

Filed on behalf of: Pharmacyclics LLC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

Pharmacyclics LLC,
Patent Owner.

PGR2024-00009
Patent 11,672,803

PATENT OWNER'S SUR-REPLY

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2006	U.S. Patent No. 10,570,139
2007	U.S. Patent No. 11,142,528
2008	[Proposed] Request for Correction of Inventorship in Patent Under 37 C.F.R. § 1.324 (Patent No. 11,672,803) (U.S.P.T.O. July 10, 2020)
2009	U.S. Patent & Trademark Office, Certificate of Correction of U.S. Patent No. 11,672,803 (U.S. Pat. Appl. No. 16/926,280), dated July 15, 2024
2010	Declaration of Michael J. Eck, M.D., Ph.D. ("Eck Decl.")
2011	<i>Curriculum Vitae</i> of Michael J. Eck, M.D., Ph.D.
2012	Declaration of David A. Scott, Ph.D. ("Scott Decl.")

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2014	Declaration of Stephen E. Spurgeon, M.D. (“Spurgeon Decl.”)
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2016	Declaration of Ingrid Hsieh-Yee, Ph.D. (“Hsieh-Yee Decl.”)
2017	<i>Curriculum Vitae</i> of Ingrid Hsieh-Yee, Ph.D.
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2111	International Patent Application Publication No. WO 2008/121742 A2
2112	Declaration of Brenda L. Danek In Response to Petitioners' Objections to Admissibility of Evidence Submitted by Patent Owner [<i>served, not filed</i>]
2113	Maestro project archive file containing Glide docking results discussed in EX2010 ¶¶116-117 [<i>served, not filed</i>]
2114	Maestro project archive file containing Glide docking results discussed in EX2010 ¶¶184-185 [<i>served, not filed</i>]
2115	Pymol session file for figure at EX2010 ¶116 [<i>served, not filed</i>]
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2118	Deposition transcript of Hollis Showalter, Ph.D., <i>BeiGene USA, Inc. v. Pharmacyclics LLC</i> , No. PGR2024-00009 (P.T.A.B. Nov. 8, 2024)
2119	Deposition transcript of James M. Veal, Ph.D., <i>BeiGene USA, Inc. v. Pharmacyclics LLC</i> , No. PGR2024-00009 (P.T.A.B. Nov. 22, 2024) ("Veal Dep.")

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2122	Errata for Deposition transcript of Michael J. Eck, M.D., Ph.D., <i>BeiGene USA, Inc. v. Pharmacyclics LLC</i> , No. PGR2024-00009 (P.T.A.B. Oct. 8, 2024) (Ex. 1110)
2123	Errata for Deposition transcript of David A. Scott, Ph.D., <i>BeiGene USA, Inc. v. Pharmacyclics LLC</i> , No. PGR2024-00009 (P.T.A.B. Sept. 27, 2024) (Ex. 1117)

I. Introduction

Pharmacyclics invented a method of treating CLL/SLL¹ by administering—despite lymphocytosis—iBTKIs having ibrutinib's structural features. That innovation prompted the field to revise the CLL/SLL treatment guidelines to account for this unexpected discovery. Pharmacyclics's claims recite this method of treatment with a genus of compounds having ibrutinib's common structural features that effectuate irreversible BTK inhibition. Petitioner centered its arguments on §112, relying on structural differences between zanubrutinib and ibrutinib as alleged evidence of unpredictability across the claimed genus. However, this evidence proved illusory upon cross-examination and rebuttal evidence from Pharmacyclics's experts. Zanubrutinib copies ibrutinib's structural features, mimics adenine's binding to BTK's active site, and achieves exactly the effects the specification teaches for treating CLL/SLL. This result is unsurprising because, as Pharmacyclics's experts explained, a POSA reading the specification would recognize the function of the recited common structural features of the claimed compounds to irreversibly inhibit BTK and treat CLL/SLL.

In its Reply, Petitioner scrambles to rehabilitate its deficient Petition. Most notably, having failed to account for the POSA's knowledge and specification's

¹ Abbreviations are defined in the POR.

teaching of the structure-function relationship for the claimed iBTKIs, Petitioner now submits a 150-page declaration from a new expert. But this new expert's prior publications repeatedly contradict his declaration. When, as here, there was a known binding mode for a lead compound, even Petitioner's experts admit that modeling and docking of kinase inhibitor structures was well known in the field. Further, Petitioner's experts admit on cross-examination that a POSA would use modeling in guiding their identification of iBTKIs for use in the claimed methods.

Petitioner's attempted backfilling cannot overcome the Petition's deficiencies. The record shows that the Challenged Claims are described and enabled and entitled to the June 2011 priority date, disqualifying the art Petitioner cites. The Board should issue a final written decision finding all Challenged Claims not unpatentable.

