

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 RESPONSE

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2102	Libr. of Cong., <i>Network Dev. & MARC Standards Off., pts. VII–X, Understanding MARC Bibliographic: Machine-Readable Cataloging</i> , http://www.loc.gov/marc/umb/um07to10.html (accessed Aug. 5, 2024, 3:40 PM)
2103	Douglas J. Marcotte et al., <i>Structures of Human Bruton's Tyrosine Kinase in Active and Inactive Conformations Suggest a Mechanism of Activation for TEC Family Kinases</i> , 19 Protein Science 429 (2010), https://onlinelibrary.wiley.com/doi/epdf/10.1002/pro.321 (copy from the Publisher)
2104	Douglas J. Marcotte et al., <i>Structures of Human Bruton's Tyrosine Kinase in Active and Inactive Conformations Suggest a Mechanism of Activation for TEC Family Kinases</i> , 19 Protein Science 429 (2010) (copy from the National Library of Medicine)
2105	Nat'l Libr. of Med., Protein Science, https://catalog.nlm.nih.gov/permalink/01NLM_INST/1o1phhn/alma997186893406676 (bibliography and Machine-Readable Cataloging (MARC) records)
2106	Nat'l Libr. of Med., LocatorPlus (May 12, 2009, archived by Internet Archive), https://web.archive.org/web/20090512190928/http://locatorplus.gov/cgi-bin/Pwebrecon.cgi?DB=local&PAGE=First (accessed June 23, 2024, 1:35 PM)
2107	Douglas J. Marcotte et al., <i>Structures of Human Bruton's Tyrosine Kinase in Active and Inactive Conformations Suggest a Mechanism of Activation for TEC Family Kinases</i> , 19 Protein Science 429 (2010) (PubMed record), https://pubmed.ncbi.nlm.nih.gov/20052711/ (accessed June 12, 2024, 2:43 PM)

Ex.	Description
2108	Nat'l Libr. of Med., PubMed (May 5, 2010, & May 6, 2010, archived by Internet Archive), at https://web.archive.org/web/20100505013751/ncbi.nlm.nih.gov/pubmed and https://web.archive.org/web/20100506160612/http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=helppubmed&part=pubmedhelp , respectively (accessed July 28, 2024, 8:49 PM & Aug. 3, 2024, 10:29 AM, respectively)
2109	References citing Douglas J. Marcotte et al., <i>Structures of Human Bruton's Tyrosine Kinase in Active and Inactive Conformations Suggest a Mechanism of Activation for TEC Family Kinases</i> , 19 Protein Science 429 (2010) (obtained from Google Scholar)
2110	Declaration of Nathaniel E Frank-White, Records Request Processor, Internet Archives (July 18, 2024)
2111	International Patent Application Publication No. WO 2008/121742 A2

I. Introduction

The entire Petition is based on a demonstrably incorrect premise. This is not a patent about a new class of irreversible BTK inhibitors (“iBTKIs”); Pharmacyclics had disclosed these inhibitors years before the patent application. The inventors of U.S. Patent No. 11,672,803 (“the ’803 Patent”) pioneered a new method of using this class of iBTKIs by doing literally the *opposite* of what had been done before: *continuing* (rather than terminating) treatment for chronic lymphocytic leukemia (“CLL”) and small lymphocytic lymphoma (“SLL”) upon the onset of lymphocytosis (an increase in circulating lymphocytes). Notably, Petitioner does not dispute the uniqueness or importance of that invention, which opened up a new paradigm of treatment, one it followed for its own product.

Against that backdrop, Petitioner’s arguments ring hollow. Even though the therapeutic compounds in the claimed method are structurally constrained—fixing two of their three main components—Petitioner argues that there are numerous possibilities for the third, relying on every conceivable substitution. But patents are not judged based on the number of random substitutions that might be possible; patents are judged from the standpoint of a person of ordinary skill (“POSA”), armed with (1) the teachings of the specification; (2) the significant knowledge and skill in the art at the time; and (3) a motivation to succeed. Applying the appropriate

standards, the claims easily satisfy the written description and enablement requirements.

Indeed, the '803 Patent provided the blueprint for Petitioner's zanubrutinib, which copies the key structural features of ibrutinib, including the components driving irreversible BTK inhibition and fixed in the claims. Not surprisingly, when zanubrutinib is used according to the patented method, it treats CLL/SLL. Following the '803 Patent, Petitioner specifically instructs physicians to continue treatment despite the onset of lymphocytosis, and not to view it as a sign of disease progression.

Focusing on the compounds in the claims, the specification provides ample description and enablement. Petitioner's arguments to the contrary fixate on the generic portion of the structure while ignoring the critical fixed components that correspond exactly to ibrutinib, and not coincidentally zanubrutinib. While Petitioner points to alleged superior safety of zanubrutinib to ibrutinib as evidence of invalidity, in reality zanubrutinib demonstrates the patent's teaching. Zanubrutinib owes its potent BTK inhibition and clinical efficacy to the structural characteristics recited in the claims and taught in the specification. Even the portion of zanubrutinib that differs from ibrutinib binds BTK in a similar fashion, mimicking adenine, and orienting the common structural features of both molecules to make the same critical interactions. Despite alleging factors that "could" affect binding or

other properties, Petitioner fails to address the teaching in the specification, which, when combined with available information in the art in 2011, provides the necessary three-dimensional structure-function correlation. Most notably, Petitioner's expert disregarded the key prior-art publication of the crystal structure of BTK bound to a compound with nearly identical binding to ibrutinib. Not only did Petitioner's expert ignore the relevant structural biology and software available in 2011, he admitted that he lacked the expertise to even comment on their impact.

Pharmacyclics's experts offer the evidence ignored by Petitioner. Accordingly, the compounds set forth in the claims and the novel method of using them are fully described and enabled, and the Challenged Claims should not be found unpatentable.

II. The '803 Patent

The '803 Patent claims priority to a June 2011 non-provisional patent application, U.S. Patent Application No. 13/153,317 ("317 Application").¹

¹ Petitioner alleges the '803 Patent specification lacks §112 support. The specification is identical to the '317 Application, to which the '803 Patent claims priority. EX1001.002. Pharmacyclics therefore refers to the specification and state of the art as of June 2011. However, for its earliest priority dates, the '803 Patent also relies on a series of provisional applications filed between June 3, 2010 and

A. '803 Patent Claims

Petitioner challenges the validity of claims 1-8, 12, and 20 (“Challenged Claims”). These claims recite methods of treating CLL/SLL by continuously dosing a therapeutically effective amount of an iBTKI having an ibrutinib-like structure² *wherein lymphocytosis is not considered progression of the CLL or SLL*. Thus, the claims capture the unexpected discovery that when treating CLL/SLL with ibrutinib-like iBTKIs, the lymphocytosis observed correlates to efficacy—not disease progression. Therefore, the claimed method requires administering the drug on a

April 5, 2011. *Id.* Petitioner has not cited art dated earlier than June 2011 or introduced arguments about the specific disclosures of the provisional applications. Pharmacyclics does not waive the ability to assert an earlier priority date based on the disclosures of the provisional applications. Because the specification provides §112 support as of 2011, it also provides support as of the filing of the other non-provisionals to which the '803 Patent claims priority.

² As used here, “ibrutinib-like iBTKIs” are iBTKIs having the structural features (based on ibrutinib) recited in the claims: fixed phenoxyphenyl and linker-warhead substituents attached to a central 5:6 heterocyclic scaffold with nitrogen heteroatoms.

continuous daily regimen *through the observed lymphocytosis*. Independent claim 1 is reproduced below.

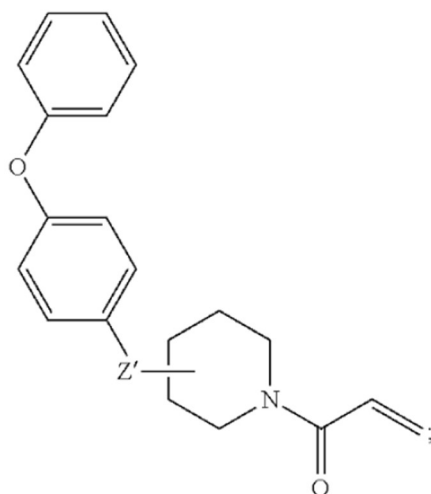
Claim 1 states:

1. A method for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual comprising:

orally administering to the individual a therapeutically effective amount of an irreversible inhibitor of Bruton's tyrosine kinase (Btk) on a continuous daily regimen until progression of the CLL or SLL or unacceptable toxicity;

wherein lymphocytosis is not considered progression of the CLL or SLL,

and wherein the irreversible inhibitor of Btk is a small organic molecule having the structure:



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms;

wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one

nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom;

and wherein the irreversible inhibitor of Btk forms a covalent bond with Cys481 of a Bruton's tyrosine kinase.

Claim 8 is similar to claim 1 but has the additional requirement that "said administration of the therapeutically effective amount is an amount that results in >90% of the Btk active sites in the peripheral blood mononuclear cells of the individual being occupied by the irreversible inhibitor of Btk twenty-four hours following said administration."

The dependent Challenged Claims include further limitations. These limitations include a requirement for specific BTK occupancy (claim 2), using pharmacodynamic parameters to determine the therapeutically effective dose (claim 3), a fixed dose (claim 4), specific pharmacokinetic results (claim 5), treating CLL and SLL with once daily dosing (claims 6 and 7, respectively), and additional limitations on the heteroatoms of Z' (claims 12 and 20).³

³ Petitioner does not separately challenge the §112 support of the dependent claims but relies on its arguments for the independent claims. Pet. 80-81, 92-93; EX2021, 207:1-210:7, 245:12-250:3; EX2018, 184:17-186:14. These dependent claims are fully described and enabled for the same reasons described below.

