 oriented properly to form a covalent bond? 22 A. As shown in this pose, it's not, but as 23 we've established, we understand that there is 24 flexibility in that region of the kinase, so I would 25 expect that it could potentially form the covalent
Page 155 1 Q. Now, we have Compound 7, and you get minus 2 6.5? 3 A. Yes. 4 Q. Does that tell you that those are in the 5 same realm of being unlikely to productively bind to 6 BTK? 7 A. You know, as I've explained at some length, 8 I wouldn't take the Glide score in isolation but 9 that's -- that's one indicator, but we'd look at the 10 poses as well as the Glide scores. 11 Q. Okay. And so is there something about the 12 pose for Compound 20 that tells you that it's unlikely 13 to productively -- sorry, I keep saying, "Compound 14 20." Strike that. 15 Is there something for the pose for 16 Compound 122 that tells you that it's unlikely to 17 productively bind BTK? 18 A. Let me see what I have written. I can't 19 visualize in my mind the docking poses for 122 or if 20 you have an image, that's great. 21 So I've said, "For Compound 122, one pose 22 was obtained in which the phenoxyphenyl 23 group was properly positioned and the 24 linker-warhead was oriented toward 25 Cys481, but the heterocyclic scaffold was	Page 157 1 bond, yes. 2 Q. "Could potentially," what does that mean? 3 Does that mean you would have to experiment 4 to figure out if it actually does? 5 A. I think, you know, the docking suggests 6 that it's positioned -- it's a combination of the 7 docking, the examination of the range of top docking 8 poses that were examined, knowledge of the 9 rotatability of that bond indicates that it could form 10 the covalent bond with Cys481. 11 Q. Okay. And is the phenoxy -- is the 12 phenoxyphenyl moiety of Compound 7 orientated to bind 13 with BTK's back pocket? 14 A. It is, yes. 15 Q. So this Compound 7, I mean, based on what 16 we see in the docking, has a scaffold that meets the 17 requirements of the orb in Formula E that you've 18 specified, correct? 19 MS. DANEK: Objection, form. 20 A. Correct. 21 Q. Just to be clear -- 22 A. Oh, sorry. Am I looking at the right thing 23 here? 24 Q. You don't have to take your cues from the 25 lawyer, but I will ask the question more clearly.

Page 158 1 A. Yeah. I'm looking at -- 2 Q. Compound 7 meets the requirements of the 3 orb in Formula E that you specified, which were that 4 it makes the appropriate H-bonds with the hinge region 5 while appropriately orienting the fixed constituents, 6 right? 7 A. That's correct. 8 Q. Okay. But it nonetheless produces a 9 docking score that you would sort of generally looking 10 at with respect to Compound 122, Compound 20, Compound 11 7, and the reference point of ibrutinib, that is not 12 favorable, correct? 13 A. I would say it's qualitatively worse, and 14 as I've explained in the declaration, if this were my 15 project and I were working on this, I would 16 deprioritize this compound over Compound 8 that had a 17 much better docking score. 18 Q. But doesn't that mean there are things, 19 other than forming the H-bonds and properly orienting 20 the linker-warhead and the phenoxyphenyl that impact 21 whether or how a structure will irreversibly inhibit 22 BTK? 23 A. I think that's -- that's certainly true. 24 You know, the other components of the 25 molecule will affect its electrostatics and how it's	Page 160 1 that. Never say, "never," but it's very unlikely. 2 Q. Okay. So, again, with respect to what you 3 were describing in Formula E as an element that a POSA 4 would understand for use in this claimed invention, I 5 think you -- I mean, it seemed to me as though that 6 you need to make the appropriate H-bond with the hinge 7 region while appropriately orientating the fixed 8 substituents, and that's going to give you the 9 functionality that you need, but that's not true, 10 right? 11 A. I think that's true. I think it's obvious 12 that there are also considerations, as I've just 13 described, having to do with the electrostatics, you 14 know, complementarity and Van der Waals interactions, 15 all of the fine details that are important for 16 inhibitor binding. 17 Q. Okay. 18 A. And that's why, you know, you use docking 19 to get a read on that. Docking is providing an 20 assessment of the chemical physics involved in 21 binding. 22 MR. DESAI: Why don't we take a 23 five-minute break now. 24 VIDEOGRAPHER: 2:26. We are off. 25 (Off the record at 2:26 p.m.)
Page 159 1 sterically fitting into the pocket and -- yeah, all of 2 these things can make a difference, and that's why we 3 use docking to assess them. 4 Q. So then when you describe the orb in 5 Formula E, those requirements of making the proper 6 H-bonds with the hinge region while appropriately 7 orientating the fixed constituents, right, those 8 are -- just satisfying those requirements does not 9 mean that you will have a compound that will 10 irreversibly inhibit BTK, right? 11 A. Well, to be clear, I think it's likely that 12 this compound irreversibly inhibits BTK. It's not a 13 particularly potent BTK inhibitor. In my mind, a POSA 14 wouldn't consider it a preferred BTK inhibitor but, 15 you know, as was seen in experiments, it's roughly a 1 16 micromolar inhibitor. 17 Q. It's certainly not one that someone would 18 be considering for a method of treating an individual, 19 right? 20 That's the context we are looking at in 21 this claim when we are talking about irreversibly 22 inhibiting BTK, right? 23 A. I think it's unlikely that one would want 24 to advance a micromolar irreversible BTK inhibitor. I 25 can't imagine that -- that anyone would want to do	Page 161 1 (On the record at 3:35 p.m.) 2 VIDEOGRAPHER: One moment, please. 3 Time is 3:35. We are back on the 4 record. 5 BY MR. DESAI: 6 Q. When it comes to evaluating the docking 7 poses, at least what I understand you have been 8 saying, is that you can't rely just on the docking 9 score, right? 10 A. Neither I nor a POSA would look solely at 11 the docking score, that's correct. 12 Q. In order to evaluate the docking that you 13 get from the software, you need to look at the score, 14 you need to look at the pose. It's something that has 15 to be individually evaluated by a human being, right? 16 A. I don't think that is necessarily true. 17 Q. Okay. Then how would this be automated? 18 A. It would be trivial to set up a script to 19 ask, you know, "Are the hydrogen bonds made? Is the 20 phenoxyphenyl properly positioned?" Et cetera. 21 Q. So you are saying you would write a script 22 to have a computer evaluate things that the person 23 would be looking for? 24 A. I wouldn't, but I would rely on a 25 computational chemist, a member of the team to do that

Page 162 1 if there was a desire to evaluate large numbers of 2 compounds. 3 Q. Right. 4 And how would you -- if you or someone on 5 your team has prepared this script that gives you 6 information, these other aspects, right, aside from 7 the Glide score, right? 8 A. You are asking me to affirm a construct 9 that's assuming I had these tools; is that what you're 10 saying? 11 Q. Okay. When we were talking earlier about 12 looking at a particular docking pose, it seemed to me 13 that you were saying that in order to figure out what 14 the docking pose informs a POSA, what it predicts, the 15 person has to evaluate it in totality, what they see, 16 including the score, right? 17 A. That's fair. Yes. 18 Q. So regardless of whether you have a script 19 that would then automate, for example, whether the 20 hydrogen bonds are -- how far away something is from 21 something, a person still has to look at it and 22 evaluate those results in order to make sense of what 23 they see, right? 24 MS. DANEK: Objection to form. 25 A. I think at some level, at some stage of the	Page 164 1 deviation of this pose to the ibrutinib binding mode." 2 And that could be, you know, one simple 3 puristic, straightforward, you know, is this in the 4 ballpark of something we want? Examining that 5 together with Glide scores. 6 If one were interested in getting beyond 7 just a few structures, one could, you know, could 8 apply statistical approaches to things that a human 9 had looked at to decide what is a range that is making 10 sense, and, you know, use those values to establish 11 guidelines. 12 Anyway, again, not -- you know, as we've 13 discussed before, a POSA looking at the '803 to make 14 an irreversible BTK inhibitor is a very different 15 thing than a POSA trying to make all possible or 16 design or "draw out" is a better word than "design", 17 draw out all possible structures of the invention, 18 that is something very different than making and using 19 the invention. So I want to -- that's an important 20 distinction to be made. 21 Q. I think what are you saying is that there 22 is a distinction between making and using a compound 23 that falls within the scope of the invention versus 24 drawing out and envisioning all of the possible 25 compounds that fall within the discovery mentioned; is
Page 163 1 process, would want a human to lay eyes on things, but 2 with respect to the ability to automate it and to 3 select what a human needed to look at, the 4 computational tools are very powerful in that respect. 5 Q. Right. 6 I guess what I'm trying to understand is, 7 at some point, you're saying that the modeling is used 8 to predict whether this is a worthwhile inhibitor to 9 pursue or not, a worthwhile inhibitor to pursue, 10 right? 11 A. Yes. 12 Q. Okay. Can a computer make that call or 13 does a human have to make that call? 14 A. I think if one were so inclined, one could 15 program a computer to make that call. 16 Q. And what would they make the computer make 17 that call based upon, the Glide score, some numerical 18 value? 19 A. As I have described, not based solely on a 20 Glide score. Again, this -- I don't want to, you 21 know, to improvise here or go too far off the cuff 22 because this isn't something that I have thought 23 deeply about. But just as a for example, something 24 that comes quickly to mind, one could simply ask, you 25 know, "What's the RMSD? The root being squared,	Page 165 1 that correct? 2 MS. DANEK: Objection. Hold on. 3 Objection to form. 4 A. It's my opinion that a POSA can envision 5 all possible molecules that fall within the scope of 6 the claims. I think that that can be -- the '803 7 specification, what's known in the art, makes it 8 possible to -- there is no structure that is not 9 possible to envision or to recognize, but that's a 10 very different thing than setting out an exercise of 11 specifically visualizing and recognizing every 12 possible structure figuratively. 13 Q. When you say, "a POSA could visualize every 14 molecule that falls within the scope of the claim," 15 how many molecules are we talking about here? 16 A. Again, as we have discussed at some length, 17 I haven't tried to calculate that. 18 Q. Then how do you know a POSA can envision 19 all of them if you can't -- I just don't follow that 20 logic. 21 A. So, again, I am trying to speak very 22 clearly here. 23 Q. Okay. 24 A. There is no molecule in the claim that 25 can't be visualized or recognized in my opinion.

Page 166 1 Q. Got you. 2 A. Setting about visualizing or recognizing 3 every one of the many is a very different thing. 4 Q. Got it. All right. Last few questions 5 here. Go to Paragraph 45. Page 23, yes. 6 A. I'm there. 7 Q. You have the figure of the structure of 8 adenine and the hydrogen bond between the adenine and 9 the hinge region, correct? 10 A. Yes, Figure 1 from the 2048. 11 Q. All right. When ATP binds to the kinase 12 hinge region, the H-bond donor is the adenine 13 substituent on the 6-membered ring and the H-bond 14 acceptor is the nitrogen also on the 6-membered ring, 15 correct? 16 A. It's the nitrogen that's part of the 17 6-membered ring, and the amine that's the exocyclic 18 amine. 19 Q. The specific residue is on the kinase hinge 20 region that form H-bonds are -- I think it's MET477 21 and GLU475; is that right? 22 A. In BTK? 23 Q. Yes. 24 A. I believe that's correct, but I want to 25 look to make sure.	Page 168 1 EXAMINATION 2 BY MS. DANEK: 3 Q. Dr. Eck, do you have Exhibit 4 in front of 4 you? 5 A. I do. 6 Q. And do you recall being asked questions 7 about the compound that's depicted in the image here 8 on Exhibit 4? 9 A. Yes. 10 Q. And I believe you've testified that the 11 compound in the image is not ibrutinib. It's slightly 12 different from ibrutinib? 13 A. That's correct. I'm a crystallographer. I 14 usually like to ignore hydrogens and turn them off as 15 distracting and so didn't notice that I hadn't 16 introduced the double bond in the acrylamide 17 substituent. So it's a propanamide rather than an 18 acrylamide. 19 Q. And how does the fact that the compound 20 depicted here in Exhibit 4 differs from ibrutinib at 21 this one portion, the warhead, affect your conclusions 22 about the comparison of the docking of the other 23 compounds that you included in this modeling? 24 A. It doesn't affect my conclusions at all, 25 and I think, actually, that it's unlikely that it's
Page 167 1 Q. Okay. Now, I think you've -- have some 2 discussion about adenine analogs on adenine mimics. 3 What makes a ligand an adenine analog or mimic, in 4 your opinion? 5 A. As far as I know, there is not, you know, a 6 specific definition in the art, but as I have applied 7 it here, being able to make the hydrogen bonds to the 8 hinge region that correspond to those made by adenine 9 and filling approximately the same space or region of 10 the ATP site that adenine fills. 11 MR. DESAI: I don't have any more 12 questions, Dr Eck. Thank you. 13 THE WITNESS: That was quick. 14 MS. DANEK: Let's take a five-minute 15 break, and I think I have just one. 16 You can stay here. 17 THE WITNESS: I'll stay, okay. 18 VIDEOGRAPHER: 3:45. We are off the 19 record. 20 (Off the record at 3:45 p.m.) 21 (On the record at 3:47 p.m.) 22 VIDEOGRAPHER: One moment. 23 Time is 3:47. We are back on the 24 record. 25 *****	Page 169 1 the difference in the compound structure that's giving 2 rise to the difference in the docking scores. 3 Q. And why is that? 4 A. Because I noticed the difference in the 5 docking scores and spent some time trying to 6 understand the genesis of the difference and noticed 7 that the runs of protein prep were different between 8 the two and so the -- sort of minimized structures of 9 BTK weren't precisely the same, and I suspect that 10 that's what was giving rise to the difference in the 11 docking scores. 12 And as I said, since I'm usually turning 13 those pesky hydrogens off, I hadn't realized in 14 looking at this, that I hadn't introduced the double 15 bond in this particular docking exercise, this 16 particular run. 17 MS. DANEK: I don't have any more 18 questions. 19 MR. DESAI: Okay. 20 MS. DANEK: All set. 21 VIDEOGRAPHER: 3:50. 22 We are off the record. 23 (Deposition concluded at 3:50 p.m.) 24 25

1 C E R T I F I C A T E 2 COMMONWEALTH OF MASSACHUSETTS 3 SUFFOLK, SS. 4 I, TERI C. GIBSON, a CSR, RPR, CRR, and a 5 Notary Public within and for the Commonwealth of 6 Massachusetts do hereby certify: 7 In the 8th day of October 2024, before me, the 8 undersigned Notary Public, personally appeared MICHAEL 9 J. ECK who proved to me through satisfactory 10 evidence of identification, which was a MASSACHUSETTS 11 DRIVER'S LICENSE; that the witness whose testimony is 12 hereinbefore set forth, was duly sworn by me, and that 13 such testimony is a true and accurate record of my 14 stenotype notes taken in the foregoing matter, with use 15 of mechanical stenography, computer-aided transcription, 16 to the best of my knowledge, skill and ability. 17 IN WITNESS WHEREOF, I have hereunto set my 18 hand this 10th day of October 2024. 19 20 TERI C. GIBSON, CSR, RPR, CRR 21 Notary Public - My Commission Expires: 2/7/2025 22 23 24 25	Page 170

Notice Date: Friday, 11. October 2024

Attention: Michael J. Eck, M.D., PH.D.

Re:BeiGene USA, Inc. and BeiGene, LTD. v. Pharmacyclics LLC
Deposition of Michael J. Eck, M.D., PH.D. (10/8/2024)

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: 10/11/2024

Deposition Date: 10/8/2024

Deponent: Michael J. Eck, M.D., PH.D.