II. Petitioner's POSA Fails to Account for Modeling

Petitioner declares the Board should "reject" any POSA definition that requires input concerning modeling because chemists "would not rely on modeling to screen the claimed compounds." Reply 3. But failing to account for a POSA's understanding of modeling the structure and function of iBTKIs used in the claims is error. The '803 Patent itself is written with an understanding of the binding mode for ibrutinib-like BTKIs that bind irreversibly via a covalent bond to Cys481 and a phenoxyphenyl group that binds with BTK's hydrophobic back pocket. POR 12-14,

17-21. The art, including materials Petitioner relies on and authored by its expert, extensively discusses how the field used structural modeling of kinase binding generally—and BTKI binding in particular—to inform kinase inhibitor design and selection. POR 25-26, 46-49; EX2120; EX2121. Most importantly, the specification teaches the relationship between irreversible BTK inhibition and the claimed methods of treating CLL/SLL despite lymphocytosis. POR 7-12.

Notwithstanding Petitioner's claims to the contrary, its chemistry expert acknowledges a POSA team would include a specialist in modeling. POR 28; EX2118, 10:10-16. Petitioner unsurprisingly seeks to disregard modeling, given its expert's admission he is not qualified to discuss modeling and did not take it into account in his analysis. POR 48-49; EX2118, 24:21-22, 29:18-30:5, 53:22-54:13. Petitioner now submits a 150-page Veal declaration. EX1106. Dr. Veal, a computational chemist, admits modeling's important role in the context of identifying inhibitors based on a lead compound with a known binding mode—as ibrutinib's binding mode was known. EX2119, 80:15-82:6, 119:7-16; POR 46-49. Further, despite his best efforts, Dr. Veal offers only a handful of “examples” of compounds he contends would not inhibit BTK according to available modeling. §VI.C.

III. Petitioner's Claim Breadth Analysis Ignores the POSA's Understanding of How to Identify iBTKIs

Petitioner's claim breadth analysis relies on a mathematical fallacy that has nothing to do with how a POSA would select compounds for use in the claimed methods. Dr. Showalter offers over 100 pages of theoretical Z'-scaffolds that a POSA would allegedly use to make iBTKIs, but, in forming that opinion, he admits he did not assess 1) whether those cores would lead to inhibition, 2) whether each of his proposed cores had precedent in the context of tyrosine kinase inhibitors (as the patent itself instructs), or 3) what percent would be expected to work. POR 54-57; EX2118, 17:9-18:2, 34:21-38:12, 53:22-54:13. Instead, he performed rote calculations for every theoretical substituent combination to arrive at his proposed breadth of compounds. POR 54-57. And, as he admits, his calculations failed to apply known drug design principles or a POSA's understanding of the binding mode for ibrutinib-like iBTKIs. *Id.*

Petitioner relies on *Idenix Pharmaceuticals v. Gilead Sciences*, 941 F.3d 1149, 1162 (Fed. Cir. 2019) to reject as "backwards" assessing the breadth of a claim reciting structural limitations by taking functional limitations into account. Reply 4. The Federal Circuit made no such broad rejection. In *Idenix*, the claims did not require binding or inhibiting any particular target but rather just that the administered compound treat HCV. 941 F.3d at 1155. There was no structure-function relationship. *Id.* Here, the claims expressly require that the compounds irreversibly

inhibit BTK, and a POSA had the structural data detailing how the ibrutinib-like compound's features bind and inhibit BTK. POR 5-6, 17-26, 46-48.

Petitioner's failure to account for a POSA's understanding of how the structural limitations relate to the functional limitations dooms its §112 analysis. On written description, Petitioner completely ignores the role of the Z'-scaffold in setting the orientation of the fixed ibrutinib features and forming hydrogen bonds to the hinge—known functions that guide a POSA to choose appropriate scaffolds for compounds to use in the claimed methods. POR 21-24, 43-50. And for enablement, Petitioner cannot show undue experimentation without analyzing the extent to which a POSA could select compounds expected to work in the claimed methods and the extent to which those selection choices would be successful. *Id.* 78-85. Instead, Petitioner resorts to improper reliance on the alleged cumulative effort required to screen every member of the genus, without regard to a POSA's informed choices. Such an analysis of the cumulative work required to test each member of a genus is legally improper. *Amgen Inc. v. Sanofi*, 598 U.S. 594, 615 (2023). §VI.B.

