

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BeiGene USA, Inc. and BeiGene, LTD.,
Petitioners,

v.

Pharmacyclics LLC
Patent Owner.

PGR2024-00009
U.S. PATENT NO. 11,672,803

REPLY DECLARATION OF DR. HOLLIS SHOWALTER, PH.D.

TABLE OF CONTENTS

I. INTRODUCTION.....	1
II. QUALIFICATIONS AND COMPENSATION	2
III. RESPONSE TO DR. ECK’S AND DR. SCOTT’S DEFINITION OF PERSON OF ORDINARY SKILL IN THE ART	2
IV. RESPONSE TO DR. SCOTT’S CRITICISMS REGARDING MY CALCULATIONS OF THE BREADTH OF THE CHALLENGED CLAIMS.....	7
A. Grossly Conservative Calculations	18
B. The 803 Patent Is Unpatentable Even Based on the Grossly Conservative Calculations	20
V. RESPONSE TO DR. ECK’S OPINIONS REGARDING DIFFERENCES AMONG CLAIMED SPECIES.....	21
VI. RESPONSE TO DR. ECK’S OPINIONS REGARDING THE SPECIFICATION’S SUPPOSED DISCLOSURE OF PARTIALLY NON- AROMATIC RING SYSTEMS	22
VII. RESPONSE TO DR. ECK’S OPINIONS REGARDING INACTIVE COMPOUNDS.....	25
A. Zhang 2020 (EX2063).....	25
B. 446 Patent (EX2024).....	28
C. WO’289 (EX1108)	30
D. WO’185 (EX1109)	31
VIII. DECLARATION.....	32

I. INTRODUCTION

1. I have been retained by Petitioners BeiGene USA, Inc. and BeiGene, LTD. BeiGene (“Petitioner” or “BeiGene”) as an independent expert witness in the above-captioned post grant review (“PGR”), in which Petitioner requests that the U.S. Patent and Trademark Office cancel as unpatentable independent claims 1 and 8, and dependent claims 2-7, 12 and 20 (“Challenged Claims”) of U.S. Patent No. 11,672,803 (“the 803 Patent”). I previously submitted a declaration in this matter, which I understand was submitted as EX1003.

2. I provide this declaration to respond to certain issues raised in the declarations of Dr. David A. Scott (EX2012) and Dr. Michael J. Eck (EX2010). Specifically, (1) I disagree with Dr. Scott and Dr. Eck to the extent that their definition of the POSA team requires a modeler; (2) even if the POSA team would include a modeler, I disagree with Dr. Eck that the POSA team would rely on the modeler to screen compounds for covalent binding, and therefore my opinions regarding written description and enablement would remain unchanged; (3) I disagree with Dr. Scott’s criticisms regarding my calculations of the breadth of the Challenged Claims, but my opinions regarding written description and enablement remain unchanged even when I account for these criticisms because the breadth remains unreasonably large and diverse; and (4) I disagree with Dr. Eck that the specification contemplates the use of partially non-aromatic structures in the

Challenged Claims. That I do not specifically address certain other opinions of Dr. Scott or Dr. Eck is not intended to imply that I agree with such opinions.

3. I have reviewed the documents referenced in this declaration, including Dr. Veal's Declaration (EX1106). I understand they have been submitted as exhibits in conjunction with either BeiGene's Petition for PGR, Pharmacyclics' POR, or BeiGene's Reply.

II. QUALIFICATIONS AND COMPENSATION

4. The declaration I previously submitted in this matter sets forth my qualifications and compensation. EX1003.

III. RESPONSE TO DR. ECK'S AND DR. SCOTT'S DEFINITION OF PERSON OF ORDINARY SKILL IN THE ART

5. As I stated in my initial declaration, it is my opinion that a POSA would have been part of a team that included at least (1) a member that had at least a Ph.D. in chemistry, organic chemistry, or related field with training as a medicinal chemist ("chemist member"), and (2) a member that had at least a medical degree with training in hematology and oncology, including several years of clinical experience in treating hematologic malignancies ("clinical member"). EX1003, ¶136.

6. I understand that Patent Owner ("PO") and its experts Dr. Scott and Dr. Eck agree with Petitioner's definition of clinical member. EX2012, ¶12; EX2010, ¶125. They disagree, however, with the definition of a chemist member. *Id.* Instead,

they propose that the POSA team ***must*** include “at least one member having at least a Ph.D. in chemistry, organic chemistry, biochemistry, or related field ***with training in the [structure-activity relationship (“SAR”)] of kinase inhibitors¹***,” and ***could optionally*** include an additional member “having at least a Ph.D. in chemistry, organic chemistry, or related field with training as a medicinal chemist and in the structure of kinases.” EX2012, ¶¶12-13; EX2010, ¶¶125-126.

7. I understand, however, that both Dr. Scott and Dr. Eck acknowledge that my definition of the chemist member already accounts for knowledge of the structure-function relationship of kinase inhibitors. EX2012, ¶13; EX2010, ¶126. Indeed, as someone who can accurately represent the views of the chemist member of the POSA team as of the June 3, 2011 and 2020 time periods, I have the required “training in the structure-function relationship of kinase inhibitors.”

8. I also qualify as a POSA under Dr. Scott’s definition. Specifically, I understand that Dr. Scott testified that either (1) working as a medicinal chemist on a single kinase project or (2) having experience in modeling can be sufficient training to qualify as a POSA under his definition. EX1117, 55:7-56:5. I have worked as a medicinal chemist on over eight kinase projects, and therefore have more than sufficient training to qualify as a POSA under his definition.

¹ Emphasis added unless otherwise noted.