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

Page:Line	Now Reads	Should Read
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

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:

WORD INDEX

< 0 >

02116 1:18**028** 118:10**033** 119:2

< 1 >

1 3:9 24:14, 18

26:25 29:21

41:10 50:2

75:2, 3, 23 87:7

88:1 118:16

151:5 159:15

166:10

1,000 140:14**1:01** 89:7**10** 11:16

104:17, 22

138:13, 21, 24

139:11, 14 140:3

10,000 139:11**10,358,446** 4:13**10:09** 36:13, 14**10:21** 36:15, 17**100** 138:13, 21,
24**1001** 4:3 8:4, 10**103** 67:24 98:13**104** 99:3, 10

100:16

105 105:9, 11**106** 4:18 108:6**1060** 4:7 85:17,
19 87:11**10s** 139:2**10th** 170:18**11,672,803** 1:4
3:13**11.049** 148:12**11:10** 65:7, 9**11:26** 65:10, 12**115** 110:23

111:17

116 115:5

116:22

118 4:23 112:15**12:10** 88:25**121** 96:10**122** 115:24, 25

131:11, 14, 21

132:8 134:12

138:4 140:17

141:1 142:21

150:1 154:24

155:16, 19, 21

156:3 158:10

125 97:16**13** 3:14 118:16

152:3

132 43:20, 21**133** 45:24 48:9,

14 51:7 53:13

135 138:16, 17**136** 131:4**137** 140:22**14** 142:8 148:16**142** 4:13**147** 3:17**148** 3:20**15** 26:24 79:10,
11, 12 124:1**150** 3:22**151** 41:17 50:10**152** 41:18**153** 3:24**16** 28:19 151:25**168** 3:5**181** 43:20, 22**184** 115:22**185** 115:23

154:4

1991 14:10

17:8, 10, 11, 15

1996 15:8**1B** 26:24 27:2

< 2 >

2 3:13 28:2, 8

41:20 43:1

73:24 74:1, 5

75:3, 9, 10, 13

77:10 100:21

2/7/2025 170:21**2:16** 130:21, 23**2:26** 160:24, 25**2:37** 130:24

131:1

20 115:24, 25

131:10 133:3, 6,

7 134:12 138:4,

12, 20, 24 139:1

150:1 154:18

155:12, 14

156:4 158:10

200 1:17 10:17**2001** 2:5**20036** 2:6**2009** 23:15**2010** 4:11 7:15,

21 127:22

2011 4:12 7:18

8:2 13:9 20:20

54:14, 17, 19, 24

55:4 56:3, 15

57:2 99:4, 20,

25 100:21

105:22 110:11

112:13, 18

113:6, 13, 22

114:5, 20

122:18, 24

127:22

20119 4:14**2012** 127:21**2015** 141:25

142:8

2016 24:18**2019** 142:2, 3**202)682-7000**

2:6

2020 116:2

140:13 144:21

153:17

2023 3:14 9:23

10:10

2024 1:18 4:13

6:6 10:15

121:3, 5 142:9,

10 170:7, 18

2024-0009 7:10**2024-2** 121:3**2028** 4:18

106:20, 24, 25

2037 4:23

118:7, 8

2046 5:3 97:14,
18**2048** 166:10**2055** 5:7 96:7,
11**209** 121:8, 19,
21, 22**2113** 146:6

147:15 151:5

2113.prjzip

3:19, 23

2114 149:14

153:8

2114.prjzip 3:21**225** 29:16, 19

23 4:14 166:5 24 3:9 153:3 25 104:17 2800 2:9 2F 28:22 29:15 2QD9 97:10 < 3 > 3 3:17 75:24 109:8, 9, 15, 16 146:4 147:8, 9 149:2 153:14 3:35 161:1, 3 3:45 167:18, 20 3:47 167:21, 23 3:50 169:21, 23 30 115:24, 25 122:5 123:23 131:10, 16, 21 132:8 134:12 138:4 140:17 142:21 150:1 312)876-7646 2:10 32 58:19 61:15 33 61:16 119:2, 17 330 2:9 38 140:25 3GEN 92:19 120:5, 15 < 4 > 4 3:20 43:1 79:12 107:10 148:24, 25 149:2, 11, 18 150:3 168:3, 8, 20 4.1 119:11	4.5 119:10 44 80:6 83:24 446 115:24 131:9 138:20 140:24 141:22 142:11, 14 154:18 45 166:5 466 138:5 141:19 481 29:20 46:8 47:12, 24 51:14 117:12 135:6 < 5 > 5 3:22 11:16 41:19 104:22 108:4, 6 109:4 111:1 150:23, 24 151:4 5.1 120:16 5.5 4:23 118:9, 25 120:21 131:16 5:6 89:19 104:3 105:4 50 153:11 53 89:22 90:12, 24 92:3 104:21 5-membered 42:9 50:7 52:3 56:12 5TR6 98:9 < 6 > 6 3:24 10:15 21:17, 18 37:12 38:5 136:15 153:4, 5 6.3 131:14	154:19, 24 6.48 153:14 6.5 153:18 154:13, 20 155:2 156:11 60 58:22 600 2:5 60611 2:10 62 65:16, 17, 21 69:8, 20 74:23, 24 75:25 76:17 77:24 80:4 83:24 84:19 105:2 620 26:18 63 50:11 61:8 65:21 69:8, 20 72:15 73:8 75:7 76:17 77:24 105:2 65 104:17 6-membered 42:9 50:13 52:4 56:12, 13 166:13, 14, 17 < 7 > 7 3:4 4:11, 12 25:11 27:3, 14, 21 31:18 78:4 116:1 140:12 144:23 145:3, 7 150:1 153:11, 17 154:5, 12, 14, 19 155:1 156:9, 11, 16, 20 157:12, 15 158:2, 11 70 67:24 85:25 74 3:13	78 86:2 < 8 > 8 1:18 4:3 6:6 27:22 28:5, 15 31:17 32:16 78:4 116:1 136:13 144:23 145:2, 7 150:1 151:9 154:5, 12, 14 158:16 8.2 133:3 8.8 134:8, 11 135:19 148:22 149:8, 23 80 85:25 86:2 803 8:9 41:9 55:6 56:11 57:7, 8 58:8, 23 69:2, 4, 9, 19 74:2 76:6 90:11 91:2 93:24 95:7 99:23 100:19 101:3, 7 105:15 128:4 141:16 164:13 165:6 81 148:5 82 55:25 151:21 820 89:14 90:24 91:5 95:19 85 4:7 89:11 8th 170:7 < 9 > 9 147:19 9.062 151:16 9.3 154:13 9.4 32:6, 13
---	--	---	---

9.575 151:10 9:16 1:18 6:7 96 5:7 97 5:3 < A > a.m 1:18 6:7 36:14, 15 65:9, 10 ability 46:5 47:9, 22 48:10, 16 51:11 53:15, 22 64:10 112:22, 24 114:20 117:11 163:2 170:16 able 18:4 29:24 31:12 45:16 49:10 56:25 70:10 71:6, 10 72:1, 8 80:22 91:25 103:12, 25 113:11, 21 122:7 123:10 141:20 149:22 167:7 abrutinive-like 30:10 absolutely 129:21 abstract 25:2 academic 17:8 40:24 academics 40:21 accept 63:9 acceptable 44:14, 18 45:13, 19 acceptor 51:24 52:10, 24 67:4 75:22 93:9	95:18 97:4 98:1 166:14 acceptors 51:1 60:23 61:1 91:23 Access 3:9 4:3 142:15, 19 accommodated 121:13 154:7 accomplish 62:14, 18, 25 122:14 130:6 accomplished 94:2 121:18 122:1 accomplishing 62:20 account 46:1 accuracy 114:19 accurate 9:16 170:13 accurately 78:9, 18 achieve 93:24 94:20 124:8 achieved 124:3 acrylamide 36:2 49:7 150:12 168:16, 18 action 38:14 activate 126:22 active 23:8 59:2, 6, 12 60:7, 14 62:11 72:25 114:24 119:23 154:8 activities 154:17 activity 110:6 added 124:2 adding 44:13 94:20 106:6	addition 50:17 82:23 101:20 106:5 135:13, 15 additional 79:2 101:25 105:13, 20 106:8 115:23 118:3 135:13 Additionally 49:15 81:8 adenine 166:8, 12 167:2, 3, 8, 10 administered 37:23 adopt 76:14 adopted 87:4 ADP 31:9 49:16 advance 39:7 41:7 159:24 advanced 38:2 40:19 affect 158:25 168:21, 24 affiliated 17:13 affirm 162:8 affixed 76:25 A-F-T-E-R-N-O-O-N 89:5 ago 13:14 36:4 agree 25:3 36:25 42:2, 5, 21 43:13, 16 47:8 54:14 56:25 58:7 67:6 71:18 78:7, 16 80:2, 15 99:20 128:19 129:5 142:13 147:22 148:3 153:16 156:16	agreed 46:11 72:23 ahead 106:2 115:22 aid 114:10 al 78:3 91:24 150:2 154:17 Alas 126:10 allosteric 38:13 allow 64:16 99:12 119:19 134:19 141:12 alternate 86:21 ambiguity 136:16 amine 72:18 73:16 166:17, 18 amount 61:4 128:20 129:6 analog 150:15 167:3 analogs 167:2 analysis 44:24 45:8, 9, 12 48:4 54:6 71:23 72:11 83:2 110:7 133:18 134:2 analyzed 70:7 76:11 Anish 2:2 6:15 anish.desai@weil.com 2:3 annealing 14:18 answer 40:10 45:4, 5 52:21 53:8 54:18 63:4, 8 64:2, 3 72:12 92:16 97:1 102:12, 14
---	--	--	---

103:4 112:9 114:21 answered 102:13 111:8 answering 9:1, 4 anyway 126:24 139:21 164:12 apologies 92:15 APPEAL 1:2 APPEARANCES 2:1 appeared 170:8 apples 137:25 application 39:5 40:23 101:15 120:24 141:25 142:5 applied 167:6 apply 64:5 76:12 92:8 141:23 164:8 applying 64:21 appointments 17:9 appreciate 149:25 approach 45:15 48:2 55:3 72:14 92:7 101:20 107:15 130:16 approaches 55:11 57:22 115:1 164:8 approaching 154:10 appropriate 61:10, 19 62:22 63:14, 24 69:10 70:5, 12, 18	71:1 75:14 77:1 90:5, 18 91:7 158:4 160:6 appropriately 49:10, 12 50:20 60:25 61:11, 21 62:23 63:15, 25 64:12 71:2 75:15 90:6, 19 91:8 140:20 158:5 159:6 160:7 appropriately- positioned 75:21 approved 41:4 approximately 50:11 123:22 167:9 approximation 50:22 apriori 93:16 area 16:16 45:20 114:24 areas 95:9 aromatic 79:14 80:16 82:6 83:18, 22 84:7 89:25 arrive 57:22 arrived 101:2 art 50:24 55:4, 12 56:15 57:2, 9, 12 64:25 68:13, 18, 21 69:6 91:3 101:2, 4, 8, 11 102:3 103:20 104:10 105:7, 22 106:4, 11 111:14 129:9	139:7 140:5, 6 142:20 165:7 167:6 Article 4:7, 18 5:3, 7 8:5 24:15 85:20, 22, 23 86:5, 22 96:8 97:15 106:13, 24 107:1, 4 108:20 aryl 79:9, 14, 18, 22 80:1, 3, 24 81:10 ascribe 137:3, 5 Aside 11:2 20:6 42:24 43:15 76:19, 23 102:18 162:6 asked 19:14, 20 53:9 66:20 82:1 83:4 86:15, 16 96:3 98:3 103:7 116:11, 16, 18 152:8 168:6 asking 9:3 51:20 84:12 123:17 162:8 aspect 26:7 31:10 41:14 42:15, 19 47:4 100:16 aspects 14:14, 17 15:15 27:11 66:14 162:6 assay 31:22 32:2, 22 33:3, 7 34:9 88:9 139:18 assays 27:22 31:2 33:10	34:20 35:13 36:21 37:10 140:25 assess 45:18 72:25 78:24 97:2, 25 159:3 assessment 160:20 assist 115:16 assistance 11:6 associated 100:5 126:9 assume 31:14 51:21 52:1 assuming 97:1 162:9 AstraZeneca 22:18 23:9, 20, 23 24:2, 4, 8 asymmetric 126:15 atom 79:16 atoms 60:24 69:16 79:15, 19 81:1 ATP 51:2 61:3, 4 62:4, 6, 10 68:19 166:11 167:10 ATP-binding 23:2 25:16 attach 92:4, 10 93:8 94:18 95:17 97:3, 25 Attached 3:25 46:16 49:7 50:19 52:9 56:10 62:9 attachment 64:16 104:8
--	--	---	--

attorneys 11:11	154:9 157:13	best 9:3, 8 66:6	binding 28:24
August 10:10, 15	161:3 167:23	170:16	29:25 30:4, 20
Author 3:9 4:3	background	beta 126:18	31:8, 13 34:4
145:6	20:24	better 9:8	38:15 49:16
AutoDock 20:12	ballpark 156:11	144:23 154:12	50:21 52:18
automate	164:4	158:17 164:16	59:11 61:3, 5
162:19 163:2	bank 99:16	beyond 45:7	62:17 65:25
automated	bar 147:16	164:6	67:7 77:23
161:17	barrel 144:9	bi 80:8, 13, 14	88:5 89:20
avail 141:20	based 37:17	biaryl 80:5, 12,	96:15, 19 97:11,
available 5:4	45:11, 16 76:6	16, 20, 21, 23	22 99:24 100:4,
99:16 101:12	99:24 100:20	81:2, 7, 13, 21	6, 21 106:21
104:11 112:12,	101:6 106:22	82:2, 5, 11, 15,	121:16 126:17,
18 127:13, 14	107:24 108:18	17, 19 83:3, 5, 7,	21 135:1 139:5,
129:9 144:7	131:19, 24	11, 12, 15, 17, 22	15, 18, 21
145:15	132:23 138:6,	84:1, 6, 9, 14, 18,	144:15 145:25
Avenue 2:9	25 140:16	23, 24	160:16, 21 164:1
aware 9:22	153:20 157:15	bicyclic 82:22	binds 38:15
69:5 99:11	163:17, 19	big 115:2	56:18 59:2, 6, 9
111:18	basic 113:20	billions 42:2	60:7 104:1
< B >	basically 116:21	43:4, 14, 17	109:5 114:12
B2 3:13 4:13	152:25	45:2 46:13	166:11
B43 56:18	basis 35:2	47:3, 7 124:12,	biochemical
120:12	be-all 137:10	22	37:10 154:17
bachelor's 13:15	bear 104:12	bind 17:6	biochemistry
back 19:25	115:3 125:7	29:24 33:6, 14	14:6
29:18 33:19	bed 10:20	34:8, 16 37:4	biology 15:6
36:18 40:10	began 10:11	46:7 47:11, 24	18:18
41:10 46:6	35:5	48:12, 18 49:11,	bit 8:19 20:21
47:10, 23 48:11,	behalf 6:15, 17,	19 51:13 53:17,	29:18 30:22
17 49:11 50:1,	19, 22 7:13	24 56:19 60:14,	33:11 56:5
21 51:12 52:17	BEIGENE 1:6	21 67:17 68:3,	black 41:1 83:8
53:2, 16, 23	6:11	14, 19 126:6	BOARD 1:2
59:25 65:13	believe 10:9	127:6 131:22	63:12
89:8 90:2	12:11 26:20	132:4, 5, 9	Bob 2:11 6:4
98:11 102:8	73:13 74:3	133:8, 13, 14, 20	bold 108:23
121:7 131:1	88:11, 20 97:10	134:14, 23	bond 22:24
135:2 147:6	114:4 134:18	143:7, 20, 22	29:16 50:25
150:20, 21	152:1 166:24	153:23 155:5,	60:23 61:1
152:2 153:25	168:10	17 157:12	62:8 67:22
			75:21, 22 91:23

145:24 150:11 156:2, 6, 21 157:1, 9, 10 166:8 168:16 169:15 bonding 68:20 bonds 47:16 49:17 51:1 52:17 53:3 56:9 60:24 64:15 69:17 75:19, 23 94:21 135:4 136:7 152:16 156:17 161:19 162:20 167:7 Boston 1:17 6:9 bother 143:7 bothered 39:19 bottom 27:21 28:15 32:19 61:15 65:21 73:8 76:1 84:18 142:6 bound 17:7 35:25 36:1 40:5 53:1 121:15 144:14 box 119:9 120:9, 10 BOYLE 170:9 breadth 41:23 break 9:11, 12 36:12, 23 51:4 65:6 82:5 88:22 130:20 160:23 167:15 breaking 124:7 Brenda 2:9 6:21	brenda.danek@l w.com 2:10 brief 106:1 bright 137:18 bring 125:6 bringing 115:3 brings 133:16 broadly 82:22 brought 104:12 133:22 Brutons 3:15 Bruton's 4:9, 15 142:11 BTK 3:16 25:5 29:20 30:3, 11 31:20, 23 32:2, 5, 12, 17 35:23 51:22 52:18, 20 53:1, 4 54:3, 5 57:23 62:16 71:7, 10 72:2, 9 73:1, 2 76:5 77:2 78:12, 21 79:1 101:15 104:1, 12 105:16 114:12 117:12 119:7 120:15 121:15 131:22 132:4, 9 133:8 134:14, 24 135:17 139:1, 5 141:16 143:24, 25 144:5 153:23 155:6, 17 156:18 158:22 159:10, 12, 13, 14, 22, 24 164:14 166:22 169:9	BTK/MNK 3:11 4:5 8:6 24:15, 19 BTKI 41:24 94:2, 7 121:17 BTK-like 72:17 102:10 BTKs 88:2, 4 BTK's 157:13 bucket 110:13, 19 buckets 124:18 built 87:22 busy 126:25 < C > Cairo 150:4 calculate 60:17 125:2 165:17 calculated 132:22 134:12 calculation 42:20 44:20 45:23 47:5, 6 48:1 calculations 43:18 call 22:22 39:6 48:15 51:7, 15 106:14 113:4 127:8 136:21 146:4 163:12, 13, 15, 17 called 16:19 20:12 23:14 27:4 35:19 38:12 39:1 40:1 120:22 121:2 147:20 148:1	calls 137:1 campaign 87:10 campaigns 87:18 Cancer 21:23 37:13, 16, 19, 22, 23, 24 38:25 39:18 40:12 candidate 94:2, 7 110:5 121:17 capacity 17:14 41:4, 6 47:16 carbon 79:16, 19 81:1 carbons 82:24 carboxamide 56:8, 9 career 17:4 38:1 careful 31:14 carefully 48:1 108:25 carried 39:25 115:12 carries 109:22 carry 72:24 case 9:19, 20 10:11 12:6, 8 19:2, 13 30:7, 21 41:13 63:22 83:1 136:5 143:23 144:7, 12 cases 58:4 category 72:7 110:21 cell 38:25 cellular 38:24 cellularizer 88:13 center 150:4 central 152:13
---	--	---	---