IV. Petitioner Misconstrues the Specification and a POSA's Knowledge

A. A POSA Would Understand the Compounds of the Claims as Ibrutinib-Like

There can be no dispute that a POSA reading the specification would recognize the common structural features from ibrutinib—the phenoxyphenyl and linker-warhead—required by the claimed iBTKIs. These features correspond to the

compounds' ability to irreversibly inhibit BTK and treat CLL/SLL. Petitioner's experts admit that the phenoxyphenyl substituent binds within BTK's hydrophobic back pocket, "is important" to the orientation of the compound in BTK, and contributes to selectivity and potency. *E.g.*, EX1003, ¶¶51, 55; EX2018, 71:7-18, 104:15-105:4; EX2119, 141:9-14. Ibrutinib's Z'-scaffold mimics adenine's H-bonds to BTK's hinge, binding within BTK's active site as the specification teaches. *E.g.*, EX1001, 62:15-17; EX1003, ¶54; EX2119, 142:2-6. The linker-warhead orients toward BTK's Cys481 to form a covalent bond and irreversibly inhibit BTK. *E.g.*, EX1003, ¶¶34-35, 51; EX2119, 142:13-143:21; EX2018, 71:19-72:5 (admitting warhead is "need[ed]" "to capture cysteine 481" for irreversible BTK inhibition). Critically, as the specification teaches, it is ibrutinib's ability to occupy and irreversibly inhibit BTK that results in treating CLL/SLL patients and inducing lymphocytosis. POR 7-12, 31-34. The field includes examples of varied Z'-scaffolds appended to ibrutinib's fixed features that chiefly achieve potent irreversible BTK inhibition, as the specification teaches. POR 60. In fact, Petitioner itself explored altering ibrutinib's back-pocket-binding and warhead moieties only to retreat to ibrutinib's structural features for its iBTKI. EX1053. Thus, the evidence demonstrates these common structural features in the claims *define* the compounds that irreversibly inhibit BTK. POR 12-24, 39-49.

B. Marcotte Informs a POSA's Reading of the Specification

Petitioner entirely ignored Marcotte in its Petition and now attempts to minimize its role in a POSA's perspective. Reply 6-7. But its own experts disagree. Despite failing to cite it in his first declaration, Dr. Showalter admits Marcotte "would have been a helpful document" in developing BTKIs. EX2018, 46:12-20, 43:20-44:9. As Dr. Veal agrees, once such structural information about the binding mode for a lead compound becomes available, computational chemistry and modeling is "most effective" to identify "derivatives of the core scaffold" to bind the target. EX2119, 41:10-42:13.

The specification's description of ibrutinib's activity, in view of the POSA's knowledge of art like Marcotte, allows visualization of additional ibrutinib-like iBTKIs for use in the claimed methods. A POSA would understand the expected atomic interactions of a compound sharing ibrutinib's phenoxyphenyl group, a similar adenine mimicking scaffold, and a linker-like structure oriented toward Cys481 binding to BTK based on Marcotte. POR 46-49. Although Marcotte's inhibitor is reversible rather than irreversible, a POSA would understand how the modeled structure informs the orientation of the linker-warhead in ibrutinib and that similar linker-warhead orientations would be required in the claimed iBTKIs. POR 41-42. As Dr. Eck demonstrated—and Petitioner has not challenged, *cf.* Reply 12-

13—a POSA would have been able to accurately visualize the binding of both ibrutinib and zanubrutinib using Marcotte's structure. POR 46-49.

Petitioner argues that because certain compounds have reported poor potency, modeling must not be predictive or those compounds would not have been made. Reply 10-11. But that these compounds were made does not address whether a POSA would recognize ibrutinib-like iBTKIs and whether they could be made and used without undue experimentation. EX2118, 64:1-21, 66:2-20. As both sides' experts acknowledge, chemists may elect to test compounds despite modeling predictions. EX2119, 87:6-90:7; EX1110, 140:12-143:16. Moreover, Petitioner itself predicted the binding mode for a precursor of zanubrutinib using the Marcotte structure, demonstrating that those in the field *did* rely on Marcotte to understand how compounds with ibrutinib's features bind BTK. POR 25-26, 80-81.

C. A POSA Would Understand the Specification's Teaching of Z'-Scaffolds that Form H-Bonds to BTK's Hinge

Petitioner asserts a POSA would not understand from Formula E that the claimed methods could utilize ibrutinib-like iBTKIs with Z'-scaffolds that were not fully aromatic. Reply 8-10. But the evidence demonstrates that a POSA would recognize diverse kinase active site binding elements for use in Formula E.

Although they require a fused heterocyclic ring system consisting of a 5-membered ring fused to a 6-membered ring, the Challenged Claims do not require any particular aromaticity. Petitioner argues that the specification is limited to ring

systems in which both members are aromatic, but the evidence does not support Petitioner's argument. First, rather than aromaticity, a POSA would understand appropriate scaffolds based on their ability to form H-bonds to the hinge. POR 43-46. Indeed, Dr. Veal's own publication reported that "[t]he key features of a purine [i.e., adenine] mimetic are **hydrogen bonding functionality**[" EX2121.0026. Dr. Veal further agrees that it was known that functional groups other than those present in adenine would make H-bonds to the kinase hinge. EX2119, 69:2-9, 71:5-21. Second, as Petitioner's experts admit, known kinase active site scaffolds that mimic ATP's adenine were not limited to fully aromatic structures. *E.g.*, POR 52, EX2018, 75:10-78:7. In his pre-2011 publications, Dr. Veal identifies partially and **fully** non-aromatic "[r]epresentative substructures" that "all have precedent as adenine mimetics for protein kinases" and "offer the potential to satisfactorily replace the two hydrogen bonds formed by ATP to the backbone groups of the kinase hinge region." EX2120.0023, Fig. 16.5; EX2119, 62:3-18, 66:13-19, 112:12-21; EX2121.0026, Scheme 2.2. Thus, contrary to Petitioner's litigation-driven attempt to separate hinge-binding motifs based on aromaticity, the art in 2011—including that relied on and written by Petitioner's own experts—demonstrates the opposite: a POSA would recognize Z'-scaffolds could encompass aromatic, partially aromatic, and non-aromatic "representative substructures."