9. I understand that PO also submitted an expert declaration from Dr. Eck, who also contends to qualify as a POSA because he has “developed and expanded on [SAR] for kinase inhibitors.” EX2010 ¶127. I also understand Dr. Eck also has some experience in modeling and contends that “virtual docking and modeling tools would have ruled out inappropriate compounds.” EX1110, 17:15-19:1; EX2010 ¶219. To the extent that PO’s definition of a POSA *requires* expertise in modeling, I disagree. Indeed, the patent never mentions modeling. Moreover, in my experience as a medicinal chemist working in drug discovery, I have never consulted with a modeler to screen a library of compounds to assess which among them binds the target kinase.

10. For kinase drug discovery projects at a pharmaceutical company, the goal is to identify one or more lead compounds to advance to preclinical and clinical testing. See EX1117, 101:11-20. Typically, the first step of such a project involves screening a library of thousands to hundreds of thousands of compounds that the company has already synthesized or purchased. This would involve running enzyme assays to test all compounds in the library for inhibition against the target kinase. I understand this is consistent with Dr. Scott’s experience when working at AstraZeneca. *Id.*, 33:12-33:19 (“In the case of a kinase inhibitor project, a company might have a collection of compounds that have shown activity against other kinases and that would often be a very good starting point for a new project.”); *id.*, 33:20-

34:13 (“I believe the entire AstraZeneca collection might have been hundreds of thousands of compounds. I think we did a more focused screen on compounds that were likely to have confirmed the compounds we thought could have a chance of activity against JAK2 and that would have been a subset of the larger collection”); *see also id.*, 32:14-33:4, 37:5-38:4.

11. After active compounds (“hits”) have been identified in assays, medicinal chemists will make additional compounds by optimizing those hits in order to improve their binding affinities and other pharmacological activities. The purpose of this would be to identify the “lead” compound(s) for pre-clinical and clinical testing. Medicinal chemists may involve a modeler in such optimization efforts. EX1117, 34:14-35:5 (Dr. Scott testifying that in his experience at AstraZeneca he did not work with a modeler “as part of the initial screening effort” because “[i]t wouldn’t have made sense to do that” when “[t]he value of modeling is, once you have identified -- one of the values of modeling is when you have identified a specific compound of interest.”), 36:21-38:15 (Dr. Scott testifying that working with a modeler “can be very valuable as soon as you’ve identified an active compound” and “[o]n the kinase projects I worked on at AstraZeneca, we would typically engage a modeler once we had identified an active inhibitor”).

12. Typically, however, medicinal chemists will make not only additional compounds suggested by modelers, but also compounds that medicinal chemists

believe based on their knowledge and experience to be worth making and helpful in understanding the SAR of the target kinase. That is because drug discovery is full of surprises and modeling does not accurately predict experimental results. EX1106, ¶¶4, 33-34, 36, 101-104, 114-121, 126-133, 184-186, 246, 249. In any event, modeling is not typically used to definitively answer the binary question whether a compound would or would not bind a target kinase. In my years of experience in drug discovery, I have never involved a modeler for that purpose.

13. Unlike in a drug discovery project, I understand that the question presented here is not to identify the best compounds within the claimed genus. Indeed, the Challenged Claims do not require any particular potency or efficacy. Rather, I understand that the relevant questions are whether a POSA could (a) visualize or recognize which compounds that satisfy the Structural Limitations also satisfy the Functional Limitations and (b) practice the full scope of the Challenged Claims without engaging in trial-and-error or undue experimentation. EX1003, ¶¶17-21.

14. While a modeler might have been able to provide some insight into which molecules are less likely to work, in my experience working in drug discovery during the 2011 time period, a POSA would never rely on modeling alone to assess whether a potential inhibitor would covalently bind Cys481. EX1117, 40:18-41:13 (Dr. Scott testifying that he would run an assay to confirm that the inhibitor actually

inhibits the target because “it’s valuable to validate predictions of modeling with data.”), 49:20-49:22 (Dr. Scott testifying that repeated optimization is necessary because, “[i]n some cases, a lead compound might not meet all the objectives of a drug discovery project.”). My opinion is consistent with that of Dr. Veal who confirmed that modeling software in 2011 or even now cannot accurately predict covalent binding. EX1106, ¶¶4, 33-34, 36, 101-104, 114-121, 126-133, 184-186, 246, 249. Therefore, I disagree with PO’s definition of a POSA to the extent that it requires a modeler.

15. In any event, based on my review of Dr. Veal’s declaration as well as my opinions explained *infra* Section VII, my opinions regarding the unpatentability of the Challenged Claims are the same regardless of whether a modeler would be part of the POSA team or not. EX1003, ¶¶238, 242. Specifically, a medicinal chemist on the POSA team would not consider modeling to be predictive of covalent binding and irreversible inhibition, and therefore would have relied on additional testing to screen compounds. *Id.*

IV. RESPONSE TO DR. SCOTT’S CRITICISMS REGARDING MY CALCULATIONS OF THE BREADTH OF THE CHALLENGED CLAIMS

16. PO and Dr. Scott assert that my calculations inflate the breadth of the Challenged Claims. POR 54-57; EX2012, ¶45. Not so.

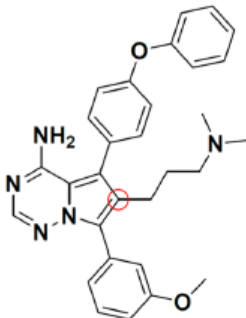
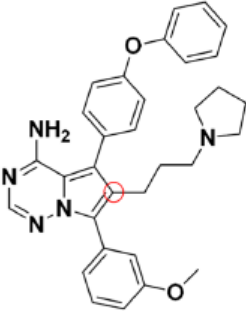
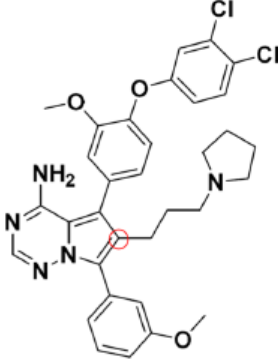
17. First, PO alleges that I shielded the foundation of my analysis regarding the Appendix A structures. POR 55. But, as I explained in my Opening Declaration and reiterated during my deposition, I did not include in Appendix A every single possible ring system, but rather included only those ring systems that have been reported as known or theoretically feasible (virtual) species showing reasonable chemical stability. EX1003, ¶176; EX2018, 147:16-148:7. These species can be found in EX1097, which I cite in my Opening Declaration. EX1003, ¶257. Notably, neither Dr. Scott nor PO identify a single ring system from Appendix A that would not be stable. Nor do they provide their own list of possible ring systems.