certain 95:9 139:17 certainly 18:7 54:21 62:13 112:24 113:22 114:22 116:17 122:23 131:25 132:18 142:14, 25 143:5 145:18 158:23 159:17 certify 170:6 cetera 66:16 106:6 161:20 chain 152:23 chance 74:13 change 120:19, 22 changes 26:21 113:10, 11, 16 characterize 30:18 58:1, 2, 5 77:7 93:21 128:7 chemical 40:2 64:11 67:11 118:5 160:20 chemist 20:25 21:8 38:22 72:22 75:17 124:6 161:25 chemistry 13:20, 21, 22, 23, 24 14:13, 17 15:11, 13, 16, 19 17:17, 19, 20, 23 19:9, 12 21:11, 13 39:9 59:17 81:20, 22 chemists 143:6,	10 Chicago 2:10 China 29:10 41:1 choice 34:15 choosing 145:16 chose 74:13, 14 75:6, 7 circle 96:20 circumstances 30:15 cite 114:22 167:10 cited 11:14 107:8 113:24 Claim 41:10, 14, 17, 25 42:16, 19, 24 43:8, 13, 15 46:18 47:19, 20 49:2, 14, 25 50:2 52:3 53:21 55:17 66:12, 14, 17 67:9, 12 105:5 128:15 159:21 165:14, 24 claimed 42:4, 7 46:17 66:4 67:8 102:11 128:4 160:4 claims 54:4 57:23 65:4 72:21 103:21 165:6 Clarendon 1:17 clarification 32:7 78:13 111:11 clarify 33:11 34:5 46:14	123:9 clarifying 66:22 clashes 135:7, 10 class 144:15 145:25 classes 13:25 14:20 15:20 81:20 classroom 15:12 clear 30:8 34:23 43:11 46:25 47:1 49:4, 5 50:16 52:13 63:11 66:21 71:5, 25 75:1 84:8, 10 94:17 100:25 114:11 121:25 123:5 132:6 136:11 139:25 157:21 159:11 clearer 102:16 clearly 157:25 165:22 cleaved 62:9 clinic 39:7 40:13, 15, 19 41:8 clinical 38:3 39:5 40:23 close 136:21 137:1 153:15 closing 106:6 co-authors 24:25 26:3 co-crystal 17:6 cocrystallized 119:21 collaborating 38:18	collaboration 23:23 38:7, 11, 16, 20 39:3, 14, 15 collaborations 143:5 collaborative 39:10 collaborators 38:4 colleague 39:8 72:23 75:17 colleagues 23:12 29:9 31:14 38:21 Collectively 27:25 28:6 color 146:21, 23 Column 41:17, 18 65:16, 21 69:8 72:15 73:8 74:23 75:7, 25 76:17 77:24 79:10 80:4 83:24 87:7, 10 102:23 103:2, 7, 8, 15 104:14, 17, 21 109:11, 16 110:4 142:4, 6, 7 columns 105:2 combination 157:6 combined 68:18 come 38:2, 8 101:6 137:23 152:11 comes 86:25 161:6 163:24 comfortable 148:9
--	---	--	---

comfortably 45:6	components 158:24	143:20 144:15 146:1 150:1	confidently 78:9, 18
coming 107:4	compose 91:22	154:5, 23 162:2	confirm 35:13
command-line 118:24	compound 23:15 29:12	164:25 168:23	37:3 84:13
comment 121:7	87:1 88:1	comprising 50:4, 7, 12, 14	148:7
commentary 74:4	97:12 116:1, 6	computational 13:20, 21, 24	confirmation 29:25 117:10
Commission 170:21	117:11 122:25	14:13, 17 15:10,	144:15 152:19
common 20:18	123:22 131:14,	12, 15, 19 17:16,	confirmed 9:25
48:7, 21, 24	16 133:3, 6, 7	19, 20, 23, 25	109:6
49:3, 21 60:19,	134:12, 22	18:6, 12 19:9,	confirms 25:13
20 80:14 95:15	135:16 138:12,	11 20:25 21:7,	conformation 121:14
COMMONWEA	19, 20, 23, 25	11, 13 111:18,	conjoining 104:3
LTH 170:2, 5	139:5 140:7, 12	22 114:10, 16	conserved 68:3
companies 87:17	144:23 145:2, 3,	124:6 125:6	99:7
compare 137:25	7, 21 147:22	145:18 161:25	consider 21:10
compared 21:9	148:11 152:17	163:4	95:8, 14 111:5
113:13 144:23	153:10, 17	compute 123:2	139:2 159:14
154:12, 13 156:4	154:18, 19, 23,	computed 131:10	consideration 77:11 103:20
comparing	24 155:1, 12, 13,	computer 123:2,	140:19 141:13
114:1 133:12	16, 21 156:8, 9,	16 125:8	considerations 132:17 160:12
154:23	11, 16, 20	142:15 161:22	considered 11:18, 23 69:25
comparison	157:12, 15	163:12, 15, 16	considering 34:15 43:15
168:22	158:2, 10, 16	computer-aided 1:19 170:15	159:18
comp-chem 19:8	159:9, 12	conceived 39:16	consistent 144:6
competitive 31:10	164:22 168:7,	concept 23:15	consisting 42:8
complementarity 61:4 160:14	11, 19 169:1	24:5 30:3 39:5	consists 50:6
complete 92:25	compounds 39:1 40:4 43:5	40:22	constantly 33:16
completed 14:9	65:3 78:5	concluded 169:23	constituents 158:5 159:7
15:8	81:10 87:17	conclusions 168:21, 24	constrained 152:18
completely 129:8, 10 144:6	89:18 111:25	conduct 77:3	constraint 60:3
148:20	115:23, 24	conducted 28:11 34:21	constraints 57:18 59:16
complied 21:20	116:5, 24	confident 95:3	
25:12 58:21	118:19 122:20	133:14	
96:22 98:14	123:6, 10, 25		
121:9 131:6	131:10, 21		
	132:7 134:14		
	138:3, 4 140:17,		
	18, 25 141:4, 7,		
	14 142:21		

93:23 101:21 119:25 144:17 construct 162:8 consult 11:3 72:22 75:17 consulted 11:10, 14 contain 82:23 contained 26:4 contend 128:25 context 58:5 59:17 62:16 64:5, 22 81:13 82:2, 4 100:11, 12 123:23 127:23 143:25 159:20 contradict 143:18 contradiction 145:14 contradicts 145:10 contribution 102:4 contributions 16:17 controlled 118:22 Cool 123:19 copies 85:18 copy 7:20, 24 8:8 103:16 corollate 149:22 correct 7:13, 14 11:13 13:5, 9, 10 14:8, 11 17:9, 11 19:4 22:6, 17, 25 23:1 26:17 27:18 28:3, 9,	17, 25 29:1, 16 31:5 32:3, 13, 14, 18, 21 37:14, 15 38:9 44:5, 6 47:12 54:12, 15, 20 57:2, 6, 11 58:9, 10, 24 59:4, 5, 14 61:23 63:1 64:14, 15, 17, 18 65:22 66:2, 5, 7, 9, 18 67:4, 5, 13, 18 68:15 69:11 70:13 71:4 75:8 79:17, 21, 24 80:5 84:4, 7, 16, 20, 25 86:4, 6, 7, 10 87:6, 12 88:3, 8, 11, 17 89:16, 21, 23 90:1, 22 92:13 93:9 94:4 95:20, 21, 24 96:16, 25 97:6, 18, 19, 23 98:2, 3, 6, 7, 18, 25 99:9, 14, 18, 22 100:2, 23 107:7 108:5 109:7 110:14, 20, 22, 25 111:24 112:4, 13, 14, 20 113:7 114:9 115:10, 15, 21, 25 116:3 118:15, 18 119:5 120:3 123:18 127:17, 18 128:1, 6 129:2 131:12, 15, 18 134:2, 19,	20 135:21 137:14 138:11 140:15 141:1, 5 142:23 145:5, 8 147:17, 21 148:13, 18 149:6, 9, 24 150:13 151:7, 17, 19, 23 152:1, 5 153:9, 12, 19, 24 157:18, 20 158:7, 12 161:11 165:1 166:9, 15, 24 168:13 correcting 13:7 correctly 68:5, 6 126:16 correspond 78:5 167:8 corresponded 78:4 corresponding 30:2 35:23 corresponds 151:20 153:16 Counsel 2:7, 11 6:13 11:1, 2 12:5, 25 73:19, 22 75:11 103:3 count 60:9 couple 12:13 79:8 114:25 150:17 course 13:22 35:4, 5 37:7 courses 13:23 14:14, 23 16:13 coursework 16:5, 9	court 6:4, 24 75:10 covalent 22:24 23:16 29:16 31:13 36:1 88:5 156:21, 25 157:10 covalently 46:7 47:11, 24 48:12, 18 51:13 53:17, 24 covered 102:19 120:14 CPU 122:22 123:11, 12 CPUs 123:14 124:8 create 55:15 108:18 creating 100:15 105:21 135:9 CRR 1:20 170:4, 20 crystal 18:17 92:20 97:10 98:9 120:5, 15 126:14 144:13 crystallographer 168:13 crystallography 14:17 18:19 29:12 40:6 109:6 CSR 1:20 170:4, 20 cues 157:24 cuff 76:7 163:21 curious 117:9 current 112:8
---	---	--	--

CV 4:12 7:19, 24 13:8, 9 21:18 36:7 Cys481 30:3 35:23 49:13 53:3 154:10 155:25 157:10 Cys797 52:19 cysteine 22:25 23:7 25:16 29:16, 18, 19, 20 30:3, 5 35:22 46:8 47:12, 24 50:22 51:14 117:12 135:6 152:23 153:2 < D > D.C 2:6 Dana-Farber 38:21 39:9 Danek 2:9 3:5 6:21 49:1 52:12 58:12 59:20 63:4, 17, 19 71:3 73:19 74:3, 9 77:6 78:22 79:4 85:1 86:11 88:24 100:24 101:9 103:3, 11 110:15 116:12, 19 129:20 130:7 133:21 138:14 145:13 146:16 147:11 154:2 157:19 162:24 165:2 167:14 168:2 169:17, 20	data 99:16 142:5 144:2, 7 database 25:22 26:4 127:8, 11, 14, 17 128:2, 22 Date 3:13 4:13 6:6 13:11, 12, 13 David 39:8 day 10:21 12:13, 14 34:3 170:7, 18 days 12:13 126:1 decide 76:12 164:9 Declaration 4:11 7:13, 16, 21 9:25 10:1, 3, 7, 14, 25 11:4, 8, 12, 17 12:1, 6, 8 13:2, 5 19:2 21:17, 19 37:12 43:19 48:3 49:4 55:2, 24 56:6, 14 58:20 67:20, 25 80:25 81:9 86:1 89:12 90:3, 12, 21, 25 94:9 96:10 98:13 100:16 105:10, 11 108:7 110:24 111:17, 23 113:14 117:5 131:5 132:15 134:25 138:15 148:5, 15 151:22 153:18, 25 154:21 158:14	deeply 30:25 163:23 default 120:9, 11 define 119:20 defined 59:11 67:10 79:9 80:24 defining 120:8 definitely 59:9 127:20 definition 46:16 59:13, 15 60:1 61:24 63:16 64:1, 2, 4 80:1, 3, 21, 23, 24 81:7 82:19 83:12, 15, 20 84:6, 9, 14, 18, 24 91:12 167:6 definitions 59:18 degree 13:15 113:2 deliberate 94:25 Demetrius 19:19 demonstrated 31:3, 23 32:4, 11 demonstration 28:23 30:19 depend 125:5 137:20 depending 31:10 depends 17:18 depicted 69:17 104:20 168:7, 20 depicting 108:10 deposed 8:13 DEPOSITION 1:13 6:10 7:10 12:4, 10, 22 98:10 169:23	deprioritize 141:6, 12 142:20 158:16 deprioritized 140:18 der 160:14 Desai 2:2 3:4 6:15 7:4 32:8, 10 36:19 65:5, 14 73:21, 23 74:6, 11, 15 78:14 89:9 103:6, 14 116:14, 20 130:19 131:3 142:9 146:4, 17, 19 147:5, 13, 14 160:22 161:5 167:11 169:19 describe 16:13 17:2 20:6 29:22 53:12 58:25 61:8 108:14, 15, 16 159:4 described 25:4 26:20 27:3, 20 43:12 66:13, 14 73:4 83:9 96:14 107:22 127:24, 25 128:17, 21, 22 160:13 163:19 describes 89:18 109:2 118:13 Describing 27:22 111:4 119:12 160:3 DESCRIPTION 3:8 4:2 5:2
--	---	--	---

27:14 43:5 66:12, 17 Design 4:20 104:10 139:7, 9 164:16 designed 28:23 designing 108:10 desirable 77:13 desire 162:1 desired 62:19, 20 70:15 93:25 104:4 135:4 detached 46:15 detail 45:15 129:16 130:3 141:22 details 113:16 160:15 detectable 139:14 determinant 55:8, 11 determine 45:12 70:14 91:25 93:15 119:22 determined 16:18 40:5 126:14 determining 17:6 133:18 137:1 develop 23:15 33:12 40:21, 23 107:5 developed 23:12 38:25 39:6, 18 40:14 54:17 87:18 113:6, 8 developing 39:4 58:2 87:15	development 23:6, 19 38:10 40:7 88:16 109:23 114:25 deviation 164:1 devise 130:13 devised 39:23 devote 123:15 diagram 50:17 difference 139:25 159:2 169:1, 2, 4, 6, 10 differences 113:18, 19 137:20 different 29:19, 24 30:4, 5, 13, 14 38:14, 15 74:17 82:1 94:8 98:18, 24 99:8 128:20 143:22 151:14 152:6 156:15 164:14, 18 165:10 166:3 168:12 169:7 differently 82:8 differs 168:20 difficulties 109:22 digging 56:5 dimensional 16:18 dimensions 120:10 dimer 126:16, 19 127:6 dings 156:8, 12 direct 28:13 103:5 directly 41:4	disagree 41:22 43:4 discipline 21:11 disclosed 86:12, 22 discloses 86:9, 18 88:1 disclosure 105:6 discover 25:4 discovered 38:19 39:13 128:6, 8 discoverers 55:5 Discovery 3:10 4:4, 7 5:3 8:6 21:23 24:15, 19 37:7, 13 45:17 77:20 86:6 87:18 97:15 164:25 discuss 111:23 113:15 117:4 discussed 20:10 64:10 85:25 88:20 92:5 99:2 108:6 124:25 128:11 132:17 142:16 152:22 164:13 165:16 discusses 86:5 131:9 discussing 64:21 discussion 31:19 167:2 disease 102:11 distinct 25:16 distinction 123:16 164:20, 22	distracting 168:15 divide 136:11 division 40:1 divorced 42:23 43:7 46:20 doable 129:8, 10 doc 133:6 dock 57:22 75:18 92:19 112:22, 24 113:22 114:1 115:7 122:7, 14 125:10 140:1 151:20, 21 docked 56:18, 23 115:20, 23 116:1 123:24 128:24 150:1 docking 14:1, 21, 24 15:21 16:2 18:15 19:3, 7 20:11 21:6 28:11, 18 29:23 30:10, 14 32:23 33:20 34:2 35:3 53:13, 19 54:25 55:13 72:24 77:22 78:6 94:1, 11 111:19 112:1, 17, 25 113:3 114:10, 14, 19 115:4, 8, 11 116:4, 23 118:3 119:25 120:13, 17, 18, 22 121:7, 17 122:17 123:21 128:25 131:9, 13, 19, 24, 25
--	--	---	--

132:2, 13, 20, 21, 22, 24 133:2, 6, 9, 12 134:7, 11, 13, 17 135:12, 13, 16, 24 136:6 137:7, 19, 21, 22 138:2 140:16 141:8, 11, 23 144:4, 16, 18, 19, 22 145:18, 23 148:4, 20 149:24 151:15 152:4, 7, 9, 25 153:17, 20 154:4, 11 155:19 156:2, 7, 10, 16 157:5, 7, 16 158:9, 17 159:3 160:18, 19 161:6, 8, 11, 12 162:12, 14 168:22 169:2, 5, 11, 15 dockings 122:15 docks 135:8 Doctor 154:2 document 10:9 11:20 27:17 28:16 73:22 74:25 75:11 86:3 119:16 doing 55:14 117:8 122:18 127:7 143:2 145:23 domain 126:21 donor 75:21 166:12 donors 51:1 60:23 61:1 91:23	double 150:11 168:16 169:14 doubt 47:4 downstream 126:8, 22 Dr 4:11 7:8, 16 12:7 41:23 42:21 43:17 44:1 46:1 47:5 48:2 63:23 74:4, 16 124:11 167:12 168:3 draft 10:25 Drafted 11:1 drafters 81:6 83:8 drafter's 80:20 drafting 11:7, 11 draw 55:12 56:2 73:12 74:18, 19 75:4 76:4, 8 135:23 136:1, 2 164:16, 17 drawing 73:6, 17 75:5 128:24 164:24 drawn 57:7, 8, 9, 12 67:11 69:15 91:10 drew 75:2, 13 DRIVER'S 170:11 drug 21:23 22:18 37:13, 16, 19, 22 40:12 45:17 55:5 77:19 87:18 88:16 drugs 37:25	Dual 3:11 4:5 8:6 24:15, 19 duly 1:14 170:12 dynamics 14:18 18:16, 17 < E > E4 84:25 85:4, 10 EAI-432 38:13 39:6 earlier 148:17 162:11 early 9:22 33:18 earnest 10:11 easier 22:21 Eastern 6:7 easy 144:12 eat 88:22 ECK 1:13 3:3 4:11, 12 6:10 7:2, 7, 8, 16, 19 24:18 63:23 74:16 146:4 148:23 149:10 150:23 151:4 167:12 168:3 Eck_Ex2114 3:24 153:6 Eck's 74:4 effect 114:24 effecters 126:22 effector 126:17 effectors 126:8 efficiencies 124:4 effort 40:25 103:4 126:5 efforts 41:7	EGFR 22:1, 14, 25 23:13, 16, 17 36:1 38:13 39:17, 18 40:5, 6 eight 65:19, 23 66:3 67:2, 6 69:7, 10 70:4, 17 72:7 77:23 78:8, 10, 16, 19, 25 79:19 82:16 84:2, 5, 13, 23 either 29:7 83:15 97:9 98:6 elaborate 23:11 129:4, 11, 23 130:14 elaborated 92:25 106:10 127:13 elaborating 94:12 104:13 128:23 elaborations 58:18 electrical 13:15 electrophile 153:1 electrostatics 158:25 160:13 element 61:9, 19 90:5 96:15, 19 100:4, 6, 21 101:14 106:21 107:23 160:3 elements 99:24 E-mail 2:10 embedded 15:24 18:17 embodiment 85:6, 10, 12, 13
--	---	---	---