B. '803 Specification and Related Technology**1. Treatment of CLL/SLL with Therapeutically Effective Amounts of Ibrutinib-Like iBTKIs Through Lymphocytosis**

CLL and SLL, often grouped together as CLL/SLL, are understood to be the same disease with slightly different manifestations. EX1001, 35:21-30. CLL, one of the most common types of leukemia, is characterized by unregulated growth of B-cells, a type of lymphocyte. *Id.* 35:39-40. CLL patients present with elevated lymphocyte counts in the blood and bone marrow. *Id.* 35:29-30, 35:61-63. In SLL, instead of localizing to the blood and bone marrow, lymphocytes accumulate in the lymph nodes, frequently grossly enlarging these structures. *Id.* 35:25-28, 35:60-61. In 2011, CLL/SLL was generally considered incurable. *Id.* 35:39-36:23; EX2014 ¶¶40-43. Many patients eventually experienced worsening disease after initial response to treatment (“relapsed”) or become resistant to available treatment (“refractory”). These refractory/relapsed patients faced poor outcomes and a median overall survival of less than three years. EX2014 ¶¶44-46.

Prior to the '803 Patent, the principal CLL/SLL therapies consisted of chemotherapy or chemoimmunotherapy (chemotherapy coupled with immunotherapy) and stem cell transplantation. Chemotherapy resulted in significant toxic side effects. *Id.* ¶¶47-49. Stem cell transplants had high mortality rates and were considered too high-risk for frontline treatment. *Id.* ¶¶47, 51. For

refractory/relapsed patients, there were limited treatment options and they faced poor prognosis. *Id.* ¶¶45, 50.

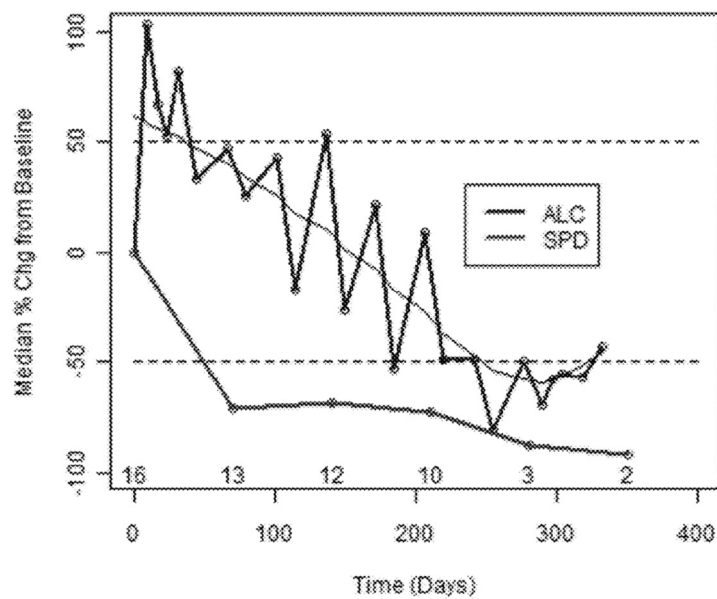
In 2011 and today, clinicians monitor patient lymphocyte counts to track CLL/SLL disease progression. EX2002.0005-.0007; EX2014 ¶¶41, 61-62. The treatment guidelines in 2011 instructed that patient responses to treatment were based on improvement—decreases—in circulating lymphocytes, thus, lymphocytosis was a sign of disease progression. EX1001, 135:18-19 (“IW criteria for CLL are based on improvement in circulating lymphocytes[.]”)⁴; EX2002.0005-.0007. Therefore, when a patient receiving treatment experienced lymphocytosis, that was a sign of disease progression and treatment failure. EX2002.0005-.0007; EX2014 ¶¶41, 61-62.

The '803 Patent discloses the treatment of CLL/SLL with ibrutinib-like iBTKIs. BTKIs inhibit Bruton's tyrosine kinase (BTK), a protein kinase involved in the development, signaling, and survival of B-cells. EX1073.008-.009, Tbl. 2; EX2014 ¶55; EX1072.004. Aberrant BTK activity had been associated with various lymphomas, including CLL/SLL. EX2014 ¶56; EX1073.004-.005. Well before 2011, scientists designed and disclosed the selective iBTKI's discussed in the '803

⁴ Unless otherwise noted, all emphases are added, and internal quotations, citations, and footnotes are omitted.

Patent, including Pharmacyclics's lead iBTKI, ibrutinib. EX1060; EX2025; EX2111; EX2014 ¶¶56-57.

The '803 Patent describes ibrutinib's remarkable efficacy in treating CLL/SLL patients. In particular, Examples 6, 7, 10, 11, and 14 together describe a surprising finding of responses to ibrutinib treatment in CLL/SLL clinical trials. Contrary to the conventional expectation that lymphocytosis indicated worsening disease and treatment failure, CLL/SLL patients treated with ibrutinib experienced rapid lymphocytosis accompanied by "a sustained decrease in disease burden" where lymph nodes dramatically shrank in size. EX1001, 135:60-64.



'803 Patent, Fig. 5

EX1001, Fig. 5, 8:40-42 (illustrating spikes in lymphocytes with ibrutinib treatment), 135:30-44, Fig. 2, 8:30-32. As the specification notes, for the "majority of CLL

patients treated with a Btk irreversible inhibitor, there was an initial, rapid, and prominent reduction in nodal disease and spleen size ... Simultaneous with these changes, patients reported symptomatic improvement.” *Id.*, 135:30-38.

To account for this unexpected effect, the inventors coined a new category of “nodal” response. *Id.*, 139:51-140:25 (Example 10), 142:26-30, 142:55-66 (Example 11). This new concept was necessary to account for the clinical benefits patients experienced from ibrutinib (shrinking lymph nodes and reduced disease burden), despite the lymphocytosis that conventional guidelines classified as treatment failure. EX2014 ¶¶62-63, 65, 79-81, 88-89. After properly accounting for such “nodal responses,” the specification describes continuous dosing of ibrutinib through lymphocytosis had extraordinary results for CLL/SLL patients, particularly for the most difficult to treat relapsed/refractory patients. EX1001, 143:25-36 (“A high proportion (85%) of relapsed or refractory patients are free-of-progression at 6 months.”); *see id.*, 135:36-38, 135:65-67, 136:10-13, 139:51-140:25, 142:18-66, 147:36-40.

The specification goes beyond observing that CLL/SLL patients experienced lymphocytosis with ibrutinib treatment. The specification teaches lymphocytosis as a class-specific phenomenon for ibrutinib-like iBTKIs. *Id.*, 143:30-31. The specification identifies the mechanism for this class-effect, teaching lymphocytosis as “likely a consequence of the inhibitory effects of a Btk irreversible inhibitor,”

which causes “mobilization” of lymphocytes away from nodal and splenic compartments. *Id.*, 135:30-36; *id.*, 11:16-22, 28:32-43, 34:42-53, 89:55-65, 129:5-13. The specification further emphasizes the importance of this finding, characterizing the disclosed invention as based in part on Pharmacyclics’ “unexpected discovery that Btk inhibitors induce mobilization (or, in some cases, lymphocytosis) of lymphoid cells in solid hematological malignancies.” *Id.*, 11:16-22; *see also id.*, 1:63-2:5, 28:32-41, 34:42-50, 89:55-65, 129:5-13.

The specification additionally provides a novel method of measuring BTK occupancy to identify a therapeutically effective dose that treats CLL/SLL and induces lymphocytosis. *Id.*, 136:28-29 (“Tests for Btk occupancy by the drug (‘occupancy’) are performed”); *see also id.*, 136:22-45 (describing dose-finding study in which BTK occupancy is assessed). Specifically, the patent teaches that using a “specially designed fluorescent probe[,]” clinical researchers can examine the inhibitors’ direct blockade of BTK—the “occupancy of the Btk active site by the drug”—and then use this assay to “determine what drug levels are required to achieve maximal occupancy of Btk.” *Id.*, 137:14-26. The inventors discovered that a direct measure of the drug’s effect is possible because of the irreversible inhibition of BTK and access to relevant samples, i.e., tumor cells isolated from patient blood. EX2014 ¶¶96, 120. Thus, the specification teaches identifying effective doses for

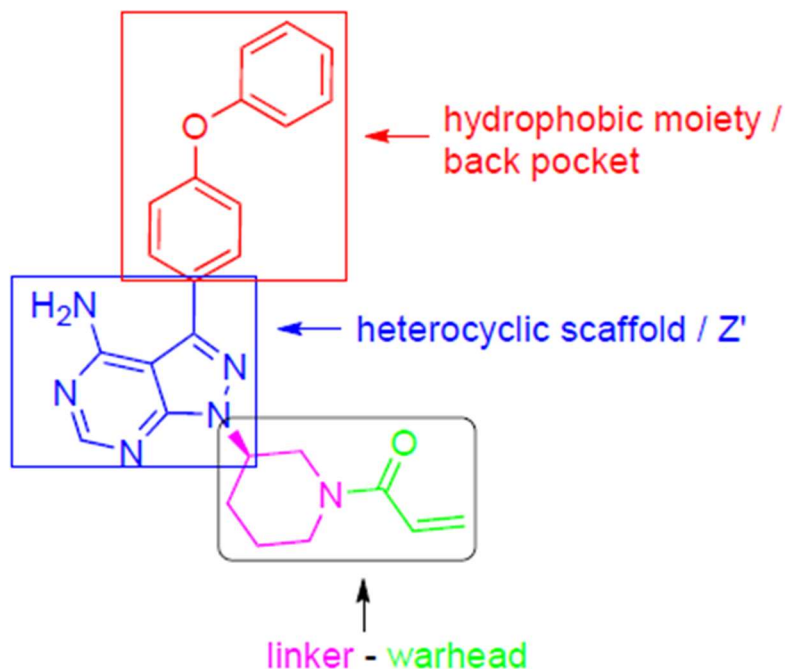
the ibrutinib-like iBTKIs of the claims by directly assessing the impact of the inhibitors on BTK in blood samples. *Id.* ¶¶95-99, 118-120.