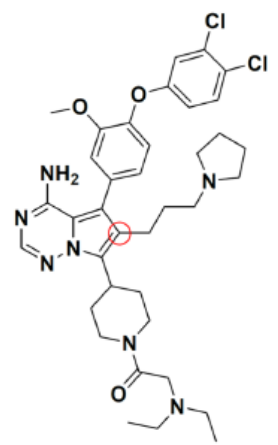
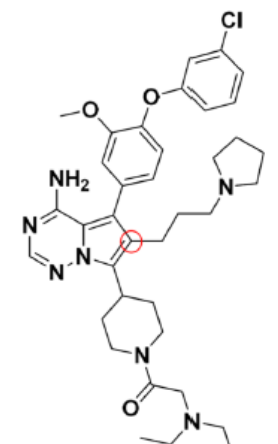
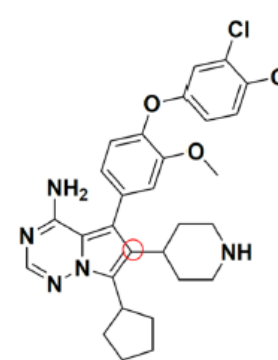
18. PO further contends that I did not consider whether any of the Appendix A ring systems would allow for productive binding to BTK when appended to the fixed substituents of the Challenged Claims. POR 55. But as I stated very clearly in my Opening Declaration, Appendix A and my related calculations considered only whether the ring systems satisfied the Structural Limitations. EX1003, ¶175. My analysis of breadth did not consider whether those candidates also satisfied the Functional Limitations. *Id.*, ¶177. That is because, in my opinion, a POSA could not visualize or practice the full scope of the Challenged Claims without trial and error or undue experimentation—*i.e.* could not predict which of the potential BTKIs that satisfy the Structural Limitation would also satisfy the Functional Limitations without testing. Modeling capabilities would not

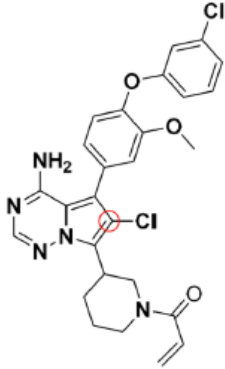
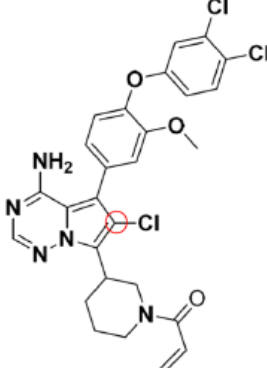
increase the predictability or replace the need for experimental testing because the accuracy of modeling in 2010/2011 or even now would have been limited. ¶¶4, 33-34, 36, 101-104, 114-121, 126-133, 184-191, 244-252.

19. That said, I did not leave my common sense at the door, and did exclude any potential inhibitors that would have been known to be toxic, unstable, or otherwise would not work. EX1003, ¶176. Even Dr. Eck agrees with my calculation of the number of compounds covered by the Structural Limitations. EX1110, 42:21-43:18.

20. Second, PO and Dr. Scott contend that my calculations allow for substitution at *each and every* available position on Z' when a POSA instead “would have understood that there would typically be at most one or two positions on Z' where additional substituents beyond the phenoxyphenyl, linker, and hinge-binding substituents that might be tolerated.” POR 56; EX2012, ¶43. Dr. Scott contends that “[e]xamples of locations where additional substitutions could have been accommodated on Z' are shown in... prior art structures” from WO'960. EX2012, ¶43 (citing EX2027, Examples 16(1), 16(2), 16(3), 21, 21(1), 25(1), 32, 32(1)).

Example	Name	Structure	IC50 (nM)
16(1)	6-(3-(dimethylamino)propyl)-7-(3-methoxyphenyl)-5-(4-phenoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine		5.8
16(2)	7-(3-methoxyphenyl)-5-(4-phenoxyphenyl)-6-(3-(pyrrolidin-1-yl)propyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine		6.5
16(3)	5-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-7-(3-methoxyphenyl)-6-(3-(pyrrolidin-1-yl)propyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine		12

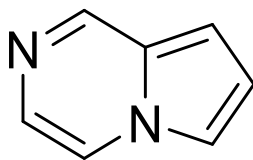
Example	Name	Structure	IC50 (nM)
21	1-(4-(4-amino-5-(4-(3, 4-dichlorophenoxy)-3-methoxyphenyl)-6-(3-(pyrrolidin-1-yl)propyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-1-yl)-2-(diethylamino)ethanone		16
21(1)	1-(4-(4-amino-5-(4-(3-chlorophenoxy)-3-methoxyphenyl)-6-(3-(pyrrolidin-1-yl)propyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-1-yl)-2-(diethylamino)ethanone		22
25(1)	7-cyclopentyl-5-(4-(3, 4-dichlorophenoxy)-3-methoxyphenyl)-6-(piperidin-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine		62