Because of the robust structure-function relationship for hinge-binding elements, the specification's teaching of scaffold swapping around the fixed features of ibrutinib through Formula E was an established approach in the field in 2011. POR 23-24. Dr. Veal's pre-litigation publication identifies exactly this practice, stating the "role for computational chemistry in the realm of kinase drug discovery is to assist in the design of novel scaffolds" and that "scaffold morphing or hopping ... has arguably been used more in the kinase target space than in any other protein systems class." EX2120.0026; EX2119, 119:7-16 (admitting modeling would be used to identify new scaffolds for use in kinase inhibitors).

D. Modeling Is Visualization, Not Experimentation

Petitioner again tries to minimize the importance of modeling to a POSA in understanding the specification's teaching, arguing that "modeling results were highly variable and did not accurately predict Btk binding"² and "requires extensive efforts." Reply 10-13. But the analysis of Petitioner's expert, Dr. Veal, demonstrates the opposite.

Despite his attempt now to minimize the usefulness of docking scores to a POSA, Dr. Veal previously reported his "personal view is that docking or scoring

² Petitioner cites Dr. Eck's modeling of an ibrutinib analog as purported evidence of unpredictability and variability in modeling. Reply 9 & n.6; EX1106, ¶108. But Dr. Eck testified that the structural differences in his modeled compound did not change his analysis or conclusion, and Dr. Veal did not model the analog to show the change made any impact. EX1110, 168:6-169:2; EX2119, 211:12-21.

energies *should be used as a filter* to winnow down” possible kinase inhibitor structures. EX2120.0030; EX2118, 19:13-20:1. Moreover, Dr. Veal admits that a POSA would have been able to recognize from modeling whether a compound would bind BTK for almost all of the structures he modeled. EX1106, ¶¶118 n.6, 138, 141-161; EX2119, 206:10-207:1. Dr. Veal did not identify a single ibrutinib-like iBTKI that he was unable to model in Marcotte’s structure. Consistent with Dr. Eck’s analysis, EX2010, ¶¶108-118, Dr. Veal’s modeled examples demonstrate the power of modeling and a POSA’s ability to recognize the ibrutinib-like BTKIs for use in the claimed methods.

Petitioner complains that modeling requires effort. But as Petitioner’s experts acknowledge, with the knowledge of Marcotte, modeling is how a POSA visualizes a compound’s binding to BTK. EX2119, 94:19-95:5 (modeling involves a “visualization of how [well] the compound is binding to the target” from which a chemist can “prioritize structures on their likelihood of being successful inhibitors”); EX2018, 181:20-184:2 (modeling software is used to “examine[] visually” kinase inhibitors). Modeling software is part of the POSA’s toolkit in picturing the detailed available structural data to predict the properties of a proposed compound. EX2120.0030 (“visual inspection” from modeling “should be used to guide selection of the final set of analogs to pursue synthetically”). Petitioner cites no support for the premise that a POSA is limited to seeing only with his eyes or can interpret

information using only his memory. Here, the available disclosures of ibrutinib's binding mode were so detailed that a POSA used a software package to visualize the binding. Such a process still qualifies as a POSA "visualiz[ing] or recogniz[ing]" the ibrutinib-like iBTKIs for use in the claimed methods as required by *Ariad Pharmaceuticals v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010).

V. The Specification Describes the Claimed Methods

A. The Specification Provides Blaze Marks to Ibrutinib-Like iBTKIs

Petitioner argues the specification's disclosure is limited to ibrutinib and the fully aromatic Z'-scaffolds included in the specification with no "direction" to "the non-disclosed biaryl Z'-scaffolds and any non-biaryl Z'-scaffolds." Reply 13-15. But the specification is not so limited. §IV.C-D.