2. Structural Features of Ibrutinib-Like iBTKIs for Use in the Claimed Methods

In 2011, a POSA reading the '803 Patent would have understood the structural features of ibrutinib-like iBTKIs and how these features function to selectively, potently, and irreversibly inhibit BTK. EX2010 ¶¶43-44. A POSA would understand the specification in the context of the well-developed field of protein kinases. Protein kinases catalyze the transfer of phosphate from ATP to other proteins in the body to modulate their biologic activities. EX1077.002; EX2010 ¶41; EX2012 ¶21. Aberrant kinase activity had been implicated in many diseases and disorders, especially cancers, making kinases attractive targets for drug development. EX1077.001; EX2010 ¶42; EX2014 ¶¶52-54. In 2011, a POSA would read the '803 Patent specification with the understanding gained from thousands of known kinase inhibitors. *E.g.*, EX2028.0001. Nearly 1300 crystal structures of kinases had been determined and deposited in a public database, including, most importantly, the structure of BTK bound to a compound with ibrutinib-like binding. EX2010 ¶46; EX2001.

Ibrutinib has three principal components: (i) a linker connected to a terminal warhead (purple and green structures); (ii) a hydrophobic phenoxyphenyl moiety

(red structure), and (iii) a heterocyclic scaffold (blue structure). EX2010 ¶¶70; EX1003 ¶34.



Ibrutinib is identified as a preferred compound in the specification, and—as Petitioner admits, Pet. 35-36—is used in the examples to treat CLL/SLL patients. EX1001, 80:63-65, 134:26-136:13, 139:48-144:41, 146:6-148:56.

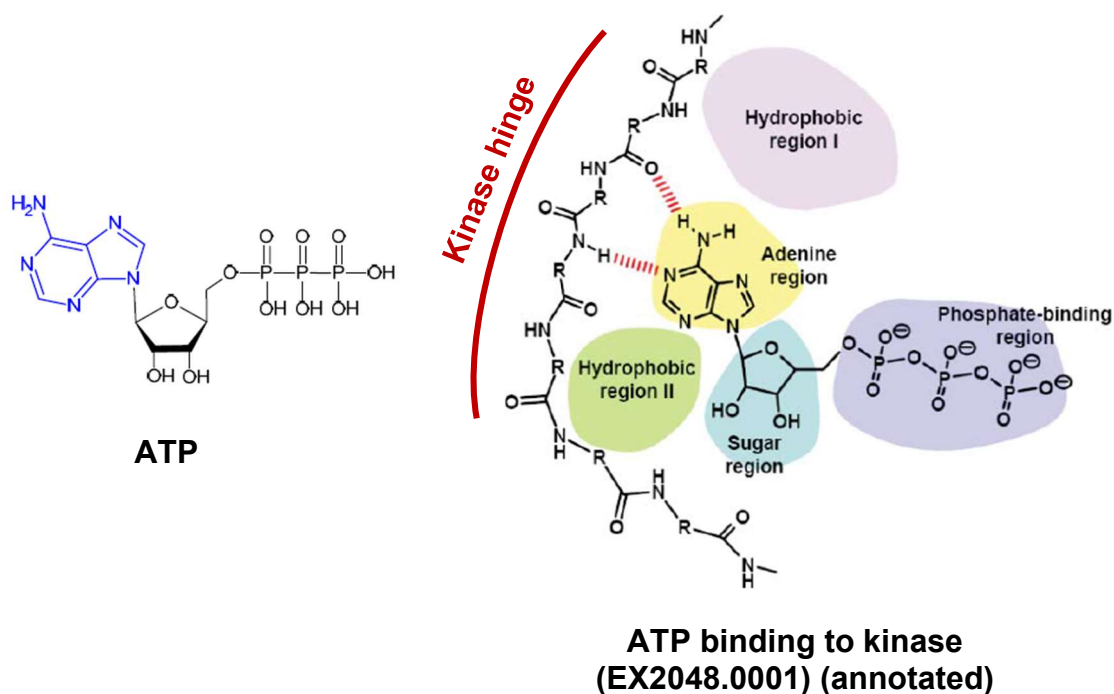
A POSA reading the '803 Patent would have been aware that BTK has a unique cysteine near the ATP-binding site (“active site”), Cys481, shared by only a handful of other kinases. *Id.*, 45:56-60; EX2111, [00208]-[00209]. EX2010 ¶¶49-50, 72. Because cysteines have a reactive side chain, they will form covalent bonds with particular electrophilic “warhead” groups on an inhibitor compound. EX1001, 26:23-31; EX2010 ¶¶49-51, 72. In the '803 Patent, the warhead is attached via a

“linker” moiety that allows for positioning the warhead to react with the cysteine. EX2010 ¶¶47-49, 72; EX2111, [00209].

As for the phenoxyphenyl hydrophobic moiety, a POSA reading the '803 Patent understood that another feature of kinases is conserved hydrophobic pockets, termed “specificity pockets” or “back pockets,” adjacent to the active site. EX2010 ¶¶58-59; EX1052.002; EX1077.002-.004, .009. Although the existence of these pockets is conserved, they differ between kinases by their size and accessibility. EX2010 ¶¶58-59; EX1052.002. A POSA reading the '803 Patent understood that the choice of substituents interacting with the “specificity” or “back pocket” contribute to an inhibitor's specificity and potency. EX2010 ¶¶55-59, 81; EX1052.002; EX2028.0002. The specification highlights the phenoxyphenyl group for binding within BTK's back-pocket because *all depicted structures* in the specification include this component to selectively inhibit BTK. EX1001, 65:9-80:35. As the Institution Decision (“ID”) correctly noted, “[t]here is no dispute that the Specification describes the phenoxyphenyl hydrophobic moiety and the linker-warhead of [ibrutinib].” ID 25.

Because all protein kinases bind ATP, the active site is highly conserved across kinases. EX2010 ¶¶45-46; EX1052.002; EX1075.003; EX2028.0001-.0002. The adenine of ATP (blue substructure in figure below) hydrogen-bonds to the kinase “hinge region”—a connection between two lobes of the kinase. EX2010 ¶¶45,

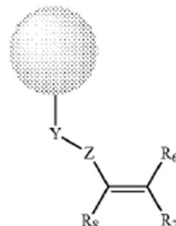
61; EX2012 ¶¶21-25; EX1052.002-.003; EX1077.002. Thus, the hinge residues are particularly conserved across kinases because of their specific involvement in binding ATP. EX2010 ¶¶45-46, 61-63; EX2028.0002. A POSA reading the '803 Patent understood that numerous kinase inhibitors included scaffolds that mimic the bonding of ATP to the hinge residues. EX2010 ¶¶63, 67, 83-89; EX2012 ¶¶22, 27-28.



The hinge-binding scaffold (Z') of the claims is also disclosed in the '803 Patent. Formula E teaches that the linker-warhead attaches to a scaffold that binds to the BTK active site and identifies examples of 5:6 fused rings that could be used. Importantly, the specification identifies that Z' is a moiety that binds to the active

site of a tyrosine kinase, expressly invoking the detailed knowledge of how the scaffold portion of such compounds would bind to the hinge region.

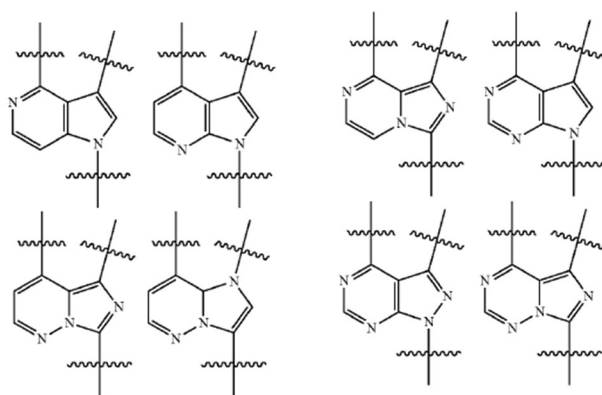
Formula (E)



wherein:

wherein $\odot$ is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

EX1001, 62:1-17. As Pharmacyclics taught in its earlier patent disclosing these compounds, “the core scaffold” “fit[s]” “into the active site ATP binding pocket” to allow the linker-warhead to form a covalent bond with Cys481. EX2111, [00340]; *id.* [00453]-[00454]. Among the wide variety of 5:6 heterocyclic scaffolds known in the art to bind the kinase active site, the specification discloses a sampling:



EX1001, 62:44-63:21. Despite introducing these example scaffolds as “biaryl,” a POSA reading the specification would not consider that term to encompass only fully aromatic structures. EX2010 ¶¶65-68. Contrary to Petitioner’s attempts to

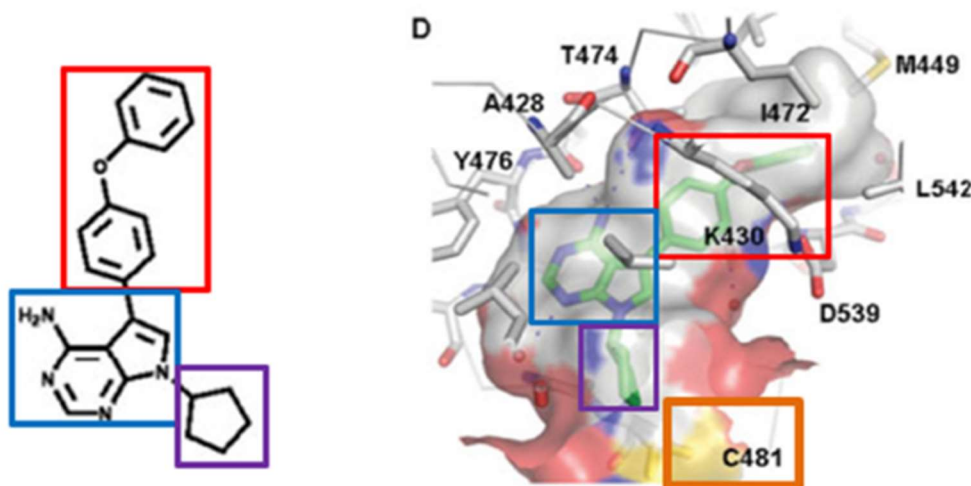
distinguish aromatic and non-aromatic structures, and emphasize other extraneous distinctions, a POSA would instead understand that the appropriate focus for such “active site” binding structures would be limited to those that make appropriate hydrogen-bonds to the BTK hinge-region. §II.C.3; EX2010 ¶¶60-64, 83-89.