Example	Name	Structure	IC50 (nM)
32	1-(3-(4-amino-6-chloro-5-(4-(3-chlorophenoxy)-3-methoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-1-yl)prop-2-en-1-one		2
32(1)	1-(3-(4-amino-6-chloro-5-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-1-yl)prop-2-en-1-one		2

21. These examples do not support PO's proposition. They all contain the same biaryl¹² Z'-scaffold. There are numerous other possible biaryl ring systems that could have more than one or two possible locations for substitution. For example, the following biaryl ring system from Appendix A has 3 locations available for

² I understand that the 803 Patent uses the terms "aryl" and "biaryl" inconsistently. For example, the 803 Patent defines "aryl" as excluding heterocycles (EX1001, 15:4-12), but later uses the term "biaryl" to refer to ring systems with two heteroaromatic rings. EX1001, 62:44-63:22. When I use the term "biaryl" in this declaration and in EX1003, I refer to ring systems containing two heteroaromatic rings.

substitution beyond the hydrophobic moiety, the linker-warhead, and hinge-binding substituents. EX1003.147 (Appendix A at 9).



22. Therefore, Dr. Scott's cited examples do not show that there are typically only 1-2 possible locations available in every biaryl ring system—only that there are 1-2 locations available in this particular biaryl ring system.

23. There would be even more locations available for substitution beyond the hydrophobic moiety, linker-warhead, and hinge-binding substituents for non-biaryl ring systems. It is basic chemistry (and therefore a POSA would have known) that the number of possible locations for substitution increases as the number of nonaromatic rings increases and the more saturated each nonaromatic ring is. In other words, the Z'-scaffolds in three non-biaryl subgenera have more possible locations for substitution than those in the biaryl subgenus.

24. Dr. Scott also points to “post-priority” structures that he contends “further show where a POSA in 2011 would have understood limited substitutions may be tolerated on Z’.” EX2012, ¶44. As Dr. Scott admits, these post-priority structures would not have been available to a POSA in 2010/2011 and therefore would not have informed a POSA's understanding of the possible locations for the

optional substitution. Nor would a POSA have had the IC₅₀ data that confirm their potency. Even if a POSA had access to such structures and IC₅₀ data, these structures are limited for the same reasons explained above—they are specific biaryl ring systems, do not represent all biaryl ring systems, and certainly do not represent any non-biaryl ring systems.

25. Third, Dr. Scott contends that my calculations violate Lipinski's rules. EX2012, ¶46. Specifically, Dr. Scott states that a POSA would have recognized that “[t]oo many substituents, especially large ones such as aromatic rings, would increase the molecular weight to significantly above 500 Da, where achieving any level of oral exposure would be unlikely.” EX2012, ¶46. Rather than abide by Lipinski's rules, the specification itself violates them by expressly listing 75 potential optional substitutions for use in the claimed invention, including bulky substitutions such as heteroaryl groups that would result in high molecular weight species. EX1003, ¶¶163-164. Dr. Scott himself testified that these 75 moieties are exemplary optional substitutions for the claimed molecules, and that he has not seen any evidence that any of these moieties could not be used in the claimed invention. EX1117, 88:7-92:16.

26. Nevertheless, my calculations conservatively accounted for only 21 potential substitutions—a fraction of the disclosed 75 options—that I considered relatively less bulky. EX1003, ¶166. Even Dr. Scott agrees that the specification's

list of 21 categories of substitutions is representative of the types of substitutions that can be introduced into the claimed molecules. EX1117, 72:5-74:19. As Dr. Scott acknowledged, a POSA in 2011 did not rigidly apply Lipinski's rules and instead would have used them as "guidelines rather than hard rules." *Id.*, 66:19-70:19. Dr. Scott further testified that, a POSA in 2011 would not, for example, disqualify a compound for use in treatment simply because it had a molecular weight of greater than 500 Da. *See id.* This is consistent with industry practice. In 1991, FDA approved azithromycin, which has a molecular weight of over 700 Da. *See* EX1123.002, .003. As of April 2023, "a total of 30 of the 74 FDA-approved small molecule protein kinase inhibitors fail to conform to Lipinski's [Rule of Five]." EX1133.006.

27. A POSA in 2011 would not have assumed that the larger substituents among the list of 21 possible substitutions would not result in covalent binding without testing. This is exemplified by a 2020 publication cited by PO—Zhang 2020. EX2063. The authors of Zhang 2020 investigated the impact of introducing various optional substitutions on the Z'-scaffold to a compound that satisfies the Structural Limitations. EX2063.002-.005. This involved synthesizing and performing IC₅₀ assays on five different compounds (compounds 7-11) comprising the same biaryl Z'-scaffold, but with various different optional substitutions attached at the same location of Z'-scaffold. EX2063.003. They found that compounds with

smaller substituent groups such as H and Me resulted in inhibition of Btk, but that “[i]ntroduction of larger substituent groups, such as –Et (10) and –CH₂CF₃ (11), lead to a complete loss of activity.” *Id.* The fact that scientists in the field were still investigating the impact on Btk inhibition of introducing larger optional substitutions on the Z'-scaffold in 2020 demonstrates that a POSA would not have assumed in 2011 that the larger substitutions listed in the specification would not covalently bind Btk; instead, a POSA would have engaged in trial-and-error.

28. Notably, despite their criticisms of my conservative estimation of the breadth of the claims, neither PO nor any of its experts have themselves provided an estimation of the breadth of the claims. EX1110, 42:6-20 (Dr. Eck testifying that he has not tried to determine how many structures satisfy the Structural Limitations); EX1119, 94:7-10 (Dr. Spurgeon testifying that he relied on Dr. Eck's opinion regarding the scope of the Structural Limitations); EX2010, ¶¶216-222; EX2012, ¶45; EX2014, ¶¶145-146.