In Formula E, the specification teaches a genus of iBTKIs with a linker-warhead structure attached to a moiety that "binds to the active site" of BTK. EX1001, 61:65-62:17. As Petitioner's experts admit, the active site is a well-conserved structure across kinases, *e.g.*, EX2018, 103:12-104:2, and a POSA would understand, when appended to the fixed phenoxyphenyl and linker-warhead of ibrutinib, diverse scaffolds would bind within the active site to form H-bonds to BTK's hinge. §IV.C; EX1106, ¶44 n.4. The Patent further specifies "some

embodiments” of this active-site-binding moiety, listing eight example scaffolds.³ EX1001, 62:44-63:21. As Petitioner’s expert admits, each of the disclosed embodiments has the structural features of the claims: 5:6 fused heterocyclic ring system with 2-4 nitrogen heteroatoms and one nitrogen heteroatom in each ring. EX2119, 179:1-180:21. As such, *Regents of the University of Minnesota v. Gilead Sciences*, 61 F.4th 1350, 1358 (Fed. Cir. 2023) is inapposite. There, the description included structures “so extensive and varied” that “encompasse[d] a significantly larger genus than that claimed.” *Id.* Here, the claimed genus ***encompasses the described embodiments***, reciting common structural features that “constitute the near-entirety” of the claimed Z'-scaffolds. *Id.* A POSA reading the specification would recognize the ibrutinib-like iBTKIs included in the claims. POR 66-72.

³ Petitioner asserts that “modeling suggests that no claimed compound comprising E2-E3 would covalently bind.” Reply 14 n.9. Dr. Veal’s opinion on these compounds was based on Dr. Eck’s “conclusion” that compounds having a heterocyclic ring that does not H-bond to BTK’s hinge would be inactive. EX2119, 218:18-224:22. Dr. Eck did not opine that E2-E3 could never be scaffolds in a BTKI but rather identified that particular compounds made ***no*** H-bonds to the hinge. *E.g.*, EX2010, ¶184. But these particular compounds lacked other structural features, such as the amine substituent, that form necessary H-bonds to support binding. EX2119, 220:20-221:20; EX1106, ¶¶142-149. Further, Dr. Veal modeled a single compound for both scaffolds, which does not support that ***no compounds*** with these scaffolds would covalently bond. *E.g.*, EX1106, ¶¶142-149.

B. The Fixed Features of the Claimed Ibrutinib-Like iBTKIs Correlate to the Claimed Function

The evidence demonstrates that the structural features of the claims *define* the genus of compounds that irreversibly inhibit BTK. §IV.A. A POSA would therefore understand how these features, drawn from ibrutinib, correlate with their ability to bind and irreversibly inhibit BTK and thus be useful in the claimed methods. POR 12-24.

Petitioner argues that because certain compounds falling within the scope of the claims have reported poor potency, the fixed features of the claims legally cannot qualify as common structural features. Reply 16. But “written description does not require a *perfect* correspondence” but a “more modest[.]” “*correlation* between structure and function.” *Ajinomoto Co. v. Int’l Trade Comm’n*, 932 F.3d 1342, 1360 (Fed. Cir. 2019). Moreover, as Dr. Eck explained, and Dr. Veal’s own analysis demonstrates, because of the sophisticated structure-function relationship for the Z’-scaffold, modeling in 2011 would identify those compounds not expected to inhibit BTK. §§IV.D, VI.C.

C. Zanubrutinib Exemplifies the Teaching of the Specification

In a reversal from the Petition, Petitioner criticizes Pharmacyclics’s discussion of zanubrutinib as exemplifying the function of the common structural features. Reply 17-19. But *Petitioner* put zanubrutinib at the center of its arguments. *E.g.*, Pet. 9-20, 64-67, 70-73.

Pharmacyclics demonstrated that Petitioner's reliance on alleged differences between zanubrutinib and ibrutinib were irrelevant or based on the wrong legal standard.⁴ POR 50-54. The specification teaches the importance of inhibiting BTK in the claimed methods and ibrutinib's critical features incorporated into the claim limitations. *Id.* In this context, zanubrutinib reflects the interchangeability of Z'-scaffolds—despite different degrees of aromaticity and planarity. *Id.*

Petitioner now wants the Board to ignore the evidence validating the specification's teaching as “hindsight” and impose a requirement that the specification must “guide a POSA to zanubrutinib.” Reply 19-20. However, “post-priority-date evidence of a particular species can reasonably bear on whether a patent” discloses “structural features common to the members of the genus.” *Amgen, Inc. v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017). Further, the law “does not require that an applicant describe in his specification every conceivable and possible future embodiment of his invention.” *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121-22 (Fed. Cir. 1985). Rather, the specification must identify common structural features or representative species so that a POSA can visualize

⁴ Dr. Veal newly alleges that zanubrutinib's 6-membered ring “projects into a region of Btk that may be used to generate selectivity[.]” EX1106, ¶80. But he does not identify any BTK residues uniquely contacted by this ring, nor does he dispute the unbiased Ligplot+ comparison which shows nearly identical BTK contacts for ibrutinib and zanubrutinib. EX2010, ¶¶96-102; EX2119, 197:11-17. Even this belated attempt to differentiate zanubrutinib has no substance.

or recognize the compounds within the claims. *Ariad*, 598 F.3d at 1350. The specification does so here. POR 39-50.