embodiments 65:20 70:9 80:11 83:25 85:8 105:3, 5 empirically- tested 145:7 empirically- testing 145:11 employ 141:17 145:16 enabling 105:8 encompass 43:16 59:18 128:9 encompasses 43:14 59:15 128:4 end-all 137:11 ended 117:17 energetic 132:25 engage 126:21 engaged 18:7 engineering 13:16 enlist 19:5, 14 entirety 100:4 entitled 4:7, 18 5:3 24:19 25:11 environment 112:2, 3 115:9 122:11 envision 57:14 58:11, 14 165:4, 9, 18 envisioned 25:14 envisioning 164:24 epidermal 22:4 equipped 91:3, 12 92:6	error 77:4, 8 errors 13:4 especially 139:19 Esq 2:2, 3, 4, 9 essential 133:25 establish 164:10 established 38:5 49:24 122:12 156:23 establishing 92:21 ester 62:8 estimate 10:13 125:11 129:15 et 66:16 78:3 91:24 106:6 150:2 154:17 161:20 evaluate 124:17 125:9 128:13 161:12, 22 162:1, 15, 22 evaluated 161:15 evaluating 36:22 125:21 126:11 127:10, 23 128:16, 21 161:6 events 32:25 evidence 31:9 170:10 evokes 101:19 evolved 113:17 Ex 3:18, 21, 23 EX2024.0001 4:16 EX2024.0164 4:17 exact 8:16	exactly 33:23 122:19 127:20 154:1 EXAMINATION 7:3 157:7 168:1 examine 93:22 examined 157:8 examining 132:20 164:4 example 19:22 30:10 35:7, 10 36:4 38:6, 10 40:16 54:8 56:7 64:21 65:1 71:14 72:15 77:10 82:17 92:15 97:21 98:16, 19, 22 99:2 103:22 104:21 105:21 108:3 122:3 123:21 135:18, 22 140:12 141:4 145:9 162:19 163:23 examples 35:14 65:20 82:14, 16 103:22 150:1 excellent 26:15 Excerpt 142:11 excluded 121:11 excluding 119:21 exclusively 34:12 execute 130:3 exemplified 104:23 105:2 exercise 29:23 30:14 72:25	93:17, 18 95:21 97:7 100:9 111:9 129:4 134:9 136:16 137:8, 22 144:16, 20 148:20 152:10, 25 165:10 169:15 exhaustively 102:19 Exhibit 3:9, 13, 17, 20, 22, 24 4:3, 7, 11, 12, 13, 18, 23 5:3, 7 7:15, 18, 21 8:2, 4, 10 13:9 24:11, 12, 14, 18 26:25 73:20, 24 74:1, 5 75:10 85:17, 19 87:11 96:7, 11 97:14, 18 106:24, 25 118:7, 8 142:9, 10 146:6 147:7, 8, 9, 15 148:24, 25 149:11, 14 150:3, 23, 24 151:5 153:4, 5, 8 168:3, 8, 20 exist 120:21 existing 87:5, 14 111:9 exocyclic 166:17 expect 36:9 52:20 130:12 137:23 139:20 143:2, 20 144:1 145:25 156:25 expected 70:15 75:19 77:23
---	--	--	--

135:17 140:1 152:13 experience 21:9 34:25 35:8 45:17 60:11, 13 125:20, 21 143:12, 19 experienced 21:4, 5 experiment 31:11 137:21 157:3 experimental 31:3 36:21 37:2 138:6 142:23 143:18 144:2, 7 experimentally 140:2 experimentation 79:2 experiments 28:1, 6 31:20 118:5 159:15 expert 7:12 19:8 21:10 expertise 21:2 45:11 Expires 170:21 explain 45:16 68:16 113:11 121:25 137:10 139:24 156:10 explained 48:3 55:2 64:20 75:16 77:18 93:13 105:23 124:12 134:25 141:11 155:7 158:14	explaining 57:16 explore 25:21 expression 144:8 expressly 105:22 130:2 extended 113:4 extensive 110:5 extent 145:17 extra 85:17 113:3 eyes 163:1 < F > fact 37:9 77:21 114:9 168:19 faction 40:8 factor 22:4 factors 101:25 facts 30:15 fair 11:10 26:2 27:8 30:17 34:18 43:11 81:18 87:16 99:1 125:17 128:8, 18 134:3 136:22 156:5 162:17 fairly 26:9 30:18 fall 41:24 42:3, 18 65:3 66:4 67:7 110:13, 19, 21 124:13 164:25 165:5 falls 52:2, 8 164:23 165:14 false 124:21 familiar 8:19 22:9 54:11 104:9 family 126:23	far 12:1 24:3 39:19 54:16, 21 57:11 83:13 88:18 120:10, 20 162:20 163:21 167:5 fast 94:24 faster 95:1 103:24 fatally 48:4 favorability 132:25 favorable 135:14, 25 152:20 158:12 FDA-approved 22:16 feature 49:14 51:2 features 49:3 50:16 feel 11:22 129:24 fellow 17:10 21:1 29:6 fellowship 15:5, 22, 25 16:6, 10 felt 124:9 field 15:18 16:21 83:14 100:7 115:2 fields 113:17, 18 figuratively 165:12 figure 19:24 26:24 27:2 28:13, 22 29:21 76:1, 16, 24 77:2, 5, 15 91:19 92:10 93:7, 19 95:16	108:4, 6 109:4 111:1 119:10 148:22 157:4 162:13 166:7, 10 figuring 54:2 file 3:17 116:10, 16 146:10 148:2 153:8 filed 141:25 files 12:18, 23 112:10 147:25 151:5 filling 167:9 fills 167:10 final 92:12 111:13 financial 130:10, 12 find 56:6 57:1 80:22 103:24 127:5 143:21 149:22 fine 74:8, 22 96:21 105:25 160:15 finish 9:1 92:16 firm 9:19 first 9:20, 22 12:7 16:19 23:12 25:13 32:14 33:3, 9 35:12, 17, 18 72:18 75:3 102:8 130:9 137:16 fish 144:9 fit 49:15 61:2 72:25 135:11 fitting 91:11 159:1
---	--	--	---

five 79:18 115:23 123:25 152:9 five-minute 160:23 167:14 fixed 61:12, 21 62:23 63:15, 25 69:22 70:4 71:2 75:15 78:11, 20 79:1, 6 90:6, 20 91:8 158:5 159:7 160:7 flawed 48:4 flexibility 118:1 156:24 Flip 75:25 151:14 focus 21:23 37:14 41:13 100:15 focused 87:21 127:7 focusing 42:15 151:4 follow 18:8 165:19 following 42:14 67:11 Footnote 148:16 FORBES 170:9 force 113:16, 18 foregoing 170:14 forget 33:15 125:8 form 23:17 29:15 39:21, 22 47:16 49:1, 16 52:12 58:12 59:20 60:24 63:17, 19 64:10	70:15, 18, 25 71:3 77:1, 6 78:22 79:4 85:1 86:11 100:24 101:9 110:15 129:20 130:7 133:21 138:14 145:13 156:21, 25 157:9, 19 162:24 165:3 166:20 formal 14:23 15:12, 23 33:20 formally 10:10 formed 79:18 85:5 forming 79:15 158:19 forms 22:24 52:17 156:17 Formula 58:23, 25 61:9, 18 65:15 67:16 68:1, 8, 13 78:8, 17 90:2, 4, 13, 18 91:6, 16 93:6 101:18, 19, 20 102:18 103:1 104:15 132:23 157:17 158:3 159:5 160:3 forth 19:24 170:12 found 105:22 111:13 four 50:4 fraction 114:13 fragment 93:18	fragments 107:11 108:23, 24 frankly 114:15 front 7:20 168:3 full 7:5 12:14 31:18 full-time 21:7 124:5 fully 106:9 fully-formed 94:11, 13 function 59:7, 9, 22, 24 60:6 62:15, 19, 20 95:12 123:14 functional 59:13, 15, 18 60:1 61:24 62:14 64:1, 4 functionality 112:16, 21 113:20 115:14 120:6 160:9 functions 62:24 63:1 fungible 67:17, 19 68:4, 14, 24 69:1 further 39:4 40:7, 22 43:2 44:9 46:14 61:8 113:5, 8 140:19 141:13 145:3 154:15 fused 42:8, 25 50:3, 6, 13 52:3 66:16 80:12 84:1, 23 89:20	96:23 104:3 < G > gatekeeper 75:23 general 67:21 100:7 116:25 118:25 140:3 generalization 37:5 generally 98:21 158:9 generally-agreed 83:14 generate 105:13 106:8 119:7 generated 105:19 120:2 generation 23:13 119:3, 19 genesis 169:6 genus 44:17 47:18 geometric 92:23 geometry 64:14, 16 get-go 25:7 getting 164:6 Giannini 2:11 6:4 GIBSON 1:15, 20 6:5 170:4, 20 Give 26:22 35:7, 10 38:10 74:18 83:10, 12 85:17 132:23 146:18 150:19 160:8 given 7:1 30:14 106:21 107:23 120:11 129:8
---	--	---	---

gives 135:24 162:5 giving 169:1, 10 Glide 4:23 18:14 20:14, 16 111:22 112:1, 5 113:12 115:8 118:9, 12, 25 119:25 148:11, 14 149:7 151:9 153:13 155:8, 10 162:7 163:17, 20 164:5 Glide/Maestro 113:13 GLU475 166:21 glue-type 126:5 GNF 40:1 go 9:4 11:16 25:11, 19 28:19 32:16 40:10 41:10 43:19, 20 45:24 58:19 65:16 73:14, 15 77:3 89:11 96:9 97:16 98:11 105:9 106:2 108:8 109:8 110:23 111:16 115:5 118:10, 20 119:2, 6, 13 120:4, 16, 17 121:6 126:11 129:16 131:4 135:10 149:2, 10 150:21 152:2 153:3 154:16 163:21 166:5	goal 25:3, 7 goes 110:3 GOEZ 106:18 going 10:22 31:16 36:10 41:18 56:19 59:25 62:21 71:24 83:19 90:2 93:2 97:1 105:25 115:5 127:21 137:15 143:7 146:2 148:23 150:17, 21, 22 152:24 156:9 160:8 Good 6:2 22:13 36:11 72:24 148:8 Gotcha 111:16 GOTSHAL 2:2 grab 85:15 103:1 graduate 14:15 graft 68:21 grafting 36:2 56:17 111:10 graphic 18:17 graphical 120:23 Gray 35:18 38:22 Gray's 29:7 great 155:20 greater 140:7, 13 green 146:21, 22, 25 147:2, 12 Grid 119:3, 7, 19 120:9 grids 119:24 120:2 ground 8:23	group 44:4 51:23 52:9, 23 67:3 69:22 73:14, 16 78:20 84:23 92:4, 10 93:8 95:17 97:3 98:1 102:2 145:15 150:7 155:23 groups 67:21 76:15 79:22 growth 22:4 guess 8:23 38:5 46:16 49:20 117:19 163:6 guide 62:19 102:1 guidelines 164:11 guys 67:19 Guzgalas 19:19 20:4, 8, 24 < H > half 12:13 32:14 122:9 124:1 hand 85:16 91:12 146:2 148:23 150:20 170:18 handed 24:17 hands 19:4 Hanna 38:22 happens 35:21 happy 74:18 hard 34:13 Harvard 17:9, 13 H-bond 160:6 166:12, 13	H-bonds 46:4 47:9, 21 48:9, 16 51:11 53:15, 22 61:10, 20 62:22 63:14, 24 64:11 69:11 70:5, 12, 15, 18 71:1 75:14 77:1 90:5, 18 91:7 158:4, 19 159:6 166:20 head 14:4 112:7 121:1 heading 108:23 heard 81:12 held 17:8 help 19:5 26:24 helpful 83:1 133:24 hereinbefore 170:12 hereunto 170:17 heteroatom 42:10 50:13, 15 52:5 heteroatoms 43:2 50:5 81:3 heterocycle 50:6 66:16 heterocycles 104:3 105:4 heterocyclic 42:8 43:1 46:19 50:4 56:10 155:25 HHS 3:9 4:3 high 144:13 high-energy 62:7 higher 124:3, 8
---	--	--	---

highlighted 147:19 149:18 151:9 153:10 highlights 152:8 highly 68:3 99:7 highly-valued 140:5 high-throughput 40:2, 4 hinderance 44:12 hinge 46:4 47:9, 17, 21 48:16 49:17 51:2, 11 52:17 53:4, 15, 22 56:9 60:25 61:2, 10, 20 62:17 63:14, 24 64:11 65:25 67:6, 17, 23 68:3, 18, 20 69:11, 18 70:6, 15 71:1 75:14 89:20 90:6, 19 91:7 94:21 96:15, 18 97:22 99:8, 24 100:4, 5, 21 109:5 135:4 150:8 156:2, 7 158:4 159:6 160:6 166:9, 12, 19 167:8 hinge-binding 98:17, 23 99:5 101:14 107:23 hinges 68:14 history 87:23 hit 30:5	Hold 85:15 146:17 165:2 hole 10:23 Hon 29:6, 13 hope 37:20 hopping 55:3 69:6 100:8 hour 9:12 36:10 94:17 122:9 124:1 hours 10:16, 17, 18, 19 human 38:2 123:16 161:15 163:1, 3, 13 164:8 hundreds 10:16 45:7 hydrogen 47:16 49:17 50:25 51:1 52:17 53:3 56:8 60:23, 24 61:1 64:15 67:22 68:19 69:17 75:19, 21, 22 91:23 94:21 135:4 136:7 145:24 156:1, 6, 17 161:19 162:20 166:8 167:7 hydrogens 168:14 169:13 hydrophobic 46:6 47:10, 23 48:11, 17 51:12 hypothesis 30:7, 9 hypothetical 84:11	hypothetically 83:21 < I > i.e 121:12 ibrutinib 56:18, 19, 21, 24 71:15, 17, 21 75:18 76:20 77:25 86:6, 9, 13, 20 87:3 92:19 103:22, 25 104:1, 16, 22, 25 105:14 114:11 115:7, 13, 17 116:23 117:3 120:13 122:4, 8 123:21 134:4 136:14 138:2 147:23 148:1, 4, 12, 15 150:3, 5, 6, 8, 13, 14, 15 158:11 164:1 168:11, 12, 20 ibrutinib-like 56:21 71:6, 10 72:2, 9 73:2 76:5 86:14 101:15 121:16 IC 32:6 IC50 32:2, 12, 23 88:9 138:8, 13, 21 139:4 140:7, 13 141:4 143:1 IC50=250 26:17 idea 32:25 44:19 45:1 58:13 111:6 142:24 ideal 135:11	identification 7:16, 19 8:5 24:14 74:1 85:20 96:7 97:14 107:1 118:8 142:10 147:9 148:25 150:24 153:5 170:10 identified 13:4 37:16, 18, 24 40:2, 19 46:3 48:15 88:20 108:24 121:11 identifies 140:13 identify 18:5, 11 25:23 26:3 48:23 53:20 54:1 65:1 126:5 ignore 168:14 ignores 44:1 IL 2:10 illustrate 67:3 illustrated 69:13 77:9 81:2 83:10 148:4 illustration 73:8 illustrations 65:23, 24 69:17 image 155:20 168:7, 11 imagine 34:12, 13 54:1 129:3 159:25 immediately 91:11 immersed 34:1 impact 117:9, 13 158:20
--	--	---	---

implications 62:2	incremental 123:24	143:21 153:24 158:21 159:10	33:12 35:19, 21, 25 36:3, 22
important 8:25 114:16 117:21, 22 133:17	I-N-D-E-X 3:1	inhibited 39:20	38:25 40:9, 18
136:24, 25 137:5, 13, 25 145:25 152:9 160:15 164:19	indicate 69:14 133:7 134:13 139:4 140:8	inhibiter 23:16 25:15 26:4, 16 31:4 37:7, 8 54:5 102:8 107:5 108:17, 18 135:17	51:3 56:15, 23 57:20 85:7 87:22 89:19 102:10 103:21 105:14, 20 106:8, 9 141:16 142:12 144:5
imported 120:5	indicated 72:19 119:10	inhibitors 16:25 17:7 30:16 35:24 36:1 39:17 86:14 138:10	inhibits 25:5 26:16 159:12
imposes 62:5	indicates 85:13 154:6 157:9	inhibiting 139:16, 17 159:22	initial 38:19 39:13 87:10
impossible 129:22	indicator 135:13, 25 155:9	inhibition 37:10 105:16 117:25 139:14	inspiration 27:9 inspired 40:15
improved 114:20	individual 159:18	Inhibitor 3:11 4:5 5:5 8:6 22:14 23:13 24:16, 19 25:4, 22 28:2, 7 30:5 36:3 37:4 38:11, 13 39:20 51:22 53:4 57:23 71:11 72:17 73:2 77:20 94:11, 13 95:12 99:25 101:15 104:10 121:15 139:1, 7, 8, 20 160:16 163:8, 9 164:14	instability 109:25
improvement 143:15	individually 161:15	inhibitors 16:25 17:7 30:16 35:24 36:1 39:17 86:14 138:10	instance 81:15 122:6
improvements 113:12	individuals 11:7	information 23:6 93:14 101:7, 10 104:11 105:8 106:23 107:25 112:9 162:6	instances 81:9
improvise 163:21	industry 20:19 143:6	informal 15:14	instruction 103:11
inadvertently 116:16	informative 137:9	information 23:6 93:14 101:7, 10 104:11 105:8 106:23 107:25 112:9 162:6	intended 80:19, 20 82:20 87:22
inclined 163:14	informed 23:6 93:23	informing 95:11	intentionally 116:18
include 11:24 116:18	informs 162:14	inhibits 32:5, 12 37:9 39:21 52:20 54:3 77:2 78:11, 21 79:1 131:23 132:4, 9 133:8, 14, 15 134:15, 24 139:6	interact 61:2 127:1
included 12:1 168:23	inhibit 32:5, 12 37:9 39:21 52:20 54:3 77:2 78:11, 21 79:1 131:23 132:4, 9 133:8, 14, 15 134:15, 24 139:6	inhibition 37:10 105:16 117:25 139:14	interacting 126:8, 25
including 20:20 46:20 59:3, 12 60:7 70:16 77:20 78:7, 16 106:9 110:12, 18 136:14 162:16	informative 137:9	inhibitor 3:11 4:5 5:5 8:6 22:14 23:13 24:16, 19 25:4, 22 28:2, 7 30:5 36:3 37:4 38:11, 13 39:20 51:22 53:4 57:23 71:11 72:17 73:2 77:20 94:11, 13 95:12 99:25 101:15 104:10 121:15 139:1, 7, 8, 20 160:16 163:8, 9 164:14	interaction 126:20
inconsistent 144:2	informed 23:6 93:23	inhibitors 3:15 4:8, 16, 22 17:6 23:7 24:8	interactions 24:2 64:13 67:22 99:7 126:18 160:14
incorporates 27:11	informing 95:11		interest 17:3 37:11 68:23 70:14 77:16 87:20 114:25
incorporating 85:7 108:17	informs 162:14		