C. The '803 Patent Reflects the POSA's Understanding of the Structure-Function Relationship for Ibrutinib-Like iBTKIs

In 2011, a POSA reading the '803 Patent would have had available three types of valuable information 1) information about the structures of ibrutinib-like iBTKIs; 2) information about BTK and how inhibitors with ibrutinib's features interact with it, including modeling software and methods to guide the selection of additional active inhibitors; and 3) functional data from the '803 Patent confirming the role of irreversible BTK inhibition in the claimed methods of treating CLL/SLL.

A POSA reading the '803 Patent would have known that the class of ibrutinib-like iBTKIs, including ibrutinib itself, and other iBTKIs had been disclosed by the ibrutinib inventors years before 2011. EX2025; EX2111. Further, consistent with Formula E, a POSA would have been aware of numerous other structures that inhibit BTK (*e.g.*, EX1073.008-009, Tbl. 2), as well as the crystal structure of BTK bound

to a compound (B43) with ibrutinib-like binding (“Marcotte”).⁵ EX2001. Given the benefit of the clinical and irreversible inhibition data in the ’803 Patent, Marcotte confirmed the orientation and binding of the key structural features of ibrutinib-like iBTKIs. EX2010 ¶¶71, 111-112. The bound B43 has the same phenoxyphenyl moiety (red box) as ibrutinib and a similar heterocyclic scaffold (blue box). Although lacking a warhead, B43 has a cyclopentyl group in a similar location to ibrutinib’s linker (purple box) that is oriented toward BTK’s Cys481 (orange box). *Id.* ¶73.

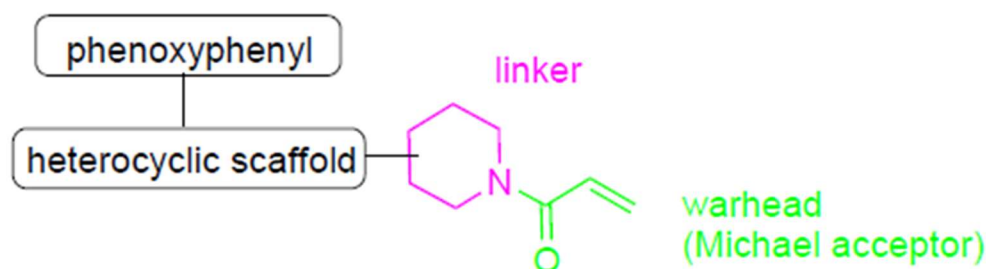


**Ibrutinib Scaffold Bound to BTK Active Site
EX2001.0003 (cropped and annotated)**

⁵ The Marcotte structure was publicly available by June 2011, and the specific coordinates were available to use in modeling software. EX2016; EX2010 ¶¶71, 111-112.

Because of the '803 Patent's disclosure, a POSA would have understood Marcotte reveals the structure-function relationship for the structural components of ibrutinib-like iBTKIs and their binding to BTK.

1. Linker-Warhead Binds to BTK's Active-Site Cysteine Residue



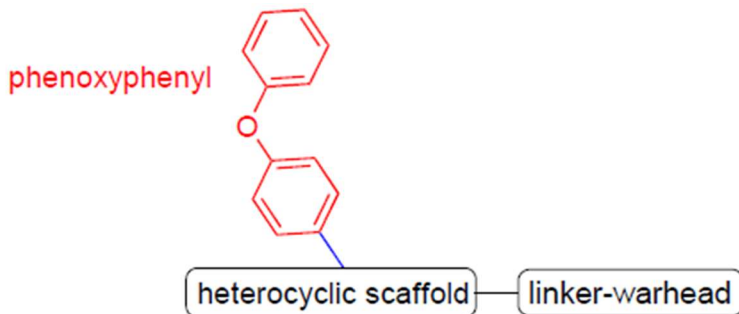
A POSA would have known from the '803 Patent that the linker-warhead forms a covalent bond with BTK's Cys481, making this class of iBTKIs irreversible. EX2010 ¶¶47-48, 72-75; EX2111, [00208]-[00209]. The strength of the covalent binding to Cys481 is a critical driver of inhibition by ibrutinib-like iBTKIs, which Petitioner's expert Dr. Showalter agrees is "directly responsible for the binding of Btk[.]" EX1003 ¶56; EX2010 ¶¶47-48, 72-75. The specification further confirms that ibrutinib irreversibly binds BTK, providing data demonstrating irreversible inhibition and reporting that ibrutinib occupies BTK in patients. EX1001, 138:33-43; EX2014 ¶¶96-97.

Post-priority data confirm the importance of the linker-warhead. The ibrutinib and zanubrutinib crystal structures show that the linker-warhead bonds to Cys481. EX1003 ¶55; EX2010 ¶¶74, 94. Further, Petitioner's own experiments demonstrate

that removing the warhead from iBTKI structures results in over 100-fold decrease in BTK inhibition, verifying the critical role of this component. EX1053.003-.004 (reporting difference in IC₅₀ for structures with and without warheads); EX2010 ¶136.

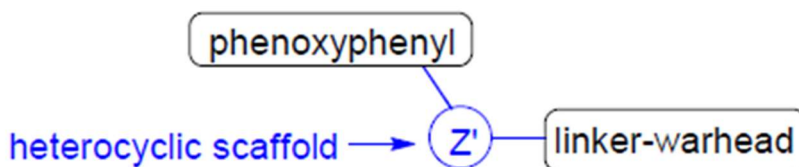
In 2011, a POSA reading the '803 Patent would understand that the linker-warhead could covalently bond with Cys481 from a variety of orientations. First, the specification reports various orientations of the linker-warhead. EX1001, 52:45-53:18 (disclosing different orientations of the linker), 80:1-18, 80:38-65 (disclosing ibrutinib, its enantiomer, and racemic mixture as iBTKIs); EX2010 ¶¶53-54, 76. Second, Marcotte confirms Cys481 is located on the solvent-exposed surface of BTK and can rotate. EX2010 ¶¶76-78; EX2001.0003. Third, a POSA would understand, in view of Marcotte, that Pan reports a number of different iBTKIs with linker-warhead components having varied orientations, lengths, and composition all irreversibly inhibited BTK with similar potency. EX1060.003. Thus, in 2011, a POSA would appreciate that changing the geometry of the linker-warhead did not disrupt the ability to bind Cys481. EX2010 ¶¶78-80.

2. Phenoxyphenyl Group Binds within BTK's Back Pocket



A POSA reading the '803 Patent would know that hydrophobic moieties binding within the back pocket confer potency and selectivity to protein kinase inhibitors. EX2010 ¶¶55-59, 81-82; EX1052.002; EX2028.0002. Marcotte demonstrated that the phenoxyphenyl of inhibitors with ibrutinib-like binding occupies BTK's back pocket. EX2010 ¶81; EX2001.0004-.0005. And all structures depicted in the '803 Patent maintain this important determinant, like the claims.

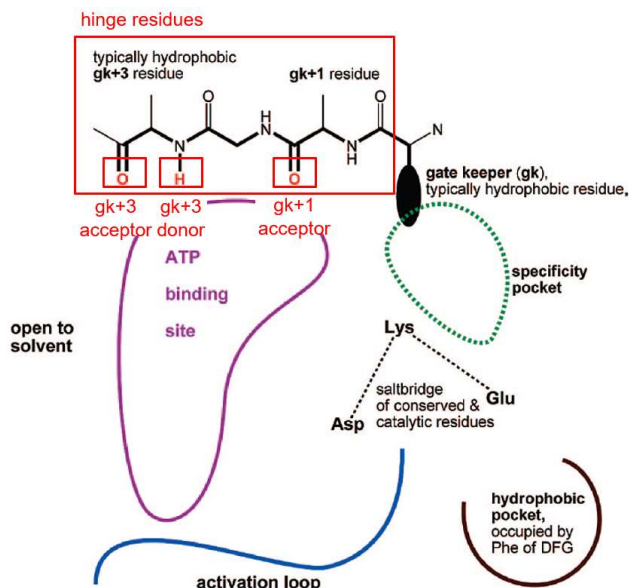
3. Z'-Scaffold Makes Predictable Hydrogen Bonds to BTK's Hinge



The '803 Patent describes the Z'-scaffold as binding to the active site of BTK where ATP binds. EX1001, 62:15-17. In 2011, a POSA reading the specification would understand that ATP's adenine forms key H-bonds with specific residues within the conserved kinase hinge. EX2048.0001; EX1052.002; *see also* EX1052.0003, .0007 (entry 1 of Table 2, showing that 40 unique kinases have

identical binding to an adenine scaffold); EX2010 ¶¶45, 61; EX2012 ¶¶21-25. Particularly given the teaching of Marcotte, a POSA would expect the Z'-scaffolds of ibrutinib and ibrutinib-like iBTKIs to mimic these hinge-region bonds. EX1052.002, Fig. 1 legend; EX1077.003 (stating “[m]ost” inhibitors form H-bonds to the hinge “mimicking the hydrogen bonds that are normally formed by the adenine ring of ATP”); EX2028.0003, Fig. 3 legend (describing hinge-binding elements “based on targeting the available hydrogen bond interactions[.]”); EX2028.0003-.0004; EX2010 ¶¶61-63, 111-112; EX2012 ¶¶26-27.