D. *UroPep* Applies

Trying to minimize the clear parallels to *Erfindergemeinschaft UroPep v. Eli Lilly*, 276 F. Supp. 3d 629 (E.D. Tex. 2017), Petitioner attempts to limit how a POSA would understand the Z'-scaffold's binding within BTK's active site. Reply 20-21. In particular, Petitioner dismisses teaching regarding scaffold swapping and the well-understood structure-function relationship for hinge binding in 2011 because such teaching was not limited to BTK or compounds having the claimed Structural Limitations. *Id.* The evidence again fails to support this assertion.

Here, the common structural features of the claims, derived from ibrutinib, correlate with BTK inhibition. §IV.A. A POSA would understand the Z'-scaffold forms H-bonds to the kinase hinge, which as Petitioner's experts admit, is well-conserved across kinases. EX2018, 103:12-104:2; POR 14-15. Indeed, in his own prior publication, Dr. Veal reported that the ATP binding site "is common to all kinases" and that the "commonality of binding elements provides inhibitor design features that can be *applied to all kinases*." EX2121.0025-0026. Here, far from all kinases, a POSA would only need to apply the teaching of the specification and the claimed features to the Z'-scaffold and its well-understood interaction with BTK's hinge. Because of the "conservation of tertiary structure and mechanism," there is

“a portability of learning from one kinase to the next.” EX2121.0035. Thus, the specification teaches the effect of irreversible BTK inhibition in treating CLL/SLL and reflects the “mature area” of BTK inhibitor design based on the application of the structure-function relationship for diverse heterocyclic hinge-binding elements. *UroPep*, 276 F. Supp. 3d at 639, 645-46.

Petitioner's reliance on *Forte BioSciences v. University of Massachusetts*, PGR2023-00014, Paper 45 (P.T.A.B. June 24, 2024) does not save its arguments. Reply 21. There, the Board found evidence that “certain anti-IL-15 antibodies that inhibit IL-15 signaling *in vitro* have been shown to ... have the opposite effect, *in vivo*.” PGR2023-00014, Paper 45 at 18. But in *Forte*, there was no known structure-function relationship for the claimed antibodies, unlike the sophisticated understanding of BTK binding known to a POSA here. And Petitioner identifies no evidence for any discrepancy between *in vitro* and *in vivo* activity for any ibrutinib-like iBTKI. Instead, Petitioner points to two compounds that it alleges demonstrate a discrepancy between modeled and *in vitro* activity and conclusory testimony from its expert Dr. Rosen that BTK inhibition “is necessary, but not sufficient for treating CLL/SLL and inducing lymphocytosis.” Reply 22. But Petitioner does not describe any BTKI that fails to have the claimed *in vivo* effect, and Dr. Rosen admits his suggestion that inhibiting BTK would not be sufficient is “a presumption that would have to be proven by experimentation” and that he does not “know any negative

results.” EX2021, 94:4-97:2, 219:12-220:19. Instead, the evidence demonstrates ibrutinib-like iBTKIs potently inhibit BTK and would be expected to have the claimed *in vivo* effects. POR 31-38.

VI. The Specification Enables the Claimed Methods

A. Ibrutinib's Activity Guides the POSA to the Use of the iBTKIs in the Claimed Methods

The specification provides considerable data from ibrutinib demonstrating that occupying and irreversibly inhibiting BTK treats CLL/SLL patients and induces lymphocytosis. POR 74-77. As discussed above, a POSA would recognize ibrutinib's common structural features responsible for irreversible BTK inhibition and how to identify additional compounds to achieve the claimed effect. §IV.A. Despite this, Petitioner claims that identifying therapeutically effective doses for other ibrutinib-like iBTKIs would require undue experimentation. Reply 21-23, 25. The evidence fails to support Petitioner's argument.

Petitioner asserts that a POSA would need to engage in preclinical and clinical testing to confirm occupancy and inhibition of BTK by a candidate iBTKI. *Id.* The specification exemplifies multiple clinical trials, and Petitioner offers no reasons why clinical testing of additional compounds would require deviation from these designs or other unreasonable experimentation. POR 83-84. And the specification teaches monitoring and tracking dosing efficacy using an accessible and straightforward occupancy assay, rendering such testing routine. *Id.* In fact,

consistent with the specification's teaching, Petitioner monitored BTK occupancy in assessing zanubrutinib's dosing. *Id.* 77-78. Petitioner's assertion of undue experimentation is improperly grounded on cumulative efforts to test every iBTKI within the claims. §VI.B. Petitioner identifies no evidence that, having the specification's guidance regarding ibrutinib in hand, identifying a therapeutically effective dose for any particular ibrutinib-like iBTKI would require anything more than routine testing. POR 83-85. Further, Petitioner's assertion that BTK occupancy and inhibition is not sufficient to identify therapeutic doses is based on conclusory testimony its expert agrees is a mere "presumption." EX2021, 94:4-97:2, 219:12-220:19.