29. Even accounting for Lipinski's rules, however, I estimate *infra* Section IV.A that the Challenged Claims remain exceptionally broad. These calculations rely on the below list of eleven optional substitutions, which Dr. Scott agrees are generally not bulky compared to other substitutions and/or could potentially be used in the Challenged Claims, as well as hydrogen, which Dr. Scott agrees could be located at any one of the available positions on Z'. EX1117, 72:5-88:6. The six

substitutions bolded and in brackets identify substituents that a POSA would understand are capable of forming hydrogen bonds with the hinge region.

Table 1		
No.	Substitution	Molecular Weight (Da)
1	H	1
2	Methyl	15
3	[NH₂]	16
4	[OH]	17
5	F	19
6	CN	26
7	[HC=O]	29
8	[OMe]	31
9	CH ₂ F	33
10	Vinyl	27
11	[CH₂NH₂]	30
12	[H₂NC=O]	44

30. Finally, Dr. Scott and PO contend that my calculations include substitutions at locations on Z' that a POSA would have known to result in steric clash and interfere with the ability to make the appropriate H-bonds to the hinge region. EX2012, ¶45; POR 56. The only support that Dr. Scott provides for this statement is EX1003, ¶168 of my declaration, which illustrates 9 available positions for substitution for zanubrutinib—2 assigned to the hydrophobic moiety and linker-warhead and 7 available for optional substitutions. EX2012, ¶45. Dr. Scott has not explained which particular substitutions at which particular locations would result in steric clash. *Id.* He provides no examples but merely conclusively states that some would not work and a POSA would know it. *Id.* Further, my calculations in

EX1003 were based on a *single* core of zanubrutinib, rather than all 1,726 cores depicted in Appendix A. EX1003, ¶¶167-174. Similarly, Dr. Eck contends that a POSA would understand that the orientations and potential steric hindrance/clash resulting from substituents would limit the scope of acceptable Z'-scaffolds. EX2010, ¶¶181-182. Dr. Eck, however, does not provide any opinion regarding how this limits the scope of the claimed Z'-scaffolds (or whether this would be predictable). Dr. Eck has not provided an opinion regarding the size of the genus that he refers to as “acceptable Z’ scaffolds,” has not tried to do that calculation, “wouldn’t want to put a number on it,” and has not “thought in detail about how [he] would approach it.” EX1110, 43:19-45:15. Further, Dr. Eck explained that “[i]n my many years working in this area, that’s never something that’s been a necessary part of my work, and so I haven’t thought about that kind of calculation.” *Id.*, 45:16-23.

A. Grossly Conservative Calculations

31. Though I disagree with PO’s criticisms of my calculations, I have provided updated calculations that account for these criticisms. It is my opinion that the breadth of the Structural Limitations is still unreasonably broad.

32. Consistent with Dr. Scott’s testimony, my updated calculations assume that each of the 1,726 Appendix A ring systems has only 3 positions available for substitution after the hydrophobic moiety and linker-warhead have been added—

two of which can be any of the 12 optional substitutions listed in Table 1 and one of which can only be one of the 6 optional substitutions capable of forming an H-bond. This latter limitation is based on Dr. Scott's statement that a POSA would know that Z'-scaffold must form 1-3 H-bonds with Btk.³ EX2012, ¶20. With these parameters, there would be a total of 864 (6×12^2) species for each ring system.

33. Further, the Structural Limitations do not prescribe the attachment points in the linker. Hence, the linker can be connected to the Z'-scaffold at three different points—leading to $3 \times 864 = 2,592$ species per ring system.

34. Finally, Appendix A contains 1,726 ring systems, meaning the total number of possible ring systems for independent claims 1 and 8⁴ is **4,473,792** ($1,726 \times 2,592$).

35. In reality, the final calculations are a gross underestimation. First, these calculations do not take into account that the hydrophobic moiety and linker-warhead can be connected to different positions on the Z'-scaffold, *e.g.*, the positions

³ That said, it is entirely possible that a Z'-scaffold's ring heteroatoms form the necessary 1-3 H-bonds and that none of its substitutions do so. Therefore, this limitation also contributes to a grossly conservative estimate.

⁴ Dependent claims 12 and 20 are limited to only those Appendix A structures that have three nitrogen heteroatoms (685 ring systems). Using the same parameters above, dependent claims 12 and 20 likewise are overly broad as they are directed to at least **1,775,520** ($685 \times 2,592$) possible ring systems. *See* Appendix A at 3-4, 10-12, 16, 23-25, 32-36, 42, 49-50, 56-58, 62-63, 71-77, 93-101, 110-111 (3 Nitrogen ring systems); *see also* EX1003, ¶¶226-231, 265-270.

of the hydrophobic moiety and linker-warhead for zanubrutinib are different from ibrutinib. Nor do these calculations consider the stereochemistry for any potential chiral centers. Additionally, many ring systems, including most non-biaryl ring systems, of the Z'-scaffold would have had more than 3 positions available for substitution and none of those 3 substitutions would necessarily need to form an H-bond with the hinge region. As explained above, it is basic chemistry that the number of positions available for substitution increases as the number of nonaromatic rings increases and as the amount of saturation increases.

B. The 803 Patent Is Unpatentable Even Based on the Grossly Conservative Calculations

36. My opinions regarding written description and enablement do not change even based on the grossly conservative calculations in Section IV.A above. EX1003, ¶¶275-280. For the reasons explained herein and in Dr. Veal's Declaration, it is still my opinion that a POSA would not be able to predict which of those species that satisfy the Structural Limitations also satisfy the Functional Limitations. *Id.*, ¶177.

37. Specifically, it is my opinion that a POSA would not have been able to visualize the full scope of at least over 4 million potential species that would have satisfied the Functional Limitation of covalently binding Cys481 or any other residue of Btk without engaging in trial and error. EX1003, ¶¶188-220, 275.