interested 35:19 51:20 56:20 94:20 164:6	117:10, 15	January 24:18	87:15, 18, 19, 22
interface 113:20 120:23 127:4	investigation 5:5	JBj-125 39:1	88:16 89:19
interfaces 126:18	invoicing 10:18, 19	JBj-63 39:1	95:11, 12 98:18,
interpret 62:12	invoking 52:15	jobs 119:25	24 99:8, 12, 16,
interpretation 144:18	involve 15:10 38:11 128:16	Jolla 40:1	25 104:10
interpreted 105:6	involved 23:5	Joseph 7:7	106:21 107:16,
interrupting 92:16	26:8, 9 38:6, 16	judges 63:21 83:4	24 139:7, 8
intervening 113:17	128:21 160:20	Jul 4:14	142:12 156:24
intolerable 135:9	IP 31:22 32:1	June 3:14	166:11, 19
introduce 6:13 150:11	Irreversible 4:8	54:14, 19, 24	kinases 16:16
introduced 168:16 169:14	23:7 28:24	56:3 57:2	17:5, 7 25:17
introducing 135:6	30:19 35:21	99:20, 25	28:3, 8 34:16
introduction 102:6	41:24 139:8, 20	100:21 105:22	35:22 126:23
invent 57:24	159:24 164:14	110:11 113:6	Kinase-targeted
invented 73:3 81:17	irreversibly 32:5, 12 37:4	juxtapose 117:11 135:5	4:19 107:2
inventors 58:7 140:24	77:2 78:11, 21	< K >	kind 40:6
invention 58:3, 18 83:9 160:4	79:1 131:22	Kai 29:6, 13	45:22 99:8
164:17, 19, 23	132:9 133:8	Kathryn 2:4 6:19	100:9 105:24
inventors 69:2, 4 70:17 78:9, 18 81:6, 16	134:15 139:6	kathryn.leicht@	114:16 139:16
141:19 142:14	153:24 158:21	weil.com 2:5	141:22 156:17
inventor's 80:19	159:10, 12, 21	keep 31:16	kinds 114:18
inversion	isolated 96:5	105:25 126:7	kinesis 16:7, 11
	isolation 133:10 155:8	150:16 155:13	kit 56:22 57:20
	isomers 117:18	Kin 29:8	knew 118:4
	issue 8:9	Kinase 3:16	know 8:16 9:8,
	issued 142:2, 3	4:9, 15, 21 5:6	12 10:23 12:1,
	issues 109:25	16:18, 25 22:7	24 14:15 15:16,
	its 46:19	25:22 26:4	17 19:24, 25
	110:12 114:19	28:12, 25 30:20	20:10, 11, 13
	117:11 158:25	31:20, 22, 23	21:7, 8 24:3
	168:17	32:2, 17 35:19	29:4 30:9, 22,
	< J >	37:4, 11 39:21,	24 31:10 33:2,
	JAK 36:2	24 51:2 55:5	5, 6, 12, 15, 16,
	JAK3 35:20, 21,	56:14, 22 57:20	17, 22, 25 34:15,
	24 36:3, 6	59:2, 3, 7, 12	16, 18 35:20, 24
		60:7, 8, 14	37:8 39:19
		62:11 77:20	40:18, 20, 24
			43:1, 7 44:23
			45:6, 7 47:25
			48:10 49:23
			54:15, 16, 19, 22

57:10, 11 58:17, 18 60:10 62:1, 3, 4, 12, 13 63:6, 18 64:13, 14, 23 66:15 67:10 69:16 70:8, 24 71:14, 16 72:14, 19 73:3 74:7 75:2, 16 76:7, 10, 14 77:9, 18 81:23 82:5, 14, 15, 18, 19, 21, 22 83:9, 10, 13 85:4, 6 88:18 91:11, 14 92:6, 14, 18 94:16, 22 95:13 101:19 102:16 106:3 113:24 114:9, 12, 13, 22 117:16, 23, 24 118:25 120:7, 10, 21 122:3, 4, 6, 14, 17, 22, 23, 24 123:21, 22, 25 124:2, 6 125:1, 7, 17 127:12 129:17, 25 130:10, 13, 17 132:2, 23 133:13 136:5, 6, 14 137:6, 16, 24 138:18 139:8, 9, 10, 14, 16, 24 140:3 141:6, 23 143:11 144:6, 8, 11, 16, 17 145:14, 17, 20, 22, 24 152:24 155:7 156:7 157:5 158:24	159:15 160:14, 18 161:19 163:21, 25 164:2, 3, 7, 10, 12 165:18 167:5 knowing 111:12 knowledge 33:23 34:24 68:17 91:3 99:22 101:11 105:7 106:4 113:9, 15 138:5 141:20 157:8 170:16 known 26:5 30:16 51:2 55:4, 14 56:15 64:6, 24 86:25 87:4, 8, 14 98:18, 24 99:6, 17, 19, 24 100:13, 17, 20 101:1, 4 102:3 103:20 108:11, 17, 19 111:7 121:14 127:10, 16 128:5, 16 165:7 knows 54:23 < L > La 40:1 lab 11:7 17:19, 22 18:1, 12, 20, 23 19:6, 9 26:9 29:11 38:2, 8 41:4 113:23 labeled 107:11 149:5 151:5, 15	laboratory 21:24 37:14 38:24 39:24 lack 156:6 laid 49:3, 25 83:8 landmark 16:20 large 109:22 122:13, 15 162:1 LATHAM 1:17 2:7 6:8, 21 LAWRENCE 170:8 lawyer 157:25 lawyers 12:9 lay 163:1 laying 10:20 lead 54:24 56:2 88:1 102:20 106:22 107:17, 24 132:3 leads 87:14 learn 9:20 18:9 103:21 104:6 Learned 14:14 learning 115:1 led 40:12 100:1, 22 101:17 left 72:15 73:8 96:24 114:14 142:4, 6, 7 146:13, 20 147:1 149:3, 17 left-hand 147:18 Leicht 2:4 6:19 length 119:9 152:22 155:7 165:16 Leukemia 3:12 4:6 8:7 24:16, 20	level 95:4, 8, 10 114:15 162:25 libraries 4:19 87:17, 20 107:2 LICENSE 170:11 ligand 14:1, 21, 24 15:21 16:1, 4 18:13, 15, 22 21:6 98:18, 24 99:6, 12 112:22, 25 113:2, 21 118:14 119:21, 25 120:7, 8, 12, 16, 17 122:17 125:23 126:13 127:7, 8, 10 144:14 167:3 ligands 111:19 127:12, 16, 24 137:9 light 105:6 lightly 140:4 LigPrep 115:14 118:14, 20, 23 limit 44:13 62:18 100:3 103:5, 12 limitation 124:14 limitations 43:3 49:24 53:21 64:7, 9 65:2 66:11 Limited 6:11 62:25 100:8 Line 41:19, 20 50:11 79:12 80:6 83:24 102:23 103:8, 16 104:14
--	--	---	--

124:10 135:23 136:1, 2 137:18 152:12 lines 24:4 38:25 104:17, 22 linker-warhead 44:3 46:7 47:11, 15, 23 48:11, 18 49:6, 13 50:23 51:13, 24 52:10, 19, 24 53:3, 17, 24 55:10 57:19 64:18 67:4 69:23 72:21 73:15 78:21 92:23 93:9 94:19 95:18 97:4 98:2 101:23 102:3 104:5, 8, 20 135:5 150:9 152:16 154:10 155:24 156:20 158:20 list 11:17 listed 36:7 47:2 52:3, 14 116:5 literal 124:13 literally 82:5 literally- speaking 83:17 literature 10:22 104:12 109:13, 17, 21 110:14, 20, 22 111:7 114:23 128:10, 11 little 20:21 LLC 1:9 6:12 LLP 1:17 2:2, 7	located 1:16 6:9 101:25 locations 69:14 103:23 lock 126:6 logic 165:20 long 94:14 122:20 123:13 124:17 125:4, 8, 12, 14, 24 129:13 long-time 17:3 look 12:16, 22 13:8 21:16 24:11 25:2 26:11, 23 31:17 55:22, 23 67:24 78:2 98:8 133:9, 10 136:6, 10, 13, 18 153:25 155:9 156:16 161:10, 13, 14 162:21 163:3 166:25 looked 48:1 97:10 120:11 126:19 136:11, 17 148:9 164:9 looking 21:18 29:14 30:23 33:16 42:6, 13 43:11 46:11 50:2 56:18 69:7 70:21 75:20 76:11 90:23 92:19 103:19 118:13 121:19 131:8 132:19 133:11 135:1 139:10 145:22 148:16 151:2 153:7	154:3, 22 156:13 157:22 158:1, 9 159:20 161:23 162:12 164:13 169:14 looks 72:16 148:6 150:10 loosely 82:12 83:11 lot 38:16 low 143:14 lower 72:15 Lu 29:8 lunch 88:23 lung 38:25 39:17 Lymphoma 3:12 4:6 8:7 24:16, 20 < M > M.D 1:13 3:3 7:2 MA 1:17 machine 115:1 Maestro 3:17, 20, 22, 24 18:14 20:14, 16 112:1, 3 115:8, 14 122:6 147:10 149:1 150:25 153:6 Maestro/Glide 112:16 major 16:20 21:23 29:11 37:13 making 33:14 35:19, 20 40:8 62:22 72:17 76:5 90:18	101:15 127:14 143:8 145:21 159:5 164:9, 18, 22 MANGES 2:2 manner 127:1 Manual 4:23 114:9 118:9, 12 manuscript 3:10 4:4 35:6 Marcotte 91:24 154:6 mark 24:12 73:23 74:10, 13 147:7 148:23 153:3 marked 7:15, 18 8:4 24:14, 17 74:1, 5 75:8, 13 85:16, 19 96:7 97:14 106:25 118:8 142:10 146:3 147:9 148:25 150:24 153:5 markedly 144:22 154:11 156:3 market 41:1 marking 74:4 mass 88:5 Massachusetts 1:16 6:9 170:2, 6, 10 match 150:8 matches 148:3 materials 11:13, 17 12:5, 8, 15 matter 6:10 40:3 94:2, 6, 16 102:9 121:8, 18,
---	--	---	--

24 122:1, 8, 10, 21 123:6, 20 125:15, 19 141:11 170:14 MD 14:6, 12 mean 9:23 17:18 34:11 37:22 51:16 57:3 59:21 67:12 74:16 81:19, 21 82:2, 8, 13 83:18 86:16 91:17, 18, 20 94:15 112:21 119:9 123:4, 10 125:13 132:21 157:2, 3, 15 158:18 159:9 160:5 meaning 69:22 80:14, 15, 20 82:20 83:3, 5, 7 87:21 means 80:8, 13, 16 83:22 144:9 meant 104:24 measure 32:23 37:10 132:23 142:25 measured 154:16 measurements 110:7 measuring 32:2 Mechanical 1:19 170:15 mechanism 38:14 40:8 medical 14:10 15:1 17:9	medicinal 38:22 39:8 72:22 75:17 meet 43:5 47:19 48:7 49:21 52:10 53:6, 20 60:6 65:2 67:8 84:6, 17 90:13 91:5, 15 meetings 12:9 meets 52:22 53:5 157:16 158:2 member 72:13 95:10 161:25 members 92:8 memory 26:7 mention 112:15 mentioned 20:7, 12 79:5, 6 164:25 mentions 26:12 menu 147:16 Met 12:5 92:24 MET477 166:20 method 37:19 159:18 methodology 109:23 MICHAEL 1:13 3:3 4:12 6:10 7:2, 7, 19 51:24 52:9, 24 67:3 93:9 95:18 97:4 98:1 micromolar 139:11, 15 140:4 159:16, 24	middle 10:21 31:19 44:7 97:17 million 122:19 125:4, 9, 10 millions 42:22 45:2 123:6, 10 125:21 126:12 mimic 167:3 mimics 167:2 mind 55:20, 24 73:6 81:6 155:19 159:13 163:24 mine 85:17 minimal 123:11, 12 minimized 169:8 minus 131:14, 16 133:3 134:8, 10 135:19 148:12, 22 149:8, 23 151:10, 16 153:13, 18 154:12, 13, 19, 20, 24 155:1 156:11 minute 26:22 71:13 146:15 minutes 10:22 94:3, 6 121:8, 18, 25 122:2, 5, 8, 10 123:6, 20, 23 124:1 125:15, 19 141:12 mis-selected 150:4 missing 145:24	misspoke 111:3 mistakes 13:4 Mister 20:3 MNK 25:5 28:18 29:25 30:2 31:8 MNK1 28:2, 8 MNK1/2 29:19 31:4 MNK2 26:16, 19 28:12, 25 30:20 mode 19:23 20:7 28:24 30:4 31:8 77:23 97:11 115:13 164:1 model 54:25 57:13, 25 91:19, 24 92:9, 12 93:3, 10 98:5 114:14 117:7 modeled 29:17 98:8 117:4 118:19 134:22 147:23 modeling 12:18 28:17, 22 29:2, 11, 14 30:6, 19 32:17 33:3, 9, 18 34:19, 20 35:12 36:21 37:3, 17 55:15 77:4, 11, 14, 19 79:2 88:15, 21 92:8 93:17 95:23, 25 96:1, 4, 5 97:9, 12 111:25 112:2, 3 114:17 115:9, 17 133:18
--	--	--	---

134:19 142:15 143:17 144:2, 4 145:12 163:7 168:23 modification 27:6 107:17 110:8 modifications 111:4 modify 21:12 modifying 34:17 100:14 108:11 moiety 50:25 56:8, 9 80:12 84:1 157:12 molecular 14:18 18:16 29:10, 14 32:17 33:9 34:19 35:3, 12 55:15 molecule 23:13 30:10 34:16 37:11, 22 38:1, 12 39:6 40:14 51:23 52:16 54:3 78:10, 19, 24 110:11, 13, 19, 22 127:5 158:25 165:14, 24 molecules 33:6, 13 34:1, 4, 7 40:15 52:20 55:16, 17 62:7 109:12, 17, 21 126:6, 7, 16 133:13 143:11 165:5, 15 moment 36:16 42:24 65:11 89:6 102:8	130:25 161:2 167:22 months 13:14 126:3 morning 6:2 124:15, 25 morphing 57:22 69:6 106:5 motivated 130:10 motivation 145:21 motivations 143:1 move 33:15 53:11 moved 100:9 mTOR 26:16, 17 multiple 20:2 35:4 124:7 mutant 23:17 39:21, 24 40:5 < N > N.W 2:5 name 7:5 19:18 20:4 22:9 names 20:16 nanomolar 26:18 32:13 138:13, 22, 24 139:2, 10, 11 nanomolars 140:8, 14 Nathaniel 29:7 35:18 38:22 native 12:18, 22 112:10 116:10 nature 23:14 near 23:8	necessarily 59:16 69:16 70:9, 22 95:7 137:23 161:16 necessary 37:2 45:21 47:16 124:9 need 24:12 46:4 47:8, 21 48:9, 16 51:10 53:14, 22 63:8 71:16 73:11 92:14 109:3 117:6 134:13 151:1 160:6, 9 161:13, 14 needed 57:19 163:3 needs 13:6 103:4 neglected 10:23 150:11 neighborhood 10:17 Neither 161:10 neutralize 127:3 never 37:2, 6, 24 45:21 83:14 95:16 126:10 160:1 nevertheless 143:3, 8 new 29:9 73:2 87:15 88:15, 16 100:15 105:21 107:5 108:11, 17, 18 109:4 111:6 122:6 night 10:21 nine 79:19	nitrogen 42:10 43:2 50:5, 7, 12, 14 52:4 60:24 81:3 166:14, 16 nitrogens 64:12 82:23 Nodding 14:4 non-covalent 28:2, 7 31:4, 8, 13 normal 39:22 North 2:9 Notary 1:15 170:5, 8, 21 notes 170:14 notice 1:14 168:15 noticed 13:6 127:3 169:4, 6 notion 35:20 Novartis 38:20 39:14, 24 40:1 novel 4:20 58:3 106:14, 23 107:5, 16, 25 108:21 109:2, 5 111:14 nucleophilic 153:1 NUMBER 3:8 4:2 5:2 8:16 17:21 38:21 39:10 44:25 45:5, 10 46:12 48:5 55:12, 16 62:25 75:2, 9, 13 77:10 102:24 103:2, 9, 16 104:14 112:5 121:5
---	---	--	---