B. Petitioner's Experts Erroneously Focus on the Cumulative Effort to Use Every Ibrutinib-Like iBTKI

In forming their enablement opinions, Petitioner's experts applied the legally incorrect premise that undue experimentation is grounded in the *cumulative* effort of making each species within a genus. EX2118, 18:3-19:2, 56:22-57:6; EX2119, 236:1-237:5. No such requirement exists. Instead, a POSA must only be able to use the *full scope* of the genus. As the Supreme Court made clear, "enablement is not measured against the cumulative time and effort it takes to make every embodiment within a claim." *Amgen*, 598 U.S. at 615. A specification is not necessarily "inadequate just because it leaves the skilled artist to engage in some measure of adaptation or testing." *Id.* at 611. Nor must a specification "describe with

particularity how to make and use every single embodiment within a claimed class,” where “the specification also discloses some general quality running through the class that gives it a peculiar fitness for the particular purpose.” *Id.* at 610-11. Here, the specification provides exactly this “general quality”—fixed structural features drawn from ibrutinib that correlate to irreversible BTK inhibition.

Further, there is no evidence that a POSA would be unable to identify compounds across the full scope of the ibrutinib-like iBTKIs for use in the claimed methods. The claims recite clear structural features a POSA would recognize. *E.g.*, EX2018, 163:18-167:4. In addition, Dr. Veal was able to model compounds having a variety of Z'-scaffolds to visualize their binding to BTK. *E.g.*, EX1106, ¶¶139-161. Consistent with Dr. Veal's modeling, Dr. Eck testified that “a POSA can envision all possible molecules that fall within the scope of the claims ... there is no structure that is not possible to envision or to recognize.” EX1110, 164:21-165:25; *id.* 53:19-54:6.

Similarly, Petitioner's argument that a POSA would be required to undertake a large screening process is founded on the incorrect and unsubstantiated idea that a POSA would need to make *all possible embodiments* in order to find an operable BTKI. Neither expert offered any opinion about how many of the compounds would not work. *E.g.*, EX2118, 17:9-18:2. In fact, as numerous potent BTKIs and Dr. Veal's own modeling revealed, different Z'-scaffolds result in active inhibitors or

would be expected to have geometries that would be effective. EX1106, ¶118 n.6; EX2119, 206:10-207:1; EX1003, ¶76; EX2012, ¶43. Further, as Dr. Showalter admits, a POSA would understand, guided by modeling, how to select substitutions that would engage the target. EX2118, 28:8-29:9, 41:20-42:11, 48:5-49:3. He also admits that he had not even tried to assess whether the varied structures he proposed would work or not, offering no opinion on the subject. POR 54-55. And Dr. Veal did not analyze the structures Dr. Showalter proposed. *See* EX1106. Without such an analysis, Petitioner's undue experimentation argument is little more than speculation.

Formula E, as understood by a POSA, teaches that various components can be used to bind within the active site of BTK because of the well-established structure-function relationship. POR 23-24, 43-46. It is precisely because of the well-understood binding within the kinase active site that, as Dr. Veal admits, scaffold swapping and morphing was known in the field. Indeed, Dr. Veal's pre-litigation publications identify exactly this practice. EX2120.0026; EX2119, 119:7-16 (admitting modeling would be used to identify new scaffolds for use in kinase inhibitors). As guided by Formula E, a POSA looking to succeed would understand how to select appropriate scaffolds with the fixed components to achieve the specification's teaching of inhibiting BTK to treat CLL/SLL patients. POR 43-50; *Union Oil v. Atl. Richfield*, 208 F.3d 989, 997-1001 (Fed. Cir. 2000) (finding §112

support because a POSA is “aware of the properties of raw petroleum sources and know how to mix streams of such sources to achieve a final product with desired characteristics”).

C. BTK Binding for Ibrutinib-Like iBTKIs Was Predictable

Petitioner argues BTK inhibition was unpredictable. Reply 25-26. The Petition failed to identify a single ibrutinib-like iBTKI that does not inhibit BTK and treat CLL/SLL. Instead, Petitioner's expert identified only potent iBTKIs and conclusory assertions of unpredictability that admittedly failed to account for the known structure-function relationship for iBTKIs. *See* POR 60. At his first deposition, Dr. Showalter attempted to fill this void, identifying two new references containing compounds he asserted were inactive. *Id.* 60 n.8. Yet Pharmacyclics's expert, Dr. Eck, demonstrated that a POSA would recognized using modeling these compounds would poorly bind BTK. EX2010, ¶¶183-185. These belated examples did not demonstrate unpredictability in inhibiting BTK. *Id.*

In reply, Petitioner tries a second time to cure its deficiency, citing compounds from yet more new references it alleges show unpredictably inactive ibrutinib-like iBTKIs. Reply 10-11. Once again, Petitioner's evidence fails.