Further, it is still my opinion that a POSA would not have been able to practice the full scope of the Challenged Claims without engaging in undue experimentation because a POSA would have needed to conduct multiple experiments of at least over 4 million potential species to figure out which of those species would have satisfied the Functional Limitation of covalently binding Cys481 or any other residue of Btk. *Id.*, ¶¶232-258, 276-280.⁵

V. RESPONSE TO DR. ECK'S OPINIONS REGARDING DIFFERENCES AMONG CLAIMED SPECIES

38. Dr. Eck contends that my Opening Declaration pointed to irrelevant differences among species suitable for use in the claimed methods. EX2010, ¶¶230-231. I disagree.

39. In my opinion, the attachment point of the linker and the chirality of the linker attachment both impact Btk binding activity. As described below, Compounds 2 and 9 of WO'185 are positional isomers, but Compound 2 has an IC₅₀ value that a POSA would understand to mean that it is active (< 10 nM) and Compound 9 has an IC₅₀ value that a POSA would understand to mean that it is inactive (greater than 1000 nM but less than 100,000 nM). EX1109, [00348], Table 4. *See infra* Section VII.D. Similarly, while Compounds 20 and 30 of the 446 Patent

⁵ My opinions regarding written description and enablement likewise remain the same for Claims 12 and 20, which are directed to at least over 1.7 million potential species.

are positional isomers, Compound 20 has an IC_{50} value that a POSA would understand to mean that it is active (10-100 nM) and Compound 30 has an IC_{50} value that a POSA would understand to mean that it is inactive ($> 10,000$ nM). EX2024.0118-0119. Further, isomers of zanubrutinib and ibrutinib have distinct IC_{50} values. EX1003, ¶¶71-73.

VI. RESPONSE TO DR. ECK’S OPINIONS REGARDING THE SPECIFICATION’S SUPPOSED DISCLOSURE OF PARTIALLY NON-AROMATIC RING SYSTEMS

40. PO and Dr. Eck contend that the specification’s definitions of the terms “aryl” and “non-aromatic heterocycle,” as well as its disclosure of the E4 ring system, demonstrate that the specification contemplates the use of non-aromatic Z’-scaffolds in the Challenged Claims. EX2010, ¶¶65-68; POR 68-69. I disagree—a POSA reading the specification would conclude that the specification does not describe the use of non-aromatic Z’-scaffolds in the Challenged Claims.

41. First, a POSA would consider the specification’s depiction of the E4 ring system to be a mistake because a POSA would understand the term “biaryl” as used in the specification refers to a core with two heteroaromatic rings and E4 is the only exemplified Z’ ring system that does not contain two heteroaromatic rings. EX1003, ¶115, n. 2. As Dr. Eck testified, the prefix “bi” means “two,” which indicates that the ring system must have two rings. EX1110, 80:8-14. Moreover, Dr. Eck agrees that, outside the context of the 803 Patent, biaryl ordinarily refers to

“two aromatic rings.” EX1110, 82:1-6. Further, although the specification defines aryl as containing only carbon atoms, it is undisputed that the specification clearly uses biaryl to refer to ring systems containing heteroatoms because the eight Formula E cores all contain nitrogen heteroatoms. Therefore, a POSA would understand that biaryl as used in the specification refers to structures containing two heteroaromatic rings⁶.

42. I disagree with Dr. Eck that a POSA would understand “biaryl” as used in the specification to also refer to non-aromatic heterocycles. EX2010, ¶¶65-68. The term “heterocycle” is clearly defined in the specification to mean both aromatic and non-aromatic ring systems. EX1001, 15:66-16:62. The inventors used the term multiple times to define certain variable groups throughout the specification, such as ring, carbocyclic, carbocycle, heterocycloalkyl, heteroalicyclic, and Formulas A, B, and D. *Id.*, 14:36-42, 14:53-60, 17:30-18:33, 47:39-47, 47:66-48:6, 48:27-31, 48:44-47, 49:62-50:32, 55:11-12, 56:30-31, 61:27-58. This demonstrates that the inventors clearly knew to use “heterocycle” when they intended to refer to rings that can be both aromatic and non-aromatic, and yet, chose to use “biaryl” rather than “heterocycle,” when referring to the eight Formula E cores. Therefore, a POSA

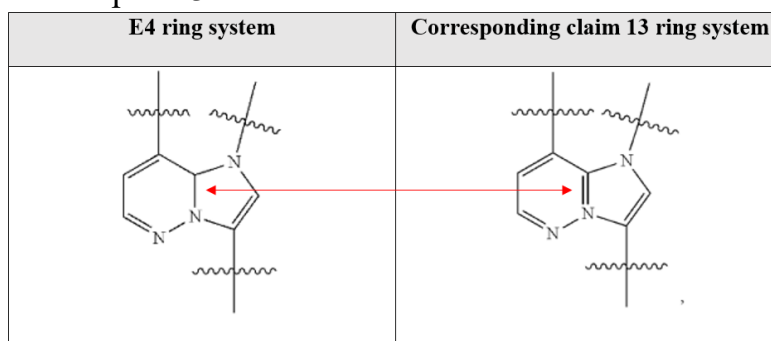
⁶ Consequently, the fact that fluorenyl, a partially aromatic ring system, is listed as an example of “aryl” is irrelevant.

would understand that “biaryl” does not include non-aromatic ring systems. As a result, a POSA would consider E4 to be a mistake because E4 is not biaryl—*i.e.*, it does not contain two heteroaromatic rings.⁷

43. Second, regardless of the definition⁸ of biaryl, a POSA would be led away from using non-aromatic ring systems. That is because if a POSA were to rely

⁷ Alternatively, I agree with the Board (ID, 21-22 n.4) that the 803 Patent does not consider E4 to be an embodiment of the claimed invention because the specification states that exemplary embodiments of the claimed invention are only the biaryl moieties selected from the Formula E ring systems—*i.e.* all depicted ring systems except for E4, a non-biaryl ring system. EX1001, 62:44-45 (“In some embodiments, [orb] is a substituted fused biaryl moiety ***selected from***” the eight Formula E ring systems.).