The hinge residues that form these bonds are named for their distance from a “gatekeeper” residue which dictates access to the back pocket: gatekeeper+1 (GK+1) and gatekeeper+3 (GK+3). EX1052.002; EX2010 ¶¶61-62; EX2012 ¶23.

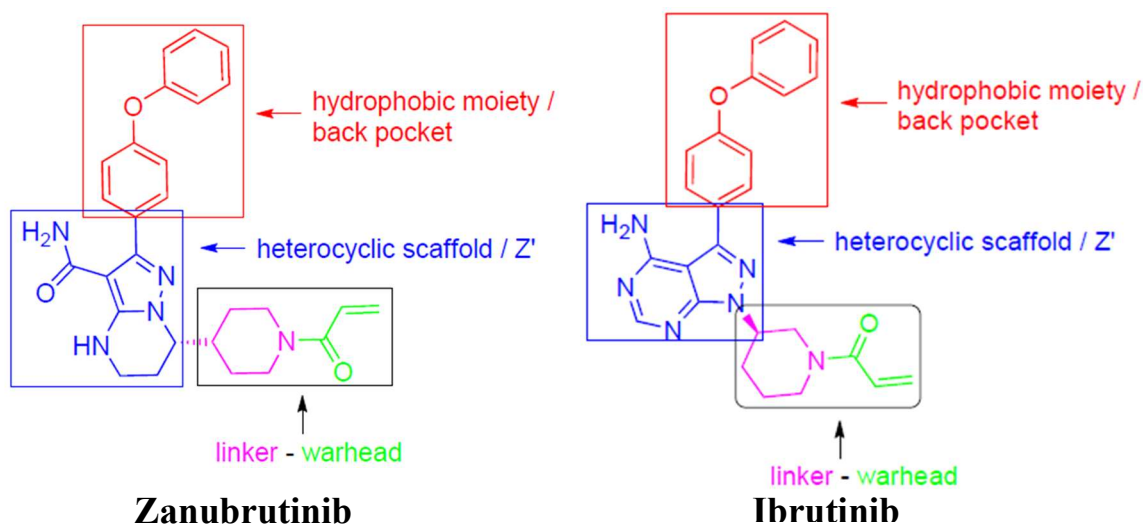


EX1052, Fig. 2 (annotated)

GK+1 presents a potential H-bond acceptor and GK+3 presents a potential H-bond donor and acceptor. EX1052.002 (Fig. 2); EX2010 ¶¶62; EX2012 ¶¶24-25. For compounds with ibrutinib-like binding, as shown in Marcotte, the Z'-scaffold hydrogen bonds with the expected hinge residues and orients the phenoxyphenyl and linker-warhead components within BTK—projecting the phenoxyphenyl toward the back-pocket and projecting the linker-warhead toward Cys481. EX2001.0001-.0002; EX2010 ¶¶71, 111-112.

The specification's Formula E recognizes the fungibility and predictability of substructures that bind to the highly conserved kinase hinge while maintaining the fixed linker-warhead and phenoxyphenyl groups of ibrutinib. EX1001, 61:66-63:21; EX2010 ¶¶60, 83-84. For the Z'-scaffold, Formula E invokes the kinase inhibitor design strategy “scaffold swapping,” where scaffolds known to bind to the kinase hinge are swapped between inhibitor structures. EX2010 ¶¶103-107; EX1077.007 (describing the design of “hybrid compounds in which a portion of one inhibitor is grafted onto a portion of another, guided by superimposition of the bound structures[]”). In this way, a POSA reading the '803 Patent would have recognized replacing “the hinge-binding element of a given kinase lead” was a “powerful approach” to generate additional ibrutinib-like iBTKIs. EX2028.0004-.0005; *see also* EX1052.019-.020; *id.*, Fig. 7; EX2010 ¶¶103-107.

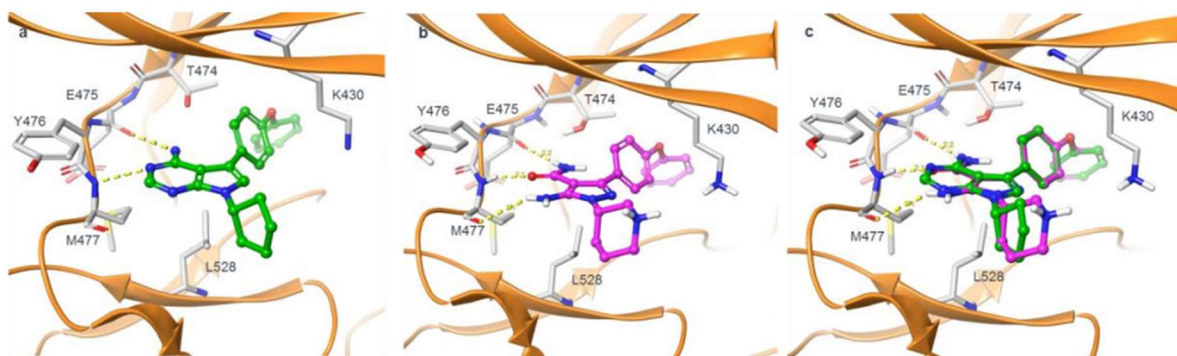
Given the high potency and clinical responses shown for ibrutinib in the '803 Patent, a POSA would expect this approach to yield additional ibrutinib-like iBTKIs for three reasons. First, the specification demonstrates ibrutinib's linker-warhead and phenoxyphenyl components resulted in significant, potent activity to inhibit BTK and treat CLL/SLL patients. §II.B.1. Second, as reflected in the specification's Formula E, the highly conserved kinase active site makes similar interactions with hinge-binding elements. Third, in 2011, a POSA would have known of hinge-binding elements that make productive interactions with the hinge residues. EX2010 ¶¶83-89. As shown below, zanubrutinib employs this approach of modifying the hinge-binding element while maintaining the structural features from ibrutinib that bestow selectivity and potency for BTK. EX1003 ¶39; EX2010 ¶¶90-92.



D. A POSA Would Know How to Use Ibrutinib and Available Modeling to Create Additional Ibrutinib-Like iBTKIs with Different Z'-Scaffolds

A POSA reading the '803 Patent would leverage the known structure-function relationship for binding to the BTK hinge to select ibrutinib-like iBTKIs for use in the claimed methods. In particular, in 2011, a POSA would have known of widely available and widely used computational tools for docking candidate iBTKIs. *See, e.g.*, EX2035; EX2036; EX2041; EX2010 ¶¶115-118. In 2011, these tools were an integral part of kinase inhibitor design, used to visualize binding modes and prioritize compounds for synthesis and potential further preclinical development. EX2010 ¶115. This would have been particularly true for ibrutinib-like iBTKIs, where Marcotte revealed the binding mode for this class of inhibitors and the '803 Patent provided functional and clinical data validating the mechanism. *Id.* ¶¶108-118.

Indeed, Petitioner itself used exactly this approach in the development of zanubrutinib. Using Marcotte's structure, Petitioner predicted how a zanubrutinib analog would bind to BTK. As seen in Petitioner's published figure below, the Marcotte structure (green structure, left panel) was used to dock the zanubrutinib analog (purple structure, middle panel). The docking revealed the precise alignment of these structures (overlay, right panel). EX2039.0003-.0004, Fig. 1; EX2010 ¶164.



The predicted zanubrutinib binding mode was later confirmed in its crystal structure. EX1044.004, Fig. 2B; EX2010 ¶164. Such accurate binding mode predictions illustrate the sophistication and precision of virtual docking and modeling for useful ib Brutinib-like iBTKIs based on Marcotte. EX2010 ¶¶108-118.

III. Claim Construction and Level of Ordinary Skill in the Art

A. Claim Construction

The parties agree on the proposed constructions for “optionally substituted fused heterocyclic ring system” and “irreversible” BTKIs. Pet. 42. Pharmacyclics further agrees that the preamble is limiting and that the lymphocytosis limitation is entitled to patentable weight because it requires the physical action of continuing to administer the iBTKI after lymphocytosis. *Id.* 43, 47.

Petitioner’s proposed construction of “therapeutically effective amount” conflicts with the express definition in the specification. As stated in the specification, “‘therapeutically effective amount,’ as used herein, refers to a sufficient amount of an agent or a compound being administered which will relieve

to some extent one or more of the symptoms [of CLL/SLL] ... [or] reduction and/or alleviation of the signs, symptoms, or causes of [CLL/SLL].” EX1001, 24:58-64. The phrases “as used herein” and “refer to” convey an intent to define the reference term. *See, e.g., ParkerVision, Inc. v. Vidal*, 88 F.4th 969, 976 (Fed. Cir. 2023).

Ignoring this clear definition, Petitioner proposes that “therapeutically effective amount” requires both “efficacy” and “safety.” Pet. 45. Petitioner cites the specification’s definition of “effective amount” for its proposed safety requirement. *Id.* 46 (citing EX1001, 24:66-25:2). But Petitioner provides no support that the specification’s definitional language for “effective amount” is meant to modify the definition of “therapeutically effective amount.” *Id.* In fact, the specification treats them as separate definitions, *see, e.g.,* EX1001, 25:2-9 (“It is understood that ‘an effective amount’ or ‘a therapeutically effective amount’ can vary from subject to subject”); *see also id.*, 24:45-25:12.

As the Board correctly noted in the ID, “therapeutically effective amount” should be construed according to the express definition and not according to the separate and distinct definition of “effective amount.” ID 9-10.

B. Person of Ordinary Skill in the Art

Petitioner proposes a POSA as “a team” with a “clinician member” and a “chemist member.” Pet. 57. Given the subject matter of the claims, which encompass treating a specific disease with a specified genus of compounds, a team is appropriate

here. *Abiomed, Inc. v. White Swell Med. Ltd.*, IPR2021-01565, Paper 39 at 27-33 (P.T.A.B. Apr. 4, 2023).