Initially, Petitioner's expert applies the wrong standard in assessing predictability. Dr. Veal opines that modeling “increase[s] [the] probability of success, although the probability remains low.” EX2119, 99:13-17, 118:10-119:6.

However, he admits that his assessment of “success” is in obtaining a compound with *improved* properties over the lead compound. *Id.* 91:4-22. But that is not the standard for enablement; the claims here do not require an optimized ibrutinib-like iBTKI for use in the claims. POR 89-92. Dr. Veal does not offer any opinion that there is a low probability of success in recognizing a compound that *retains* ibrutinib's activity.

Further, Petitioner's unpredictability evidence rests principally on two compounds—first presented in Reply—that Dr. Veal alleges a POSA would have expected to bind to BTK but have poor potency.⁵ EX1106, ¶¶118, 126-133. These do not demonstrate a POSA would not be able to recognize and use ibrutinib-like iBTKIs in the claimed methods. Dr. Veal opines that docking “suggests that th[e] compound will irreversibly inhibit Btk,” *id.* ¶126, but that itself reveals a POSA's expectation that modeling correlates with activity, as reflected in the accurate modeling in the Marcotte structure of ibrutinib, zanubrutinib, and a zanubrutinib analog. EX2010, ¶¶116-118, 164. Moreover, a POSA would readily determine the

⁵ Petitioner newly emphasizes that covalent binding was unpredictable, relying only on Dr. Veal's declaration. Reply 6-7, 25-26. Dr. Veal opines that covalently bonding BTK's Cys481 requires a “very specific geometry,” citing only a pair of related references without pincite or quotation. *E.g.*, EX1106, ¶56, citing EX1157, EX1158; EX2119, 158:8-160:10. But these references do not discuss geometry of bonding to BTK's Cys481. *See* EX1157; EX1158. The evidence specific to BTK demonstrates that a POSA would understand a warhead could approach Cys481 from numerous trajectories to irreversibly inhibit BTK. POR 20, 41-42.

compounds' activity in a routine IC50 assay. Petitioner offers no evidence that these examples reflect uncertainty across the claimed genus, as its expert admits he offers no opinion on what percentage of the compounds within the claims would not have the claimed functions. EX2118, 17:9-18:2. Two embodiments where modeling may not predict activity is not a number that "is so significant as to force one of ordinary skill in the art to experiment unduly in order to practice the claimed invention." *Warner Lambert Co. v. Teva Pharms. USA, Inc.*, No. 99-922(DRD), 2007 WL 4233015, at *14 (D.N.J. Nov. 29, 2007). To the contrary, in its Petition, Petitioner identified only potent inhibitors within the claimed genus that would be useful in the claimed methods. EX1003, ¶76.

VII. Conclusion

For the reasons set forth above, the Board should issue a final written decision that all Challenged Claims are not unpatentable.⁶

⁶ Recognizing the Petition's weakness, Petitioner now seeks to escape the estoppel consequences of a final written decision, requesting that if the Board finds the Challenged Claims described and enabled by the 2011 specification, then the Board should terminate the PGR. Reply 27 n.11. PGR is available only for a patent that "contains or contained *at any time*" a claim that has an effective filing date after March 16, 2013. Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 293, §3(n)(1) (2011). As Petitioner pointed out, the '280 Application, from which the '803 Patent issued, presented claims that were rejected by the Examiner for lack of written description and enablement. Pet. 36-38. In response, the claims were narrowed to address the §112 rejections until the present claims were allowed. *Id.* 38-41. Because the Examiner found the specification did not disclose the prior, broader claims "in the manner provided by [§]112(a)," those claims were not entitled to "the benefit of an earlier filing date." 35 U.S.C. §§100(i)(1)(B), 120. The effective filing date for those *rejected claims* would be "the actual filing date" of the '280 Application, July 10, 2020. 35 U.S.C. §100(i)(1)(A). Therefore, the '803 Patent, while pending as the '280 Application, contained claims that had an effective filing date after March 16, 2013. The pendency of such claims renders the patent PGR-eligible even though they did not issue. *Microsurgical Tech., Inc. v. Regents of Univ. of Colo.*, PGR2021-00026, Paper 12 at 13-24 (P.T.A.B. June 16, 2021). The Board has a complete record before it on which to make its determination and issue a final decision. Petitioner should be held to the consequences of having submitted a fatally flawed Petition.

Respectfully submitted,

Dated: December 13, 2024

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify that this Patent Owner's Sur-Reply complies with the word count limitation of 37 C.F.R. § 42.24(c)(4) because the Patent Owner's Sur-Reply contains 5,585 words using Microsoft Word's counting feature, excluding the cover page, signature block, and the parts of the Patent Owner's Sur-Reply exempted by 37 C.F.R. § 42.24(c).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 13th day of December, 2024, a true and correct copy of the foregoing **Patent Owner's Sur-Reply and all Exhibits** were served by electronic mail on Petitioner's lead and backup counsel at the following email addresses:

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