⁸ A POSA would still consider E4 a mistake regardless of the definition of biaryl based on claim 13. Three out of the four ring systems claimed in claim 13 other than the ring system depicted below can be found among the eight Formula E ring systems that comprise 3 N atoms.



The missing ring system is almost identical to E4 but, unlike E4, has a double bond off the bridgehead N. This structure has an error as the bridgehead N should have a positive charge. Because the corresponding structure in claim 13 appears nowhere in the specification and “biaryl” is used to describe the eight Formula E structures, a POSA reading the 803 Patent would conclude that the inventors were attempting to disclose in E4 and claim in claim 13 a biaryl ring system containing two heteroaryl rings and 3 N atoms, but failed to do so correctly.

on modeling as PO argues, the POSA would find, as Dr. Veal's modeling shows, that the claimed compounds wherein Z' is E4 (the only non-aromatic ring system disclosed for the Z'-scaffold in the specification) would not irreversibly bind Cys481. EX1106, ¶¶150-152.

VII. RESPONSE TO DR. ECK'S OPINIONS REGARDING INACTIVE COMPOUNDS

44. I understand that Dr. Eck discusses certain compounds from Zhang 2020 (EX2063) and the 446 Patent (EX2024) in his declaration. EX2010, ¶¶183-185. These are both references that I provided in response to a question asked during my deposition and PO's criticism in its preliminary response that neither Petitioner nor its experts provided evidence of any compounds that satisfy the Structural Limitations but that do not satisfy the Functional Limitations. EX2018, 12:8-15:12; POPR 64-65.

45. I also understand that, in response to Dr. Eck's opinions regarding the predictive capabilities of modeling, Dr. Veal discusses compound 81 from WO2014173289 (EX1108) and compounds 2 and 9 from WO2016007185 (EX1109). EX1106, ¶¶126-133.

46. I address each of these references below.

A. Zhang 2020 (EX2063)

47. Dr. Eck states that Zhang 2020 discloses two compounds that meet the Structural Limitations—compounds 7 and 8. EX2010, ¶185. Both compounds have similar structures, but compound 8 has an IC₅₀ value of 2.1nM, which a POSA would understand to mean that it irreversibly binds Btk, and compound 7 has an IC₅₀ value of >1000nM, which a POSA would understand to mean that the compound is inactive. EX2063.002. Additionally, there are three other compounds in Zhang 2020—compounds 9, 10, and 11—that also satisfy the Structural Limitations but that Dr. Eck failed to address in his declaration. EX2063.003. Like compound 7, compounds 10 and 11, have IC₅₀ values of >1000nM, which a POSA would understand to mean that the compounds are inactive. *Id.*, at .002-.003 (equating IC₅₀ values of >1000 with “a complete loss of activity.”).

48. Dr. Eck incorrectly states in his declaration that I acknowledged that, during the 2011 time frame, an IC₅₀ of 1000 nM may have been considered “active.” EX2010, ¶185. That is blatantly false. I very clearly testified that, “as of 2010, 2011, the standard still was that to have an active compound you had to be less than 1 micromolar IC₅₀ in a kinase assay”—*i.e.* less than 1,000 nM. EX2018, 37:22-39:3. Indeed, Dr. Eck testified that a compound with an IC₅₀ value of 1,000 nM would not fall within the scope of the Challenged Claims because a POSA would not want to administer such a compound to human as the Challenged Claims require. EX1110, 159:17-160:1 (“I think it’s unlikely that one would want to advance micromolar

irreversible BTK inhibitor. I can't imagine that—that anyone would want to do that.”).

49. Therefore, compounds 7, 10, and 11 are examples of compounds that satisfy the Structural Limitations but would not meet the Functional Limitations. Notably, it is undisputed that the authors of Zhang 2020 had access to and used Glide software, which, if predictive, would have suggested that compounds 7, 10 and 11 would not bind Btk (EX1106, ¶¶110), but nevertheless chose to synthesize and test each of these compounds to obtain their IC₅₀ values. EX2063.0002 (“Docking study of compound 8 with BTK was carried out via covalent docking protocol of Glide.”); EX1110, 145:6-146:1 (Dr. Eck testifying that authors of Zhang actually synthesized and empirically-tested both Compound 7 and 8 and did not deprioritize compound 7 for synthesis even though they “certainly could have” used computational docking). This further supports my opinion that the medical chemist member of the POSA team would not solely rely on modeling to predict covalent binding of Btk, but would rather conduct experimental testing to screen compounds.

50. Moreover, the authors of Zhang 2020 set out to discover a novel BTKI and explained that their “medicinal strategy was to keep the acrylamide moiety as a Michael acceptor unchanged initially and search for a *novel* structural motif as the central core, hoping to generate irreversible BTK inhibitor with potent activity.” EX2063.0001. This led to the “*discovery* of a novel” Z'-scaffold, compound 8. *Id.*

51. Zhang discloses that the authors “successfully *developed the SAR profile* around this series, resulting in the *discovery* of compound 8.” EX2063.0005. Zhang also reports unexpected results when measuring the IC₅₀ value of compound 8, stating that “[t]he replacement of pyrazolo[3,4-d]pyrimidine of ibrutinib with pyrazolo[3,4-d]oxazinone also afforded weaker potency against BTK (7). *To our delight*, further replacing the ‘O’ of the pyrazolo[3,4-d]oxazinone ring with a ‘NH’ led to pyrazolo[3,4-d]pyridazinone derivative 8, showing a significantly increased enzymatic activity with IC₅₀ of 2.1 nM.” EX2063.0002 (emphasis added). The fact that the authors of Zhang were investigating and developing an SAR profile for these compounds and were surprised by the results in 2020 supports my opinion that there was a lack of predictability in 2010/2011 (and even today) with respect to irreversible BTKIs satisfying the Challenged Claims. If the specification and art had revealed the SAR in 2011, then the authors would not have chosen to investigate such inactive compounds.