Although it implies knowledge of the structure-function relationship of kinase inhibitors, Petitioner's proposal fails to expressly account for this expertise. In particular, in addition to Petitioner's proposed characteristics, the POSA team would include "at least one member having at least a Ph.D. in chemistry, organic chemistry, biochemistry, or related field with training in the structure-function relationship of kinase inhibitors." EX2010 ¶¶125-126. As Petitioner's expert Dr. Showalter acknowledges, "one of those members of the team[]" would be a "specialist[]" in molecular docking or in, say, x-ray crystallography or computational modeling[.]" EX2018, 143:11-22; EX2021, 71:17-21 (agreeing that it is "important to have the perspective of someone who understands the structure and function of protein kinase inhibitors[]" on the POSA team). These characteristics are consistent with the prior art's demonstration of the level of ordinary skill. *See* EX1077.007 (noting the "continual collaboration between synthetic chemists and structural biologists[]" for structure-based kinase inhibitor design); *see also* ID 7-8 (citing *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001)). Regardless, even under Petitioner's definition, the Grounds fail.

IV. Ground 1: The Specification Describes the Challenged Claims

A hallmark of the '803 Patent is its use of the structural features of ibrutinib to define the group of compounds for use in the claimed method. The express structural limitations and the structure-function relationship between those limitations and the claimed method distinguish this case from published decisions where generic functional claims were held invalid for lack of written description. Here, a POSA—armed with the specification and the knowledge of the binding mode for the compounds of the claims—would recognize the claims as limited to compounds expected to work in the recited method because of their common structural features with ibrutinib. Petitioner's development of zanubrutinib only confirms the structural features of the claims result in compounds that work in the method. The claims are more than adequately described in view of a POSA's understanding of the specification.

A. Legal Standard

Written description requires that a POSA would find it “reasonably clear what the invention is and that the patent specification conveys that meaning.” *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002). “[A] patentee may rely on information that is well-known in the art for purposes of meeting the written description requirement, because the specification is viewed from the perspective of [a POSA].” *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d

1342, 1359 (Fed. Cir. 2019). Additionally, “the written description requirement does not demand either examples or an actual reduction to practice ... or that the specification recite the claimed invention *in haec verba*[.]” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010).

For claims that encompass a genus, the specification must provide either “a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1373 (Fed. Cir. 2017) (“*Amgen I*”), *aff’d*, 598 U.S. 594 (2023) (“*Amgen II*”). To satisfy common structural features, there must be a sufficient “*correlation* between structure and function[.]” but there need not be a “perfect correspondence.” *Ajinomoto*, 932 F.3d at 1359-60 (original emphasis). “[A]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention[.]” nor must it describe “all species that [the] claim encompasses.” *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003). When a broad genus is disclosed but a subgenus is claimed, the claimed subgenus must be “clearly discernible” from the specification, such that a POSA can recognize the inventors invented what is claimed. *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977).

B. The Inventors Possessed the Claimed Methods**1. The Specification Describes that Irreversibly Inhibiting BTK Treats CLL/SLL Patients and Induces Lymphocytosis**

The specification describes the use of ibrutinib-like iBTKIs to treat CLL/SLL by continuous dosing through lymphocytosis. Pharmacyclics' specification teaches the paradigm shift of interpreting lymphocytosis while inhibiting BTK as an on-target treatment effect, rather than a sign of disease progression, defying conventional wisdom by dosing through lymphocytosis. A POSA reading the specification would understand that the inventors possessed the method of treating CLL/SLL with ibrutinib-like iBTKIs by continuously dosing through lymphocytosis. EX2014 ¶¶76-103.

As Petitioner admits, the specification describes the use of ibrutinib to treat CLL/SLL patients in Examples 6, 10-12, and 14-15. Pet. 35; EX2014 ¶¶78-82. Examples 6, 10, 11, and 14 describe clinical data demonstrating ibrutinib's therapeutically effective⁶ treatment of CLL/SLL patients. §II.B.1; EX1001, 135:45-

⁶ Although not required to satisfy the claims' requirement for a "method of treating" CLL/SLL with a "therapeutically effective amount," the specification's description of the safety of ibrutinib at low dosing as identified with occupancy assays informs the safety of the class of iBTKIs for treating CLL/SLL patients. EX1001, 136:1-13, 142:35-52, 147:35-37; EX2014 ¶¶100-101. Indeed, a POSA in 2011 would have

67, 139:47-140:25, 143:25-36, 146:6-147:40. These examples detail the significant impact of irreversibly inhibiting BTK, reporting the dramatic decrease in lymph node size and nearly universal responses, where “85% of evaluable [CLL/SLL] patients achieved a partial response and even more has some [lymph node] shrinkage.” *Id.* 135:45-51; *id.*, Figs. 3-5, 139:48-140:25 (reporting results for 33 CLL/SLL patients, the vast majority having at least a partial or nodal response); EX2014 ¶¶63, 78-79. Even for the most difficult to treat relapsed/refractory patients who failed other available therapies, ibrutinib showed remarkable results, triggering responses in the majority of these patients. EX1001, 139:48-140:25 (Example 10), 140:28-143:36 (Example 11), 146:6-147:40 (Example 14); EX2014 ¶¶80-82.

The specification describes that irreversibly inhibiting BTK results in treating CLL/SLL patients. The specification reports that ibrutinib occupies BTK in patients, with tested doses resulting in “>95% [BTK] enzyme occupancy 4 hours post-dose in all [patients].” EX1001, 138:33-36. Ibrutinib’s occupancy of BTK correlated with inhibition of BTK-dependent cellular processes, confirming BTK occupancy results in BTK inhibition. Even at the lowest doses administered, the specification reports

considered the features of ibrutinib-like iBTKIs advantageous particularly in view of the significant toxicity of chemotherapy options and for high-risk patients who faced low survival odds. EX2014 ¶103.

ibrutinib occupied and inhibited BTK. *Id.*, 138:27-43. Additional data demonstrated CLL/SLL patients responded to ibrutinib despite varied plasma concentrations. *Id.*, 139:48-140:25, 142:35-143:36. Together, the examples in the specification describe treating CLL/SLL patients by occupying and inhibiting BTK. EX2021, 36:6-37:6, 39:1-8; EX1005 ¶¶56; EX2014 ¶¶83-85.

The specification teaches lymphocytosis induced by BTK inhibition is a sign of efficacy—not disease progression. According to the specification, “lymphocytosis was seen in the majority of [CLL/SLL] patients” treated with ibrutinib. EX1001, 143:27-31. The specification explains the biological mechanism as “likely a consequence of the inhibitory effects of a Btk irreversible inhibitor on lymphocyte homing,” which causes “mobilization” of lymphocytes away from nodal and splenic compartments. *Id.*, 11:16-22, 28:32-41, 34:42-46, 135:30-38; EX2014 ¶¶86-89. Given these teachings, it is not surprising that the specification describes lymphocytosis as a *class effect* for ibrutinib-like iBTKIs. EX1001, 143:27-31; EX2014 ¶¶90-94. The specification’s teaching was later further confirmed by mechanistic studies. EX2014 ¶¶91-92. Indeed, outside this proceeding, both Petitioner and its expert Dr. Rosen agree that lymphocytosis is a class effect for ibrutinib-like iBTKIs. Petitioner’s FDA-approved BRUKINSA label states that “[a]symptomatic lymphocytosis is a known effect of BTK inhibition.” EX1012.008; EX2101.0005-.0006 (lymphocytosis “consistent with the propensity of BTK

inhibitors to stimulate” tumor cell migration). Dr. Rosen’s own prior publication attributes the cause of lymphocytosis in CLL patients treated with ibrutinib to “the unique impact of BTK inhibition on promoting lymphocyte trafficking.” EX2022.0003; EX2014 ¶92.

2. The Specification Describes Therapeutically Effective Doses of Ibrutinib-Like iBTKIs

The specification teaches identifying therapeutically effective doses by measuring occupancy of BTK in patient blood samples—a novel approach made possible by the irreversible attachment of the ibrutinib-like iBTKIs to BTK after binding. EX1001, 136:22-45, 137:9-26; EX2014 ¶95. As discussed above, the specification teaches that occupancy of BTK correlates with inhibiting BTK. EX1001, 138:33-43; EX2014 ¶96. In monitoring BTK occupancy, the specification teaches how to identify a therapeutically effective dose. EX1001, 137:9-26; EX2014 ¶96. The specification further teaches multiple doses of ibrutinib achieved therapeutic effect in CLL/SLL patients. EX1001, 134:26-136:25, 139:47-140:25, 142:35-143:36. Doses as low as 1.25 mg/kg/day resulted in BTK occupancy. EX1001, 138:33-43; EX2014 ¶97. A POSA would understand therapeutically effective amounts as amounts that occupy and inhibit BTK to treat CLL/SLL and are not limited to optimized doses for regulatory approval or commercial marketing. EX2014 ¶¶98-99; EX2021, 235:9-22 (acknowledging the specification teaches occupancy correlates with therapeutic effect).

3. Petitioner Offers No Evidence Ibrutinib-Like iBTKIs that Inhibit BTK Would Not Treat CLL/SLL and Induce Lymphocytosis

Relying chiefly on Dr. Rosen's declaration, Petitioner asserts that not all compounds within the claims that inhibit BTK will treat CLL/SLL or induce lymphocytosis. Pet. 76-80. Dr. Rosen identifies three principal bases for his opinions: (1) different iBTKIs will have unpredictable pharmacological properties that could interfere with treating CLL/SLL or inducing lymphocytosis, EX1005 ¶¶65-66, 68-74, 99-100, (2) different iBTKIs will have unpredictable safety and off-target effects, *id.* ¶¶67, 81-98, 269-270, and (3) the differences between ibrutinib and zanubrutinib demonstrate unpredictable properties of iBTKIs, *id.* ¶¶75-77, 79. Each is factually wrong, lacking in evidentiary support, or irrelevant to the claimed method.