122:13, 15 123:14 numbers 135:19 143:10 162:1 numerical 132:19 163:17 numerous 99:11	October 1:18 6:6 142:8 170:7, 18 offered 74:9 134:18 offering 84:8 114:3 OFFICE 1:1 94:15 Oh 21:18 66:9 121:21 129:14 157:22 Okay 8:13, 23 9:9, 15 10:3, 6, 13 12:15, 21 13:8 14:12 17:22 18:20 20:2 21:16, 22 22:24 24:1, 6 25:8 26:20 27:1, 2, 6, 10, 25 28:10, 19 29:14 30:12, 17 31:16 32:4, 22 33:2 34:5, 18 35:15 36:20 37:12, 21 38:4 41:12, 16, 22 42:2, 6, 13, 21 43:6, 19, 24 44:7, 17 45:11 46:11 47:18 48:6, 14 51:4, 19, 24, 25 52:5, 6 54:7, 9, 23 55:18 56:2 59:17, 25 60:5, 12 61:18 62:21 63:11, 12, 21 64:19 65:5 67:24 69:1, 7 70:2 71:24	72:6 73:18 76:22 79:8 80:8 81:12, 16, 19 82:7 83:16, 19, 22, 23 84:5, 12, 22 86:24 87:3 88:22 89:22 90:17 92:2 93:2, 3, 6 96:9, 14, 23 97:20, 24 98:5, 11, 16 99:10, 15 100:11, 17, 18 102:18, 23 104:18 106:2 107:9, 22 108:3, 15 110:3, 23 111:22 112:19 115:19 116:14, 19 119:2 120:2, 16 121:6 124:10 125:3 127:16 128:3 129:7 130:19 131:8, 13 132:21 133:2, 5, 16 134:1, 10, 21 135:18, 22 138:4 139:4 140:24 142:18 143:4, 9, 25 144:21 145:1 146:5, 9, 11, 12, 20, 21, 24 147:18 148:14, 21 149:10, 17, 21 150:16 151:1, 3, 8, 20 152:6 153:3, 13 155:11 156:5, 15 157:11	158:8 160:2, 17 161:17 162:11 163:12 165:23 167:1, 17 169:19 older 115:4 once 20:1 122:11, 21 123:3 124:2 oncologist 38:23 ones 71:11, 20 76:23 116:5 124:19 onstrum 114:13 operable 121:12 124:19, 20 128:14, 15 operations 35:11 operative 70:9 opined 70:10 133:25 opinion 34:10 41:23 52:7 62:24 63:13, 23 66:8 67:15 68:11 72:23 77:14 82:7 85:5 90:10 105:8 114:3 129:12 134:18 165:4, 25 167:4 opinions 68:16 98:11 117:21 118:1 optimization 107:18 optional 43:3 118:22 optionally 42:7, 25 50:5 66:15 79:22
---	--	---	--

optionally-substituted 50:3 options 20:11 113:2 118:23, 24 119:18 orally 5:4 oranges 137:25 138:1 orb 59:1, 11, 13 60:20 61:18, 25 65:20 80:11 83:25 90:4, 13, 18 91:6, 15 93:6 157:17 158:3 159:4 order 8:18 25:21 26:2 34:25 35:11 36:21 37:1 43:4 57:13 62:14 76:16, 24 78:24 92:9 93:3, 10, 17 94:20 126:2 161:12 162:13, 22 ordinary 68:12 77:16 95:8, 10, 14 142:19 organic 13:22 81:22 orient 108:25 orientated 157:12 orientating 91:8 159:7 160:7 orientation 104:4, 8 152:15 orientations 44:11	oriented 106:16 155:24 156:21 orienting 61:11, 21 62:13, 23 63:15, 25 71:2 75:15 90:6, 19 158:5, 19 orients 53:2 originally 150:22 osimertinib 22:10 23:19, 21 40:16 outcome 25:6 outlined 80:25 81:8 102:11 113:1 outside 81:13 82:2, 4 overview 119:11 Owner 1:10 2:11 oxygen 60:23 oxygens 64:12 oxyphenyl 78:20 < P > p.m 130:23, 24 160:25 161:1 167:20, 21 169:23 pack 95:14 package 20:12 packages 18:18 PAGE 3:2, 8 4:2 5:2 21:18 25:11 26:24 27:3, 14, 21 28:5, 15, 19 31:17, 18 32:16, 19 43:20, 21	45:24 46:23 48:9, 14 51:7, 18 55:25 58:19 61:15, 16 67:1, 14, 24 87:7 89:22 90:12, 24 92:3 96:10 97:16, 17 107:10 108:8 109:8, 9, 15, 16 118:10, 13, 17 119:2, 17 121:21 131:4, 17 138:16, 17 140:22 148:5 151:1, 21 166:5 pages 11:16 Pan 4:10 85:21, 22 88:1, 15 117:23, 24 Panel 29:21 118:23 119:4, 19 120:22 146:13 147:19 149:4, 17 paper 23:14 24:17, 18, 23 29:11 30:24 31:6 34:20 36:5 78:3 88:19 126:9 papers 15:17, 18 114:23 paragraph 21:17 23:5 25:19 26:12 27:16 31:7, 18 37:12 38:5 43:22 44:8 50:10 53:13 58:22 61:8	63:8 67:11, 24 89:11 98:13 99:3, 10 105:9, 11 106:12 107:19 108:6, 22 109:20 110:23 111:17 112:15 115:5 116:22 121:8, 22 131:8 154:3, 4 166:5 Paragraphs 85:25 115:22 parallelized 122:24 paraphrase 62:21 paraphrasing 63:9 parse 64:3 part 15:24 34:14 37:2 45:21 66:12, 17 90:14 106:4, 7 109:2 111:5 152:9 166:16 partially 81:10 82:17 96:15, 18 97:21 particular 13:19 24:4 30:21 33:24 54:4 58:5 62:6, 17 69:14 77:15 85:2, 3 97:5 102:7 128:15 133:1 134:9 135:22 136:16 137:7, 17, 19 138:12 139:8 140:5 143:20
---	--	--	---

145:15 148:2 150:10 152:19 162:12 169:15, 16 particularly 77:12 94:24 136:24 159:13 partner 145:24 parts 55:14 56:22 57:20 Patel 2:3 6:17 147:4 PATENT 1:1, 2, 4, 10 2:11 3:13, 14 4:13, 14 8:9 12:7 41:9 55:6 57:7, 8 58:8, 16, 23 65:16 69:2, 4, 9, 20 70:3, 16, 24 71:8, 12, 13 72:3, 6 73:6 74:2 76:6 79:10 80:18, 23 81:5, 13, 25 82:3, 4, 7, 9 83:3, 6 85:9, 11 89:15 90:11, 24 91:2, 5 93:24 95:7, 19 99:23 100:20 101:7, 10, 16 102:4, 5, 9, 10, 20 103:1, 19, 23 105:15 115:24 128:4, 15 131:9 138:5, 7, 20, 23 140:24 141:16, 19, 22, 24 142:11, 14 154:18 patients 37:23	105:16 PDB 98:9 pen 96:20 people 18:2 145:10 pepperidine 49:6 perform 35:12 59:22, 24 111:25 performed 27:15, 23 31:3, 11 32:1, 24 110:6 120:1 performing 32:22 period 17:15, 20, 23 41:1 peripherally 26:9 person 21:12, 14 33:17, 19 68:12 139:9 161:22 162:15, 21 personally 170:8 persons 142:19 perspective 16:23 21:9 pesky 169:13 Petitioner 2:7 6:16, 18, 20 Petitioners 1:7 PGR 7:10 41:13 PGR2024-00009 1:3 PH.D 1:13 3:3 7:2 14:6, 10, 13, 16 15:2 20:25 pharmaceutical 87:17	pharmacology 38:24 PHARMACYCL ICS 1:9 6:12, 22 7:13 9:18 10:10 phenoxy 157:11 phenoxyphenyl 44:3 46:5 47:10, 14, 22 48:10, 17 49:5, 11 50:21 51:12, 23 52:9, 16, 23 53:2, 16, 23 55:7 57:18 64:17 67:3 69:22 72:20 73:14 76:15 92:4, 10, 22 93:8 94:18 95:17 97:3 98:1 101:23 102:2 104:5 135:2 150:7 152:13 154:8 155:22 157:12 158:20 161:20 phonetic 19:19 29:6, 8 38:23 49:7 114:14 phosphate 62:5, 8 phosphoryl 62:5 phrase 59:6 physically 1:16 physicochemical 109:24 physics 160:20 physics-based 115:4 pick 74:16	picture 41:18 114:11 pieces 46:15 pinkish 146:23 place 62:11 64:17, 18 93:15, 16 124:3 130:9 places 56:6 67:20 104:19 plain 82:10 plainly 121:12 plan 130:13 platform 25:24 play 93:19 playing 93:21 please 6:13, 25 154:2 161:2 plus 75:23 132:13 pM 26:17 pocket 38:15 46:6 47:10, 23 48:11, 18 49:11 50:21 51:12 52:17 53:2, 16, 23 127:3, 7 135:2 154:9 157:13 159:1 pockets 127:4 point 33:23 34:17 38:1 83:16, 20 87:23 102:23 103:7, 8, 15 117:8 133:16 134:1, 4 136:25 148:16 158:11 163:7 Point.One 6:5 pointed 56:7, 14 Pointing 76:2
--	--	--	--

84:21	164:13, 15	54:3 104:7	precise 113:10, 25
points 35:4	165:4, 13, 18	109:25 111:15	precisely 9:21
poor 135:12	POSAs 132:1, 17	116:15 128:14	10:8 31:11
pop 19:8	pose 102:15	129:5, 17	45:9 71:15
portion 168:21	132:14 133:1, 6,	130:14 143:2	103:25 117:1
POSA 44:9	10, 11 135:1, 14,	164:15, 17, 24	122:20 125:25
53:13, 19, 25	16 148:4 152:4	165:5, 8, 9, 12	169:9
54:2, 5, 14, 18,	153:20 155:12,	possibles 129:11	precision 113:3,
23, 24 55:5	15, 21 156:16,	possibly 139:15	4 114:7, 15
56:2, 20, 25	22 161:14	postdoc 16:4	115:12
57:14, 16, 24	162:12, 14 164:1	post-doc 19:9,	predated 24:3
62:15 64:5	posed 84:11	12	predict 53:14
67:15 69:8, 19,	poses 132:20	post-docs 29:8	70:11 77:22
24 70:2, 10, 22,	136:6 152:7, 9	post-doctoral	114:20 133:20
24 71:4, 8, 18,	155:10, 19	15:5, 22, 25	134:19, 21
25 72:2, 13, 16	157:8 161:7	16:6, 10, 15	135:16 163:8
75:12 76:4	position 29:10,	17:10 21:1 29:6	predictable
77:2, 17 80:2,	19 35:23 49:10,	potency 55:10	67:18 68:4, 15
18 81:5, 24	12 50:20 62:4	potent 4:21	69:2 93:25
84:22, 24 85:3,	70:1, 3 72:18	26:18 40:8	predicted 78:9,
10 87:13 90:10	76:14 92:22	105:16 117:24	18
91:2, 10, 12, 21	117:15 119:22	138:9, 10 139:1,	predicts 162:14
92:3, 8, 18 93:7	135:3 152:20	3, 20 140:10	preferred 85:6,
95:2, 3, 5, 6, 10	positioned	159:13	7, 12 159:14
97:3, 25 99:4,	64:13 91:23	potential 24:8	premise 124:21
11, 23 100:1, 19,	152:14 154:9	26:21 36:22	prep 120:6
22 101:2, 6, 11,	155:23 156:1	37:3 41:24	169:7
12, 13, 17 102:1,	157:6 161:20	44:11 52:13	preparation
21 103:24	positioning	54:5 57:23	35:5 113:1, 2
104:9 105:13,	64:15 118:2	65:20 84:14	118:14 122:12
19 106:8	positions 52:16,	85:12 118:2	prepare 12:3
111:18 114:17	18 61:1 62:10	152:10	103:21 113:21
121:10 124:22	85:13 117:18	potentially	125:10
129:3 131:20	Posse 38:22	26:16 43:16	prepared 13:12
132:1, 3, 7, 18	possess 58:8	47:7 91:14, 17	115:13 118:19
134:19 135:1,	possibilities	156:25 157:2	162:5
15 136:2, 4, 10	126:12 129:5	potently 132:4	preparing 10:6,
140:17 145:1	possibility 25:21	powerful 18:10	14 11:3 12:10,
153:21 154:13	possible 29:5	105:7 107:15	12, 21 13:2
159:13 160:3	42:3, 18 43:14	144:17 163:4	
161:10 162:14	46:12 53:20	practiced 55:5	

pre-priority 56:7 PRESENT 2:11 17:16 100:5 103:23 119:22 presented 64:4 105:3 presenting 104:4 Presumably 36:7 presuming 137:15 pretty 95:14 previous 40:10 previously 7:15, 18 8:4 20:17 64:20 73:5 76:12 85:19 106:10, 25 111:9 127:24, 25 128:9, 11, 17 pride 143:10 primarily 18:14 prior 56:15 57:2, 9, 12 91:3 111:7 priorities 142:24 prioritized 145:2 154:14 Priyat 2:3 Priyata 6:17 priyata.patel@we il.com 2:4 probability 143:14 Probably 9:22 10:16 23:9 36:11 73:4 94:25 112:9, 10 113:19 135:9	problem 48:2 125:7 proceed 37:9 93:23 122:7 proceedings 1:18 P-R-O-C-E-E-D- I-N-G-S 6:1 89:5 process 8:20 92:25 116:22, 23, 24, 25 118:13 163:1 produce 116:9 produces 158:8 productively 131:22 132:4, 5, 8 133:7 134:14 139:5, 22 153:23 155:5, 13, 17 professional 17:4 program 77:22 163:15 programs 18:15 20:16 Project 3:18, 21, 23 23:4, 22 24:6 26:7, 9 29:9 35:10, 18 37:8 38:15 39:11 126:4 127:19 128:20 147:10 149:1, 13 150:25 151:4 158:15 projects 17:21 23:4 35:1, 9, 17 promising 72:16	136:17, 18 proof 40:21 propanamide 168:17 proper 62:11 159:5 properly 52:18 76:14 155:23 156:21 158:19 161:20 properties 109:24 propose 72:17, 20 73:13, 14 proposed 39:23 73:7, 13, 15 proposition 107:4 145:10 protectively 134:23 protein 16:6, 10 17:5 99:16 111:19 113:1 120:6 122:12 152:18 169:7 proto-oncogenes 16:20 proud 16:17 proved 170:9 provide 9:16, 19 12:25 25:23 35:15 98:17, 22 114:6 116:9 provided 12:17, 25 13:14 24:8 68:16 112:10 116:11 146:11 provides 60:2 65:19 144:17 providing 58:25 144:14 160:19	provisional 141:25 142:5 PTAB 63:21 Public 1:15 3:9 4:3 170:5, 8, 21 publicly 99:16 publish 36:5 published 23:14 36:6 39:2 126:10 141:19 pull 9:24 pulling 122:6 127:16 puristic 164:3 purposes 10:18, 19 83:1 93:5 114:18 120:8 127:14 pursuant 1:14 pursue 136:17, 19 163:9 push 115:2 put 40:12 42:24 44:24 45:5, 10 56:23 75:1, 3 93:20 124:18 135:2, 8 138:15 140:4 puts 53:1 < Q > QL-X-138 27:4, 9, 11, 15 28:1, 7, 11, 18, 24 30:20 31:4 32:5, 11 qualitative 114:8 qualitatively 30:13 158:13 quality 132:24 question 9:2, 3, 7, 9 19:15
---	---	---	---

42:25 43:9 48:13 49:20 51:9 52:21 53:8 59:25 63:3 66:19, 25 68:7 70:8 72:12 74:7 82:1 83:4 84:10 86:15, 16, 17 90:15 93:2, 3 96:2, 3 97:24 100:12 102:12, 14 103:2, 4, 8, 9, 15 105:24 110:16 149:3 156:14 157:25 questions 19:8, 14, 20 20:8 74:19 79:8 83:21 103:13 118:6 166:4 167:12 168:6 169:18 queued 122:21 123:3 quick 79:8 118:6 167:13 quickly 90:2 163:24 quite 20:19 26:18 38:16 77:8 quote 107:14 121:3 132:24 quoting 94:10 106:18 < R > rabbit 10:23 raf 126:23	127:2 ran 120:6 range 136:13, 15 138:21, 24 139:11, 12 140:4 157:7 164:9 ranges 138:23 Ras 126:7, 14, 16, 17, 20, 21, 22 127:1, 3 Rases 126:25 raw 91:9 reach 30:22 48:5 57:20 reaching 117:25 react 49:13 152:24 reaction 52:19 read 15:17, 18 26:22 31:6 68:5, 6 71:8, 12, 13 83:14 88:19 104:2 106:15 107:19 108:24 109:20 119:14 160:19 readily 54:6 65:1 70:11, 14 91:25 101:2, 12 readily-doable 55:15 reading 28:4 32:20 55:6 61:14 64:5 69:8 70:2, 23, 24 72:3, 6 76:6 80:18 81:24 82:10 87:9 90:10 91:2	99:23 100:19 readout 31:13 Ready 89:10 real 136:21 realized 169:13 really 74:6 82:25 122:9 125:12, 13 130:4 137:3 realm 95:6 155:5 real-time 33:1 reason 9:15 47:4 83:11 85:2 reasonable 30:7 80:3 120:11 136:7, 12, 13 reasons 48:3 re-assorted 100:10 reassure 75:18 recall 15:3, 17, 23 16:3 19:20 81:14 121:4 125:25 168:6 receive 13:25 14:20, 25 15:20 received 131:10 receptor 22:5 113:21 119:3, 7, 19, 20, 24 120:1, 9, 14, 15 144:16 recited 41:17 recognize 24:23 55:7, 9 57:17 62:15 65:3 91:11 132:3 145:23 165:9 recognized 16:19 101:13	131:20 132:7 153:22 165:25 recognizes 68:2, 8 recognizing 165:11 166:2 recollection 33:21 57:6 98:7 122:25 reconnected 100:10 record 6:3, 14 7:6 36:13, 14, 15, 18 65:8, 9, 10, 13 66:21 74:8 75:6 89:1, 2, 8 130:22, 23, 24 131:2 160:25 161:1, 4 167:19, 20, 21, 24 169:22 170:13 red 96:20 redirect 103:10 redock 122:4 refer 22:4 44:18 67:20 81:10 106:13 108:20 111:17 reference 22:1 23:5 58:22 89:14, 17 106:18, 20 107:7 116:2 133:17, 22, 24, 25 134:1, 4, 7, 10 135:19 136:23, 25 137:4, 13, 17 148:16 154:19 158:11
--	---	--	---