B. 446 Patent (EX2024)

52. Dr. Eck states that the 446 Patent discloses three compounds that meet the Structural Limitations—compounds 20, 30, and 122. EX2010, ¶184. All three compounds have similar structures, but compound 20 has an IC₅₀ value of 10-100nM, which a POSA would understand to mean that it irreversibly binds Btk, and compounds 30 and 122 have IC₅₀ values of >10000nM and 1000-10000nM,

respectively, which a POSA would understand to mean that they are inactive. EX2024.0118-.0119.

53. Therefore, compounds 30 and 122 are examples of compounds that satisfy the Structural Limitations but would not meet the Functional Limitations. Dr. Eck agrees that these compounds are “poor candidates for irreversibly inhibiting BTK as required by the claims.” EX2010, ¶184. Notably, it is undisputed that the inventors of the 446 Patent had access to modeling software, which if predictive, would have suggested that compounds 30 and 122 would not bind Btk (EX1106, ¶134), but nevertheless chose to synthesize and test each of these compounds to obtain their IC₅₀ values. EX1110, 142:13-17 (Dr. Eck testifying that, in this time frame of 2015, the inventors of the 446 Patent certainly would have had access to the modeling, the computer software that he discusses in his declaration), 142:18-143:3 (Dr. Eck testifying that 446 Patent inventors synthesized and tested the compounds). This further supports my opinion that the medical chemist member of the POSA team would not solely rely on modeling to predict covalent binding of Btk, but would rather conduct experimental testing to screen compounds. Further, the fact that the inventors of the 446 Patent were investigating and developing these compounds, some of which were ultimately shown to be inactive, supports my opinion that there was a lack of predictability in 2010/2011 (and even today) with respect to irreversible BTKIs satisfying the Challenged Claims. If the specification

and art had revealed the SAR in 2011, then the inventors of the 446 Patent would not have chosen to investigate inactive compounds.

C. WO'289 (EX1108)

54. I understand that Dr. Veal relies on compound 81 in his Declaration. EX1108, [0538]. Compound 81 satisfies the Structural Limitations, but has an IC₅₀ value of 5,900 nM, which a POSA would understand to mean that it is inactive. *Id.*, [0642], Table II. Therefore, compound 81 is another example that satisfies the Structural Limitations, but does not satisfy the Functional Limitations of the claims.

55. Notably, consistent with Dr. Scott's and Dr. Eck's testimonies (EX1117, 40:18-41:13; EX1110, 36:25-37:11), the inventors of WO'289 chose to synthesize and test compound 81 to obtain its IC₅₀ value despite having access to modeling software in 2014. EX1108, [0642], Table II; EX2010, ¶118. I also understand that Dr. Veal's modeling reveals that the docking pose and score for compound 81 suggest, contrary to the reported IC₅₀ value, that compound 81 would irreversibly bind. EX1106, ¶¶126-129. This further supports my opinion that modeling cannot accurately predict Btk binding in 2010/2011 or even now. Further, the fact that the inventors of WO'289 were investigating and developing this compound, which was ultimately shown to be inactive, supports my opinion that there was a lack of predictability in 2010/2011 (and even today) with respect to irreversible BTKIs satisfying the Challenged Claims. If the specification and art had

revealed the SAR in 2011, then the inventors of WO'289 would not have chosen to investigate an inactive compound.

D. WO'185 (EX1109)

56. I understand that Dr. Veal relies on compounds 2 and 9 in his Declaration. EX1109, [0118], Table 1. Both compounds 2 and 9 satisfy the Structural Limitations. Compounds 2 and 9 are positional isomers (compound 2 has a *meta* attachment on the linker-warhead, whereas compound 9 has a *para* attachment on the linker-warhead), but compound 2 has an IC₅₀ value of ≤ 10 nM, which a POSA would understand to mean that it irreversibly binds Btk, and compound 9 as an IC₅₀ value greater than 1000 but less than 100,000 nM, which a POSA would understand to mean that it is inactive. EX1109, [00348], Table 4. Therefore, compound 9 is another example that satisfies the Structural Limitations, but does not satisfy the Functional Limitations of the claims.

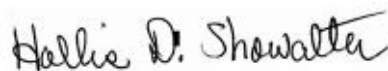
57. Notably, consistent with Dr. Scott's and Dr. Eck's testimonies (EX1117, 40:18-41:13; EX1110, 36:25-37:11), the inventors of WO'185 chose to synthesize and test compounds 2 and 9 to obtain its IC₅₀ value despite having access to modeling software in 2014. EX1109, [0348], Table 4; EX2010, ¶118. I also understand that Dr. Veal's modeling reveals that the docking pose and score for compound 9 suggest, contrary to the reported IC₅₀ value, that compound 9 would irreversibly bind. EX1106, ¶¶130-133. This further supports my opinion that

modeling cannot accurately predict Btk binding in 2010/2011 or even now. Further, the fact that the inventors of WO'185 were investigating and developing this compound, one of which was ultimately shown to be inactive, supports my opinion that there was a lack of predictability in 2010/2011 (and even today) with respect to irreversible BTKIs satisfying the Challenged Claims. If the specification and art had revealed the SAR in 2011, then the inventors of WO'185 would not have chosen to investigate an inactive compound.

VIII. DECLARATION

58. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

DATED: October 30, 2024



Hollis Showalter, Ph.D.