Petitioner's argument that different pharmacological properties for ibrutinib-like iBTKIs would unpredictably prevent treating CLL/SLL or inducing lymphocytosis is factually wrong and unsupported. Pet. 77. Dr. Rosen admits his suggestion of unpredictable interference is merely "theoretical" and he knows of no example of a compound that inhibits BTK failing to have these functions. EX2021, 39:8-40:11, 226:19-227:14, 237:17-238:18. The evidence also contradicts Dr. Rosen's "theoretical" conjecture. In contrast to their unsupported assertions in this proceeding, as discussed above, both Petitioner and Dr. Rosen have elsewhere

expressly *agreed* with the specification's teaching that inhibiting BTK induces lymphocytosis. EX1012.008; EX2022.0003; EX2014 ¶113.

The evidence also refutes Dr. Rosen's alleged concern that an ibrutinib-like iBTKI will have poor bioavailability and solubility preventing it from effectively inhibiting its target in a patient. EX2021, 111:18-112:10.⁷ Ibrutinib is "practically insoluble" with low bioavailability, yet the specification describes that it successfully treats CLL/SLL patients, ultimately achieving FDA approval for its effects. EX1014.033, .035; EX2012 ¶¶29, 40; EX2014 ¶¶104, 108. Ibrutinib's own activity, as taught in the specification, would guide a POSA that other ibrutinib-like iBTKIs could be effective despite comparable non-optimal pharmacological properties, which could be addressed by adjusting dosing to achieve BTK occupancy and inhibition. EX2014 ¶108; EX2021, 136:1-13 (acknowledging dose adjustment as approach to administer drugs with lower bioavailability). Further, Petitioner's experts do not account for the ability of a POSA in 2011 to assess an ibrutinib-like iBTKI's solubility and bioavailability. EX2012 ¶¶30-36. Dr. Rosen himself admitted

⁷ This focus on bioavailability and solubility among pharmacological properties is particularly appropriate for the claimed ibrutinib-like iBTKIs because, once bound, the drug will continue to inhibit its target unaffected by metabolism and clearance of unbound drug. EX2012 ¶¶37-39.

at deposition he lacks expertise in how a POSA would consider pharmacological properties based on structure. EX2021, 135:5-137:9; *cf. id.*, 239:17-240:3. While Dr. Rosen purports to raise concerns about factors that “might” or “theoretically” affect activity, his purported “examples” show nothing but potent iBTKIs among the claimed compounds. EX2014 ¶¶104, 109; EX1005 ¶66.

As for allegedly unpredictable selectivity, safety, and off-target effects, Pet. 77, the claims do not require any particular level of selectivity or safety in order to be therapeutically effective. §III.A; EX2014 ¶¶100, 102, 110; ID 9-10.

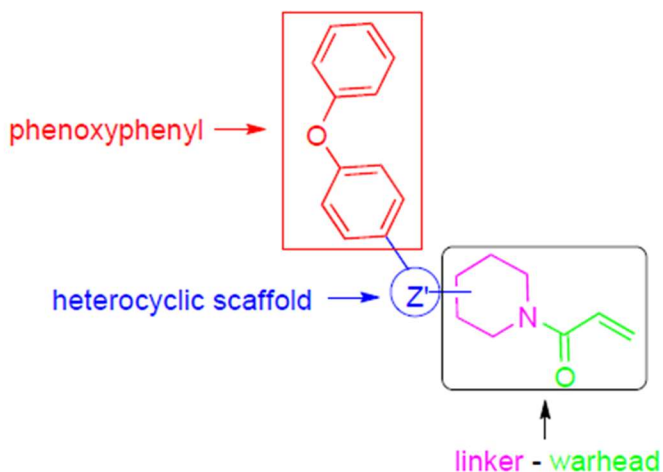
More importantly, Petitioner's evidence does not support unpredictability of ibrutinib-like iBTKIs in the claimed method. Petitioner cites (1) a hold on multiple sclerosis clinical trials for the ibrutinib-like iBTKI tolebrutinib based on observed liver effects and (2) withdrawal of two indications from IMBRUVICA's FDA-approved labeling. Pet. 77. However, tolebrutinib's clinical hold in an MS study says nothing about the safe treatment of *CLL/SLL* as patient population and safety/efficacy trade-offs differ between diseases—and tolebrutinib's development status evidences its ability to inhibit BTK in patients. EX2014 ¶110. Further, tolebrutinib's liver effects have been identified for both zanubrutinib and ibrutinib, demonstrating this is yet another *class effect* for ibrutinib-like iBTKIs as reflected in the products' amended FDA-approved labels. *Id.* Finally, IMBRUVICA's withdrawn FDA indications merely highlight the different standard for regulatory

approval and clinical efficacy, as even Dr. Rosen admits that ibrutinib remains effective in treating both withdrawn diseases. EX2021, 188:2-6; EX2014 ¶¶104, 111.

Petitioner's reliance on alleged differences between ibrutinib and zanubrutinib as evidence of supposed unpredictability is also misplaced. Pet. 22-24. Both are FDA-approved to treat CLL/SLL, and the claims do not require optimized or superior efficacy, much less regulatory approval. EX2014 ¶¶72-73, 111; §III.A; ID 9-10, 29. Further, Petitioner's citation to the compounds' safety profiles, Pet. 23-24, do not demonstrate unpredictability in *therapeutic* effect as required by the claims. §III.A. Petitioner's reliance on ibrutinib's "off-target" binding are clearly overblown, as ibrutinib exhibits such binding and yet has been an approved therapeutic for a decade. EX2014 ¶¶60, 109. In 2011, CLL/SLL was a serious, potentially fatal, disease and the specification taught that ibrutinib was safe, particularly in comparison to the harshly toxic side effects of other then-available treatments. *Id.* ¶¶49, 103; EX2018, 80:2-21. Moreover, the toxicity profiles of zanubrutinib and ibrutinib reflect similar class effects, and even Dr. Rosen admits that the differences he identifies are merely matters of degree. EX2014 ¶¶105-107; EX2021, 154:21-155:21.

Petitioner fails to identify evidence to support its assertion ibrutinib-like iBTKIs would not predictably treat CLL/SLL and induce lymphocytosis.

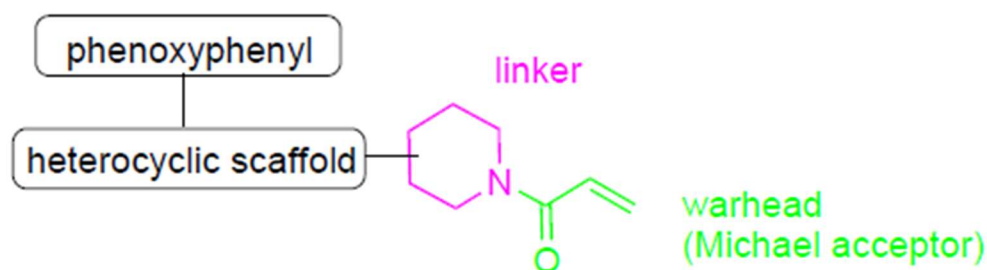
C. The Specification Describes Common Structural Features for the Ibrutinib-Like iBTKIs Used In the Claimed Method



The genus of compounds for use in the claims are ibrutinib-like iBTKIs with two **fixed** components from the specification's preferred embodiment, ibrutinib—a linker-warhead and a phenoxyphenyl moiety—and one **structurally-constrained** component—the hinge-binding Z'-scaffold. Petitioner attempts to demand express disclosure of all possible Z'-scaffolds. Pet. 67-68; *id.* 65-66, 69-70. But *Ariad* recognizes that a genus can be described by common structural **features**, not that all structures must be explicitly depicted. 598 F.3d at 1352 (stating that §112 “never created a heightened requirement to provide a nucleotide-by-nucleotide recitation of the entire genus of claimed genetic material[.]”). Moreover, there is no requirement to describe “every conceivable and possible future embodiment” or “all species that [the] claim encompasses.” *Cordis*, 339 F.3d at 1365. Petitioner thus misapplies the relevant written description law. The actual standards are sufficiently met here.

Seeking to avoid the disclosed common structural features of the claimed ibrutinib-like iBTKIs, Petitioner improperly fixates on Z' in isolation, ignoring the context of the complete compound to be used in the claimed method. But the written description analysis requires "[t]aking each claim ... as an integrated whole rather than as a collection of independent limitations[.]" *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013). Petitioner attempts to distinguish zanubrutinib from the specification's disclosure, but the supposed distinguishing features are either incorrect or irrelevant. When considering the full context, as the law requires, a POSA would understand the inventors possessed the genus of ibrutinib-like iBTKIs based on the common features from ibrutinib for use in the claims.

1. The Linker-Warhead Drives Binding and Irreversibly Inhibiting BTK



The linker-warhead is fixed as a common structural feature of every compound in the Challenged Claims. It is derived from and exemplified by ibrutinib. This moiety binds with BTK's Cys481 and therefore drives irreversible inhibition. The specification's emphasis of ibrutinib discloses the fixed linker-warhead

structure of the claims. *E.g.*, EX1001, 3:21-24, 4:64-66, 5:9-56 (identifying ibrutinib eleven times for use in the method), 6:47-49; EX2010 ¶52. The specification discloses the linker-warhead functions to form the covalent bond to Cys481, thus irreversibly inhibiting BTK. *See* EX1001, 45:56-60, 46:10-12; EX2010 ¶¶131-135; EX2111, [00208]-[00209].