referenced 90:3 98:9 99:15 referred 85:4 106:12 referring 68:9 96:17 98:19 105:20 108:22 119:8, 15 122:9 151:24 154:5 refers 46:18 79:14 82:21 refinement 14:19 18:18 reflected 140:2 refocus 102:15 regard 82:15 regarded 30:8 regarding 41:23 regardless 36:25 162:18 region 61:11, 20 63:14, 24 67:17 68:3 69:11 70:6 71:1 75:14 90:6, 19 91:7 109:5 156:18, 24 158:4 159:6 160:7 166:9, 12, 20 167:8, 9 regions 120:14 regular 35:2 regulated 16:22 regulation 17:5 reincorporated 120:8 reiterate 137:16 related 137:9 142:5 relatedness	30:15 relates 95:7 relationships 95:13 relative 64:15 137:8 relatively 13:11 29:23 123:25 relevant 11:25 12:6, 8 56:6 120:14 144:14 relied 11:13 117:25 rely 31:12 37:3 87:14 107:3, 10 134:16 161:8, 24 relying 101:17 remember 9:21 10:8 90:8 112:7 116:6 120:25 122:19, 20 127:20 remembering 20:10 26:8 121:2 126:16 remind 71:14 79:11 108:13 141:18 removed 120:7 repeat 16:8 48:13 51:8 86:17 90:14 110:16 replaced 106:22 107:24 report 11:14 77:18 113:24 133:2 144:22 152:22	reported 131:13 138:12 148:15 153:18 reporter 6:5, 24 8:24 32:7 75:10 78:13 reports 138:21, 23 represent 146:9 represented 59:1 119:24 reproducibly 152:14 requested 32:7 78:13 required 44:1, 10 46:20 49:5, 8, 10, 19 79:2 requirement 53:6 requirements 47:19 48:8, 15, 25 49:22 51:8, 10, 15, 17, 21 52:11, 15, 23, 25 53:7 62:3, 6 64:22 67:9 68:20 90:4, 13, 17 91:5, 15 92:24 93:5 101:22 157:17 158:2 159:5, 8 reread 12:6 research 15:16 16:15 38:23 resemblance 87:24 residue 22:25 23:7 166:19 residues 25:16 64:14	resolution 144:13 resourced 40:22 resources 122:22 123:14 125:6 respect 12:18 13:20 14:1, 25 16:24 19:12 21:15 23:22 24:7 28:11 31:20 48:9 49:9, 18 51:20 58:17 66:12, 13 76:5 92:2 95:11 135:24 158:10 160:2 163:2, 4 respond 103:12 response 63:10 responsive 102:17 restricted 59:16 restrictive 60:2, 10 result 25:8, 9 resulted 105:15 resulting 156:2 results 25:10, 11 31:3 32:11 44:12 113:25 138:6 140:16 142:23 143:18 144:19 152:11 162:22 Retained 4:1 9:18 10:10 retroverso 147:2 reversible 35:25 86:25 150:14
--	---	---	---

review 10:3 13:1 reviewed 11:17, 23 12:5, 6, 7, 15 30:24 31:7 85:22 reviewing 11:20 26:25 27:17 28:16 74:25 86:3 119:16 revisited 35:4 revisiting 33:17 145:17 reward 130:12 ribose 62:9 RICE 13:16, 18, 22 rich 104:9, 10 105:7 106:4 right 10:1 13:1 14:7, 10 15:4, 6 20:10 22:12 25:10, 17 26:8, 21 27:7, 13, 15, 19, 23 31:2, 15 32:24 34:22 36:23 38:7 39:12 40:13 41:17, 25 42:16 44:21 46:13 47:3 51:5, 18 53:10, 12, 17 55:20 57:9, 15, 25 58:23 59:7, 10, 19 61:25 62:7 65:20 66:1 68:4, 9, 11 69:3 70:12 71:2 72:4, 14 73:9 75:7, 25 76:1 77:5, 17	79:3, 10, 16, 20, 23 80:9, 13, 17 81:17 82:9, 25 83:24 84:3, 18 85:23 86:1, 20 87:5, 7, 8, 15 88:2, 6, 10, 13 89:15, 17, 25 90:21, 25 92:11 93:4, 6, 20 94:3, 7 96:9 99:10, 13, 17, 21 100:13, 19 102:18 103:17, 18 106:14 107:3, 6, 18 108:4, 7, 12, 20, 21 109:1, 6 110:23 111:16, 20, 23 112:2, 19 113:6, 14 114:4, 7, 14 115:9, 14, 20, 24 118:14 119:7, 17 120:18, 25 121:2, 24 124:15 125:3, 12, 22 128:17, 22 129:19 130:4 131:11, 23 133:3, 22, 23 134:5, 8 135:20 136:24 137:2 138:7, 13 139:1 140:14 141:4, 7, 14, 24 144:24 145:4, 7 146:2, 25 147:1, 16, 23, 24 148:12, 17 149:5, 8, 10, 12 150:8, 16, 20	151:6, 10, 12, 16, 18, 22 152:4 153:7, 8 154:20, 24 157:22 158:6 159:7, 10, 19, 22 160:10 161:9, 15 162:3, 6, 7, 16, 23 163:5, 10 166:4, 11, 21 rigid 152:17 ring 42:8, 9 43:1 50:4, 6, 7, 13 52:3, 4 56:10, 12, 13 66:16 79:14, 16 100:5 166:13, 14, 17 ringed 81:3 96:23 rings 79:18 80:16 81:1, 11 82:6, 24 83:22 84:7 89:25 106:6 rise 169:2, 10 RMSD 163:25 RNS 117:18 roadmap 23:18 role 29:11 39:15 40:20 70:1 root 163:25 rotamer 152:23 rotatability 157:9 rotatable 152:16 Roughly 12:13 104:17, 21 159:15	routine 37:9 routinely 121:10 Row 147:19 149:18 151:8, 15, 25 152:3 153:10, 11 rows 149:4 RPR 1:20 170:4, 20 rules 8:23 run 122:12 137:7, 19 138:2 140:25 148:20 149:25 150:10 169:16 runs 39:8 137:22 169:7 ruthenium 116:8 rutinib-like 55:17 < S > SARK 16:19 sat 130:15 satisfactory 170:9 satisfy 46:3 47:8, 21 48:25 52:24 53:14, 22 66:11 68:19 satisfying 159:8 saturated 81:11 82:17 96:15, 18 97:22 saying 8:25 33:10 43:24 52:22 53:5 67:10 97:21 98:21 122:1 129:24 132:12 136:20 155:13
--	---	---	--

161:8, 21 162:10, 13 163:7 164:21 says 21:22 25:20 26:6, 17 28:9 32:3 80:11 83:24 109:12, 20 118:21 119:18 138:20 scaffold 23:21 25:23 26:3 38:19 39:14 54:7, 11 55:1, 3 56:4 57:1, 3, 21 58:3 62:17 64:25 65:24 66:1, 3 67:7, 21 68:22 69:6, 7, 10, 12, 20, 21 70:4, 11 76:6, 8, 19, 25 77:13, 15, 24 78:8, 17 86:12, 13, 19, 25 87:4, 5, 25 88:16 89:20, 24 90:11, 23 91:4, 9, 10 92:2, 20 93:4, 14, 18 94:5, 12 95:19, 24 96:6 97:5, 13, 22 98:6, 8, 12, 16, 22 99:21, 24 100:3, 7, 8, 20 101:19 104:22 105:1 106:5, 14, 23 107:6 108:1, 11, 16, 19, 21 110:18 111:5, 6, 10, 13, 14 128:5	135:3 150:8 152:14 155:25 157:16 scaffolding 56:3 scaffolds 36:3 56:16 68:21, 22, 23 69:25 76:17 79:6 87:8, 14 99:13, 17, 20 107:17 109:3 110:6, 17 128:9, 10 scanning 87:8 SCAR 5:7 96:8 school 14:10, 15 15:1 17:9 Schrödinger 18:14 20:14, 15 112:1, 3, 6 115:8 scientists 19:1 31:14 scope 41:25 42:3, 19 44:14 45:18 52:2, 8 60:5 66:4 67:7 124:13 164:23 165:5, 14 score 131:13 132:13, 21, 22 133:2, 6, 9, 12, 19 134:7, 13, 17 135:12, 24 136:9, 23 137:4, 13, 17, 20 144:22 148:11, 14 149:7 151:15 153:13, 17, 20 154:11 155:8 156:3, 7, 10 158:9, 17 161:9, 11, 13	162:7, 16 163:17, 20 scores 131:9, 19, 25 132:1, 19 134:11 136:11 155:10 164:5 169:2, 5, 11 Scott 39:8 Scratch 3:18, 20, 22 122:5 123:23 125:18 147:10 149:1 150:25 screen 39:16, 23, 25 40:2, 4 87:19 88:21 122:18 123:6, 10 124:23, 24 screened 87:21 screening 14:1, 21, 24 15:21 16:1, 4 18:13, 15, 22 21:6 39:25 126:12 127:7, 15, 17 screenings 126:13 screens 125:23 Screenshot 3:17, 20, 22, 24 146:6, 10 147:10 149:1 150:25 153:6 script 161:18, 21 162:5, 18 scripting 124:6 se 38:8 69:15 104:23 105:1 136:9 search 10:22	searched 25:22 26:4 second 31:18 72:20 75:4 85:15 87:10 90:14 107:14 109:11, 16 137:19 146:17, 18 149:3 seconds 122:25 section 25:11 28:13 81:3 94:9 107:10 109:2 119:3 120:16 see 7:21, 25 8:11 11:19 14:9 19:21 20:1 21:22 22:2 24:21 25:25 27:2, 22 29:20 31:21 41:19 44:15 46:9 48:19 50:17 61:13 73:19 75:20 76:1 78:3 82:14 87:7 90:12, 24, 25 92:3 96:12 105:17 107:12 108:1, 8 109:14, 17 110:1, 9 117:6, 9 132:1, 10, 14 133:19 136:4 140:21 142:1, 3, 4, 7 144:1 145:14 146:5, 7, 13, 20 147:19 148:21 149:3, 15, 19
--	--	---	---

150:3, 7 151:1 153:25 155:18 156:17 157:16 162:15, 23 seeing 30:23 seen 106:10 114:1 121:5 128:10, 11 143:12, 17, 19 159:15 select 84:25 85:3 88:15 163:3 selected 84:1 selecting 84:22 87:25 118:23 Selective 4:8, 21 23:17 40:3 sense 33:4, 9 34:6 68:23, 24 73:3 77:12 81:4 94:17 114:8 162:22 164:10 sentence 25:13 26:13 32:15 107:14 109:11 separate 137:22 148:20 sequence 32:25 series 24:8 89:18 118:16 serve 93:4 servers 124:7 set 30:14 54:2 74:17 76:20 83:21 119:24 125:9 161:18 169:20 170:12, 17	Setting 76:19, 23 119:9 165:10 166:2 seven 8:18 76:24 79:19 82:15 84:5, 13 shape 61:4 Shooting 144:8 short 39:1 41:7 122:15 shorthand 73:11 shot 74:18 show 104:20 105:3 152:3 Showalter 42:21 44:1 46:1 Showalters 124:11 Showalter's 12:7 41:23 43:17 47:5 48:2 showed 126:14 shown 84:3 89:22 96:11 132:14 151:21 156:22 shows 109:4 152:25 side 76:21 146:13, 16, 20, 21, 22, 25 147:2, 11, 18 152:2, 23 sides 151:2 signed 10:15 significance 137:4 significant 41:13 129:1, 6 signing 10:4	similar 23:20 99:6 117:18 133:13 144:13 similarity 117:20 similarly 56:16 113:25 117:14 simple 8:23 164:2 simpler 115:4 simply 73:12 163:24 simulated 14:18 simultaneously 49:12 single 52:7, 22 sit 31:1 70:21 72:10, 11 92:6 site 23:2, 8 49:16 51:2 59:2, 6, 12 60:7, 14 61:3, 5 62:11 68:19 73:1 119:23 154:8 sites 25:17 Sitting 44:21 45:1 60:15 76:10 situation 24:7 Six 8:18 79:18 size 44:17 45:12, 18 47:18 119:23 120:12 skill 68:12 95:4, 9, 10 139:9 142:20 170:16 skip 115:22 slightly 168:11 Slow 32:8 50:9 94:24	small 114:13 124:1 127:3, 5 smoother 9:4 so-called 23:13 126:21 software 14:2, 22 15:22 16:2 18:14, 16, 17, 21, 23, 24 19:3 20:11, 14, 15, 18 21:6, 13 112:17 113:5, 10 114:5, 19 135:8 142:15 161:13 sold 41:1 solely 37:3, 17 132:19 134:16 161:10 163:19 somebody 34:13 124:5 somewhat 82:11 Song 29:8 sooner 9:12 Sorry 16:8 21:18, 19 24:12 30:1 31:18 32:8 34:19 41:20 43:20 46:17 48:13 51:22 54:25 61:14 63:20 65:25 74:23 76:17 83:18 84:12 86:17 87:9 90:14 103:18 105:1, 10, 12 106:19 109:15 110:16, 25 138:19 142:7 146:15,
---	--	--	--

18 154:22 155:13 157:22 sort 30:13 35:11 77:4 79:25 82:18 145:9 158:9 169:8 sounds 114:4 123:17 Southwestern 14:7 SP 115:12 space 122:15 167:9 speak 19:11 20:3, 21 141:8, 18 143:1 165:21 speaking 6:4 25:10 speaks 80:25 species 48:7, 24 49:2 specific 15:18 19:21 26:7 33:21, 22 34:24 49:6, 24 54:7 55:19 57:3, 17 58:8 62:2, 19 64:6, 8 65:1, 24, 25 67:21 70:8 78:8, 17 80:23 81:15 82:14 83:12 97:13 98:19 100:1, 22 101:22 102:6 103:9, 22 106:9 110:11, 17 112:9, 25 113:9 114:23 117:6 119:12 135:16	139:23 143:22 166:19 167:6 specifically 17:24 18:6 101:16 107:3, 9 131:25 152:18 165:11 specification 55:6 56:11 57:17 65:19 79:10 80:4 82:11 85:9, 11 93:24 101:3, 22 103:19 104:2, 6 105:6 141:21 165:7 specification's 68:1 specificity 55:8, 10 specifics 58:17 113:19 137:21 specified 49:22 52:25 157:18 158:3 specifies 56:11 specify 48:8 specifying 51:6 118:24 spectrometry 88:5 speculating 130:5 speculative 29:23 30:9, 19 spend 145:11 spending 141:13 spent 10:14, 20 12:12 169:5 spite 117:15	Spleen 5:5 spot 36:11 squared 163:25 SS 170:3 S-stereoisomer 116:8 stabilize 127:6 stabilized 126:19 staff 19:1 stage 40:22 162:25 standard 20:18 79:25 91:13, 22 113:3 115:12 start 9:4 10:6 43:24 78:15 92:15, 18, 24 93:13, 17 123:23 started 10:9 Starting 31:22 41:17 122:5 125:18 starts 98:12 107:10 State 1:16 7:5 105:10 115:7, 11 131:19 stated 90:20 93:5 153:21 STATES 1:1 27:25 station 94:16 statistical 164:8 Stay 31:18 167:16, 17 staying 124:10 Stenography 1:19 170:15 stereotype 170:14	step 75:16 83:19 113:1, 2 120:22 128:23 steps 45:17 112:25 118:16, 20, 21 119:1, 6, 8, 12, 13, 15 122:7, 12 130:14 stereocenter 117:10 stereochemistry 117:16 stereoisomer 117:3 steric 44:12 135:7, 10 sterically 49:15 61:2 159:1 stick 96:2, 3 149:2 sticker 24:13 Sticking 17:22 26:11 54:23 stopped 41:7 straightforward 55:12 144:19 164:3 strand-like 126:18 strategy 107:22 streamlined 120:23 Street 1:17 2:5 strict 81:6 82:19 83:19 84:6, 17, 24 strictly 46:16 80:25 strictly-speaking 82:16 83:17
--	--	--	--

strike 12:16 21:3 48:22 76:18 155:14 strikes 129:22 struck 117:14, 20 structural 15:5 16:23 18:18 23:20 30:15 49:2, 14, 24 50:16 53:21 57:18 59:16 60:3 62:2, 6 63:16 64:1, 6, 8, 22 66:11, 14, 17 67:8 77:19 87:23 93:14, 22 101:21 104:11 105:8 106:22 107:25 110:7 121:14 structurally 133:13 structurally- expected 139:19 structure 16:18 17:5 23:6 27:3, 12 28:12 32:18, 24 34:1 36:1 41:16 42:6 46:19 47:20 50:10, 20 51:19 52:2, 8 54:8, 12, 15, 19, 25 55:1, 19 56:3, 4, 10 57:1, 3, 13, 14, 25 58:9 59:1, 8 60:13, 25 62:4, 16 64:6, 23 67:11 68:9 70:5, 14 72:15,	16 75:18 80:16 85:3 86:8, 9, 19, 21, 25 87:4, 5 90:12, 23 91:4, 23, 24 92:3, 12, 19, 20, 21 93:1 94:5 95:12, 19 96:10, 18, 23 97:11, 13, 17 98:9, 17, 24 99:21 100:1, 17, 23 101:6, 14, 18 102:21 104:13, 16 105:15, 21 109:5 110:12, 17, 18 119:20 120:6, 15 121:13 126:14 136:17, 18 144:13 151:9, 20, 21 152:18 154:6 158:21 165:8, 12 166:7 169:1 Structure3 146:14 147:20 148:1 149:5, 18, 21 Structure8 151:15, 25 152:3 structures 17:7 26:5 34:17 35:24 41:24 42:3, 18 43:14, 17 46:13 48:6, 23 49:20 55:13, 14 56:7 58:3 59:21, 23 60:6, 19, 20 62:18, 19, 25 65:2, 24, 25 66:3 67:2, 7	68:12, 18 69:8, 10, 12, 15, 20, 21 70:18, 19, 21, 25 71:5 72:1 77:24 78:2, 8, 10, 17, 19, 25 81:3 82:21, 22 83:10 84:3, 5 87:15 92:23 99:12, 17, 19 100:5, 13, 14, 15 101:3 104:20 111:20 114:1, 2 121:11 122:14 124:12, 22 127:9, 11, 24 128:5, 16, 17, 21, 24 164:7, 17 169:8 stuck 19:23 20:7 student 14:16 studied 40:3 studies 38:24 55:15 study 13:19, 20, 21 14:13 15:10 16:6, 10, 13, 24 25:3, 6 28:11, 17 32:17, 23 33:9, 20, 24 34:20 35:5, 12 studying 17:4 40:7 subject 55:13 102:9 111:12 subjected 88:4, 9, 12 submitted 7:12 10:15	sub-portion 46:18 subsections 119:12 subsequently 39:2 40:3, 8 88:21 substituent 44:13 50:23 62:10 101:23, 24 108:18 111:10 166:13 168:17 substituents 44:2, 10 46:21 50:18 61:12, 22 62:23 63:15, 25 64:12 68:22 69:22 70:4 71:2 75:15 76:25 77:3 78:11, 20 79:1, 5, 7 90:7, 20 91:8 93:15, 16 102:7 106:6 160:8 substitute 76:13 132:25 substituted 42:8, 25 50:6 66:16 69:15 70:20 79:23 80:12 84:1, 23 85:14 substitution 46:19 72:18, 19 substitutions 43:3 74:17 94:19 substructure 59:19 99:5
--	---	--	--

substructures 68:2, 8 100:9 SUFFOLK 170:3 suggest 28:1, 6 29:15 suggested 30:6 suggesting 123:4, 5 124:21 suggests 82:6 157:5 suitable 25:24 101:14 Suite 2:5, 9 sum 21:8 summer 9:21, 22, 23 superfluous 118:4 superimposed 35:24 superimposing 92:21 117:18 supervised 18:3 support 107:8 supposed 136:8 150:18 sure 10:19 15:17 25:7 26:23 29:5 35:16, 17 37:18 41:5 54:10 55:24 56:4 66:10, 25 73:10, 21 74:21 81:14 88:19, 24 92:17 96:22 103:24 106:16, 17 107:20 111:2 113:18 116:11, 17 117:2	125:13 130:8 132:16 137:12 149:25 166:25 surface 126:20 suspect 169:9 swap 68:21 99:24 100:20 swapping 55:3, 13 57:21 64:25 98:12, 16, 22 99:12 100:3, 7 101:20 106:5 107:11 108:23 swear 6:25 switch 36:11 sworn 1:15 170:12 SYK 5:6 symmetric 127:4 synthesis 4:20 5:7 96:8 109:12, 16, 21 140:19 141:7, 13 142:21 145:3 154:15 synthesize 140:25 142:22, 25 synthesized 73:4 88:4 145:6 synthesizing 88:1 145:11 synthetic 109:23 110:8 system 43:1 50:4, 6 66:16 < T > tab 119:18 147:4, 5 153:3	table 11:24 12:2 tabs 120:17 Tagrisso 22:16, 20, 24 23:4, 21, 23 24:7 38:6, 8, 14 40:17 TAK-659 5:4 97:15 take 9:11, 24 14:20 15:20 21:16 24:11 25:2 26:11 36:12 42:23, 24 54:7 55:21 56:5 57:16 65:6 69:24 70:13, 22 71:13 77:11 80:19 81:4, 5 82:20 83:18, 19 88:22 94:5, 14 103:3 122:13 123:2, 13 124:17 125:4, 9, 12, 24 128:19 129:6, 13 130:19 141:11, 23 147:6 155:8 157:24 160:22 167:14 takeaway 31:7 Takeda 39:4 taken 1:19 14:23 56:22 95:16 97:2, 25 170:14 talented 95:13 talk 19:8 51:19 116:22 154:16	talked 38:4 129:14 talking 18:21 25:14 36:20 46:23 51:22 59:21, 23 65:15 94:8, 10, 12 100:12 119:14 123:1 141:15 143:23 159:21 162:11 165:15 talks 26:15 37:13 87:8 target 23:7 25:15, 16 33:13 34:16 111:19 targeted 29:18 targets 23:2 87:20 taught 105:15 teach 81:22 85:9 teaches 85:11 teaching 70:17 81:20 teachings 104:9 team 34:14 72:13 77:17 92:8 95:11 161:25 162:5 technical 113:16 techniques 64:24 69:5 tell 72:12 143:6 154:2 155:4 telling 148:19 tells 137:5, 6 155:12, 16 tendered 73:22 75:11
--	--	--	---

TERI 1:15, 20 6:5 170:4, 20 term 80:5 terms 90:4 133:18 137:1 test 34:8 91:19 144:2 tested 33:7 73:5 testified 168:10 testimony 9:16, 19 34:10 170:11, 13 testing 77:4 145:4 154:15 tests 27:15 32:1 88:7 Texas 14:7 Thank 65:5 167:12 the,"Molecular 28:22 thing 20:1 129:8, 10 136:10 137:6 157:22 164:15 165:10 166:3 things 9:4 34:2, 4 40:21 56:17 82:15 94:8 124:7 126:23 136:7, 11, 12, 13, 15 139:25 140:3 143:6, 12, 13 150:17 158:18 159:2 161:22 163:1 164:8 think 11:25 16:21 19:21 20:9 30:21 33:8, 11 35:14	39:7, 19 40:20, 24 42:23 46:22 48:3 49:23 52:13, 14 53:25 54:4, 5 56:7 60:2 62:1 63:2 67:14 69:4, 24 70:13, 22 71:18 73:7, 15 76:10 77:8, 10 80:2, 18 81:18 82:10 83:7 84:10 85:2 87:16 91:10, 13, 21 94:17 95:2, 6, 9, 13 97:20 98:12, 21 101:10 102:19, 22 103:16 104:24 107:14 108:22 111:3 112:8 114:8, 21 122:5, 11 123:20 125:17, 20 126:2 127:21 128:18 130:16 131:24 132:17 133:11, 24 136:4, 20 137:3, 9, 16, 24 139:7, 24 141:16 144:8 147:6, 25 149:4 150:5 152:12 153:14, 16, 21 157:5 158:23 159:11, 23 160:5, 11 161:16 162:25 163:14 164:21 165:6 166:20 167:1, 15 168:25	thinking 10:20 33:5, 13, 17 34:7 124:11 147:1 third 23:13 52:15 72:21 thoracic 38:23 thought 20:13 30:24 36:2 45:9, 14, 22 66:20 76:11 122:3 127:5 129:15, 18 130:1, 3, 11 163:22 thousand 140:8 thousands 44:22 45:2 three 12:11 16:18 49:16 51:7, 10, 15, 17, 20 52:11, 25 60:22 64:11 126:3 149:4 throughputs 124:8 time 6:7 10:12, 13 12:12 13:13 17:15, 20, 24 18:5 20:19 33:24 34:22 36:17 37:1 39:17 41:2 51:9 65:12 83:19 87:13 88:25 89:7 95:16 97:2, 25 122:16, 22 123:1, 11, 12, 16, 24 124:14 125:8, 12, 14	128:20 129:6 130:21 131:1 141:13 145:11 161:3 167:23 169:5 timeframe 142:13 times 8:15, 17 18:8 today 7:9 8:24 9:16 31:1 45:1, 16 72:11 76:10 92:6 114:6 142:16 Today's 6:6 12:3, 21 told 118:4 138:9 143:14 tool 21:14 34:15 111:23 120:24 toolkit 106:8 toolmaker 21:14 tools 14:16 17:20, 23, 25 18:6, 8, 9, 12 34:2 35:1 76:12 91:13, 22 92:8 101:12 111:18 115:4 129:9 145:15 162:9 163:4 toolset 115:3 top 27:21 28:5 45:24 48:8, 14 61:15 65:21 75:7 79:12 96:11 112:7 120:25 146:5 147:15, 16 149:13 151:5
--	--	--	---

152:8 153:8 157:7 topics 36:11 Torin2 26:12, 21 27:6, 8, 12 totality 162:15 trackable 144:12 tracked 10:17, 18 trade 91:13, 22 TRADEMARK 1:1 trainees 18:7, 25 training 14:1, 15, 21, 25 15:21, 24 transcript 3:25 transcription 1:20 170:15 transfer 62:5 transferred 62:8 treat 37:23 treating 159:18 treatment 102:11 tremendous 68:17 TRIAL 1:2 77:4, 7 trials 38:3 trick 46:22 tried 34:23 44:19 47:25 60:9, 17 125:2, 11 129:15 137:10 138:1 165:17 trivial 122:13 161:18 true 58:4 100:6 158:23 160:9,	11 161:16 170:13 Trust 6:5 truthful 9:16 try 9:11 21:8 32:9 45:10 48:5 51:4 55:18 62:21 63:5 66:25 93:2 102:15 130:15 148:21 156:15 trying 20:3, 9 22:10 41:7 46:22 53:8 94:23 100:25 117:19 129:4 139:24 163:6 164:15 165:21 169:5 turn 27:20 50:1 74:12 168:14 turned 37:19 140:20 turning 169:12 two 25:16 39:4 50:4 52:14 80:9, 13, 14, 16 82:6 83:18, 22 84:7 89:24 94:8 126:3, 6, 16, 24 127:4 137:22 151:2 152:6 154:23 156:17 169:8 type 23:17 39:18 107:5 types 21:5 typical 79:25 87:13	typically 18:2, 22, 23, 25 33:24 37:7 40:20 41:6 60:22, 23 61:3 139:9 Tyrosine 3:15 4:9, 15 5:6 16:16 22:7 59:3, 12 60:8 142:11 < U > U.S 1:4 3:13 4:13 142:5 U.S.A 6:11 Ultimately 39:6 77:1 111:13 unapproved 41:6 undergraduate 14:3 undersigned 170:8 understand 7:9 9:5, 7 12:17 28:10 34:3, 9 41:12, 22 42:11 43:9 51:6, 16 68:13 69:9, 19 70:2, 11 71:9, 19 72:3 75:12 79:9 80:8 83:1 86:24 90:11 91:4, 14 97:11 103:25 113:16 115:19 117:19 119:15 124:11, 16 128:3 136:20 147:25 156:23 160:4	161:7 163:6 169:6 understanding 16:22 40:25 56:19 66:6 83:2 84:16 111:8 152:10, 21 156:14 understood 44:9 67:16 99:4 undertake 129:4 undertaken 48:4 undertaking 129:2 undesirable 109:24 unelaborated 70:20 unexpected 109:23 unfavorable 135:14, 25 unit 126:15 UNITED 1:1 universally 77:21 134:24 University 14:7 81:20 unknown 109:12, 17, 21 110:13, 19, 22 unquote 132:24 unsaturated 56:13, 16 unsubstituted 69:13 91:9 updated 13:12 upfront 109:22 up-to-date 121:4 USA 1:6
--	--	---	---

Use 3:14 14:16, 17 15:15 18:21 20:11, 18 22:20 53:13, 19 54:1, 8, 24 69:25 73:11 77:13, 22 82:13 88:15 91:21 93:14 102:9 112:5 116:21, 23 134:1 135:15 145:18 159:3 160:4, 18 164:10 170:14 useful 92:1 104:3 User 4:23 21:14 113:20 118:9 120:23 uses 80:4 126:20 usually 9:11 13:12 168:14 169:12 utilization 107:16 utilize 19:3 < V > vaguely 121:4 validation 110:5 value 32:2, 6, 13, 23 55:7, 9 137:7, 24 138:13 139:4, 16 140:7 151:9 163:18 values 120:9, 11 138:8 141:4 143:1 164:10	valve 140:13 Van 160:14 variability 104:7, 21 105:4 118:2 152:11, 15, 21, 23 various 88:2 113:2 126:22 verb 62:13 verify 88:5 versa 144:3 version 112:5, 8, 12 113:13 114:5 120:20, 21 121:1, 4, 5 versus 6:11 31:13 36:21 114:15 164:23 vice 144:3 video 6:10 Videographer 2:11 6:2, 4, 24 36:13, 16 65:7, 11 88:25 89:6 130:21, 25 160:24 161:2 167:18, 22 169:21 view 19:25 101:5 VinaDock 20:12 virtual 14:21, 24 15:21 16:1, 3 18:13, 15, 21 21:6 53:13, 19 54:24 122:17 125:23 126:13 127:7 virtually 127:17 virtue 29:24	visualization 34:2 visualizations 35:3 visualize 34:4 65:3 94:6 155:19 165:13 visualized 73:2 101:13 165:25 visualizing 94:1 121:7, 16 165:11 166:2 < W > Waals 160:14 Wabash 2:9 wait 8:25 9:1, 3 146:15 want 9:12 21:8 30:7 34:5, 9 37:6, 8 44:24 45:10 46:25 50:9 51:8, 21 52:1 54:2 65:15 74:7, 8, 12, 16, 18 84:8 88:18, 22 94:18 98:11 102:14, 16 105:25 121:6 123:4, 9 129:3 130:9, 17 137:5 139:13 148:7 150:17 159:23, 25 163:1, 20 164:4, 19 166:24 wanted 111:11 123:15 125:6 128:13 warhead 29:15 50:22 51:24	52:10 117:11, 15 118:3 168:21 Washington 2:6 WATKINS 1:17 2:7 6:8, 22 way 33:5 34:7 58:1, 6 62:10, 16 77:4 91:15 92:18 102:7 107:4 117:1 126:7 127:2 137:8 139:19 143:20, 22 152:15 156:15 ways 36:2 54:3 wealth 68:17 weekend 122:4 weeks 126:2 WEIL 2:2 well 8:1 10:8 20:20 29:17, 25 37:10 45:11 51:22 55:2, 4 58:15 59:17 60:5 69:5 70:19 71:18 72:25 80:22 81:24 82:14 91:3 95:9 98:21 102:4 103:15 106:1 112:24 115:2 117:23 118:21 120:18 128:1, 5, 16 132:20 133:5, 11 134:10 136:2 140:10 141:15 142:3 143:3 155:10 156:7 159:11
---	---	--	--

well-defined 144:11	96:22 98:14 116:15 119:16	worthwhile 163:8, 9	10 45:20 60:11 113:17 115:1
well-established 57:21	121:9 131:6 167:13, 17	write 10:23 21:12 161:21	Yun 29:6 Yun's 29:13
well-known 50:24 68:20 106:7	170:11, 17	writing 8:24	< Z >
went 36:22 47:20 51:7 109:1	word 22:20 60:2 62:13 67:19 68:25 79:9 81:12, 16 82:8 164:16	written 121:23 155:18	zagged 117:16, 17
We're 47:1 67:14 94:8 143:23 150:21, 22	words 64:3 87:3 138:8	wrong 138:18 147:4, 5, 7	zanubrutinib 54:8, 15, 16, 19, 21 55:1, 16, 20 56:13 57:1, 4, 22 64:21 95:25 99:21 100:2, 23 101:1 102:21 104:13, 24 105:1 110:12, 18, 21 114:12 115:20 120:13 151:12, 18, 21 152:7
we've 38:20 40:15 64:10 88:20 92:5 102:19 116:5 124:14, 25 125:23 129:14 147:15 156:23 164:12	work 14:12 15:12, 14 17:16, 18 18:8, 9, 19 19:10, 12, 15 24:3 29:12, 13 34:4 39:25 40:12 45:22 77:5 92:7 94:15 128:25 130:13, 14 140:1 143:3	< X > X6 156:9 XP 113:3 x-ray 18:19 32:18 40:6 109:6 110:7 114:1	Zhang 78:3, 4 116:2 140:12 144:21 145:6, 17 150:2 153:17 154:17, 19
wharfing 100:8	worked 35:18 38:20 39:9 136:5, 14	< Y > Yeah 21:19 26:22 32:9, 20 34:11 41:6 45:7 47:1, 25 50:2 51:16 63:7 64:23 66:19, 23, 24 73:1, 21 77:10 94:24 117:24 121:3 125:11 127:12 130:8 134:17 144:10 150:18 153:15 154:22 158:1 159:1	Zhengying 4:10 85:20
WHEREOF 170:17	workflow 122:24 124:3	years 15:1 21:9 23:19 36:4 38:17, 21 39:4,	zigged 117:16, 17
wherewithal 130:11	working 10:9, 11 33:12 38:12 39:7 45:20 141:15 143:15 158:15		ZINC 127:8 Z's 49:13 128:14
white 83:8	works 9:14 16:22 137:7		Z'-scaffold 41:16 45:13, 19 50:18, 19 66:4 67:8, 16 68:9, 12 86:8, 19, 21 105:21
wholly 43:7	world 15:24 113:23 141:10		
widely 55:4 77:19	worry 47:1		
wild 23:17 39:18	worse 156:3 158:13		
witness 1:14, 16 3:2 6:23, 25 7:1 11:20 21:20 25:12 26:25 27:17 28:16 58:21 73:17 74:25 75:5, 11 86:3			

Z-scaffold 100:1, 22 102:21 110:12 Z'-scaffolding 86:9 Z'-scaffolds 44:14, 18 46:2 47:19 48:7, 24 49:21 53:14, 20 68:14 Z'-structure 42:4 43:10, 12 46:12, 24 47:2 49:9, 19 52:14 53:5 86:18 101:1 106:10 124:13 Z'-structures 124:18 130:15			
--	--	--	--