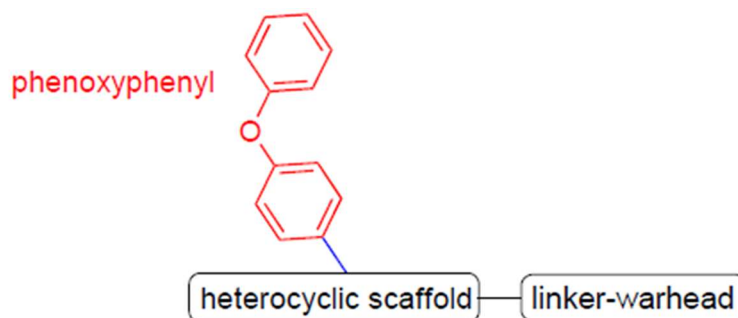
Covalent binding is a key attribute of the compounds taught in the specification and recited in the method claims. The specification describes measuring occupancy (covalent binding) of BTK as a method of confirming inhibition and dose-finding. §IV.B.1-2. Based on the specification's teaching of ibrutinib's occupancy of BTK, a POSA would have understood how ibrutinib's linker-warhead structure drives irreversible binding. Ibrutinib's inventors reported iBTKIs that target BTK's Cys481 and disclosed a model showing the linker-warhead's orientation toward the cysteine. *See* 1060.001-.002; EX2010 ¶¶72, 133. Marcotte showed how a linker in a compound with ibrutinib-like binding orients toward Cys481 to allow for covalent binding when attached to the warhead. *See* EX2001.0004, Fig. 1; EX2010 ¶¶73, 134; §II.C.1.

Contrary to Petitioner's contentions, a POSA would have understood from the specification that ibrutinib's linker-warhead structure could adopt different angles of approach towards Cys481. *See* Pet. 19-20, 72-73; EX1003 ¶48. The specification teaches that iBTKIs with different linker-warheads having different orientations,

positions, and lengths still resulted in irreversible inhibition of BTK. EX2010 ¶¶137-138, 140. In particular, the specification discloses both ibrutinib and its stereoisomer with a different orientation of the linker-warhead inhibit BTK with comparable potency. EX1001, 65:9-25, 79:50-65, 80:55-57, 80:63-65, 77:7-25, 80:38-40, 80:1-18; EX2010 ¶138.

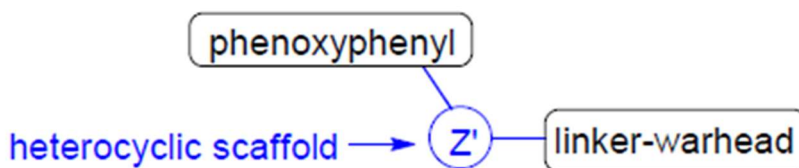
A POSA reading the specification would understand a variety of Z'-scaffolds could appropriately position the linker-warhead to react with Cys481 and could use available modeling software to identify them. The Marcotte structure shows Cys481 in two different orientations, indicating it is not rigidly fixed and can rotate to react with a warhead. EX2001.0003, Fig. 2; EX2010 ¶139. In view of the results of the '803 Patent and the binding mode for ibrutinib revealed in Marcotte, a POSA in 2011 would understand from Pan that various linker-warhead structures irreversibly inhibit BTK, demonstrating the flexibility of the linker-warhead orientation in an ibrutinib-like iBTKI. EX1060.003; EX2010 ¶¶78-80, 141; §II.C.1.

2. Phenoxyphenyl Structure Directs Selectivity and Potency in BTK Binding



A second common structural feature of the claims is the phenoxyphenyl moiety. The specification highlights the significance of the phenoxyphenyl moiety: *all example species* of iBTKIs include phenoxyphenyl. *See* EX1001, 65:9-80:35; §II.C.2; EX2010 ¶¶142-144. A POSA would have recognized the function of the phenoxyphenyl from Marcotte as binding within the “specificity pocket” and thus conveying inhibitor selectivity and potency. EX2001.0004-.0005; Ex. 1052.002, Fig. 2; EX1060.001; EX2010 ¶¶143-144; EX2018, 71:7-18.

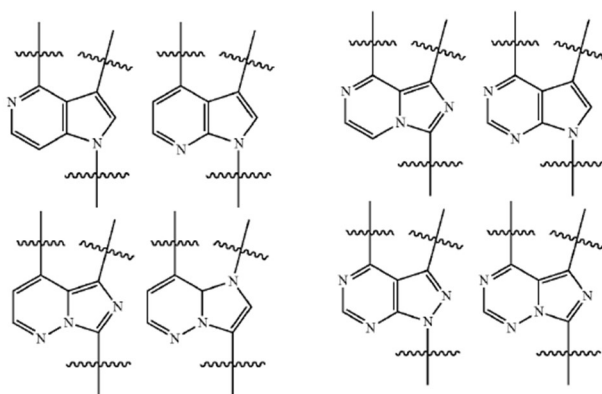
3. The Specification Describes the Claimed Z'-Scaffold Such That a POSA Could Visualize Ibrutinib-Like iBTKIs that Bind BTK



A third common structural feature involves the Z'-scaffold of the claims that directs binding within the kinase hinge region. The specification's Formula E reflects a POSA's understanding that diverse structures would bind within the active site, representing such structures as an orb. EX1001, 61:65-62:17; EX2010 ¶¶60, 145-148. In this way, the specification reflects the structure-function relationship for the hinge-binding region of the ibrutinib-like iBTKIs in the claims. EX2010 ¶147; §II.C.3. At deposition, Dr. Showalter acknowledged the fungibility of hinge-binding scaffolds known in 2011, admitting: “[a] POSA would have been aware of ring systems that had already been investigated toward generating tyrosine kinase

inhibitors ... [and] it would have been *certainly kind of an easy transition* to go from a reversible to an irreversible inhibitor simply from what was known in the literature regarding various cores which were reversible inhibitors.” EX2018, 156:18-158:5.

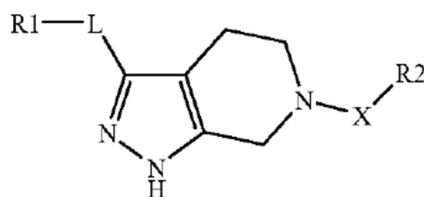
The specification exemplifies central scaffolds for binding to the BTK active site having the structural features recited in the claims—substituted 5:6 fused heterocyclic scaffolds (both unsaturated and partially saturated) with two to four nitrogen heteroatoms:



EX1001, 62:44-63:21; EX2010 ¶149. These examples with their three proposed points of substitution reflect the intended use as a scaffold, with opposing substitution locations to orient the linker-warhead of Formula E toward Cys481 and the phenoxyphenyl toward BTK's back pocket. EX2010 ¶¶149-152. The remaining location provides the opportunity to introduce H-bond donor/acceptor function to interact with the hinge, as a POSA would expect. *Id.* ¶149. Consistent with the claims' structural features, Dr. Showalter admits that for ibrutinib-like iBTKIs a

POSA would recognize that “[t]ypically, the structure of the heterocyclic core is an optionally substituted fused heterocyclic ring system (*i.e.*, Z'-structure as prescribed in the Challenged Claims).” EX1003 ¶32; EX2018, 63:19-64:8.

Consistent with Formula E and the variety of hinge-binding 5:6 fused heterocyclic rings known in the art, a POSA in 2011 would have been aware of many scaffolds that bind to the hinge. Contrary to Petitioner's argument, these scaffolds were not limited to fully aromatic fused rings that strictly replicate adenine's features, *see* Pet. 66-68, but embraced non-aromatic structures, with various heteroatom patterns, substitution patterns, and orientations within the active site, including 5:6 fused rings where the 6-membered ring is saturated, as in zanubrutinib.



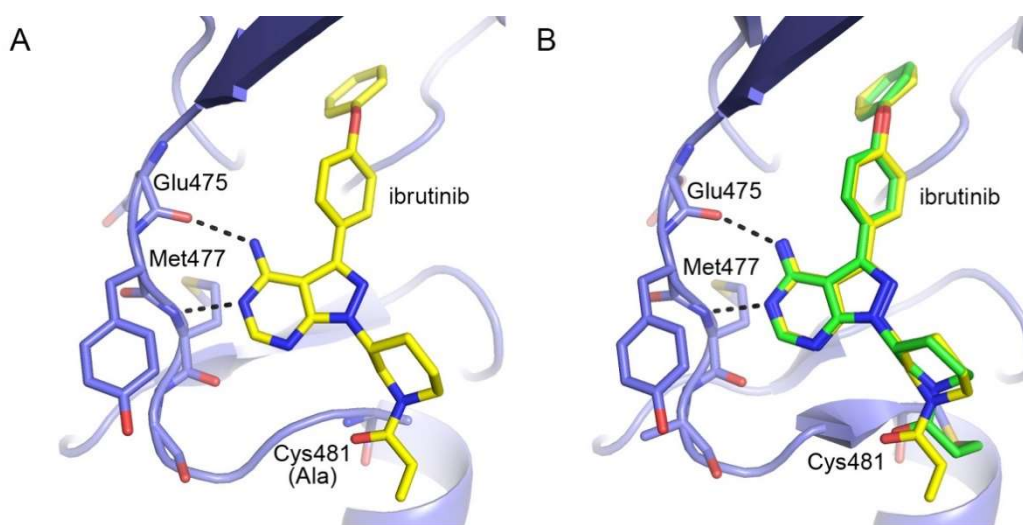
EX2023, 2:1-6; EX2010 ¶¶83-88, 148, 170-177. Even if focusing just on BTK inhibitors, in 2011, there were examples of non-aromatic scaffolds binding to BTK's hinge and crystal structures of ten different ligands bound within BTK's active site showing eight distinct hinge-binding elements. EX2010 ¶88. This diversity reflects a POSA's understanding that a rigid copying of adenine was not required to bind to the hinge, but rather varied structures could make predictable H-bonds to hinge residues. *Id.* ¶¶83-87, 148; EX2012 ¶¶22, 28; EX2028.0003, Fig. 3 legend

(explaining that hinge-binding elements are “based on targeting the available hydrogen bond interactions”). Thus, the specification’s Formula E and example scaffolds, when viewed from the full understanding of a 2011 POSA, reflects the known correlation between the scaffold structure and its hinge-binding function. *Cf.* Pet. 68 (citing *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1339 (Fed. Cir. 2021)).

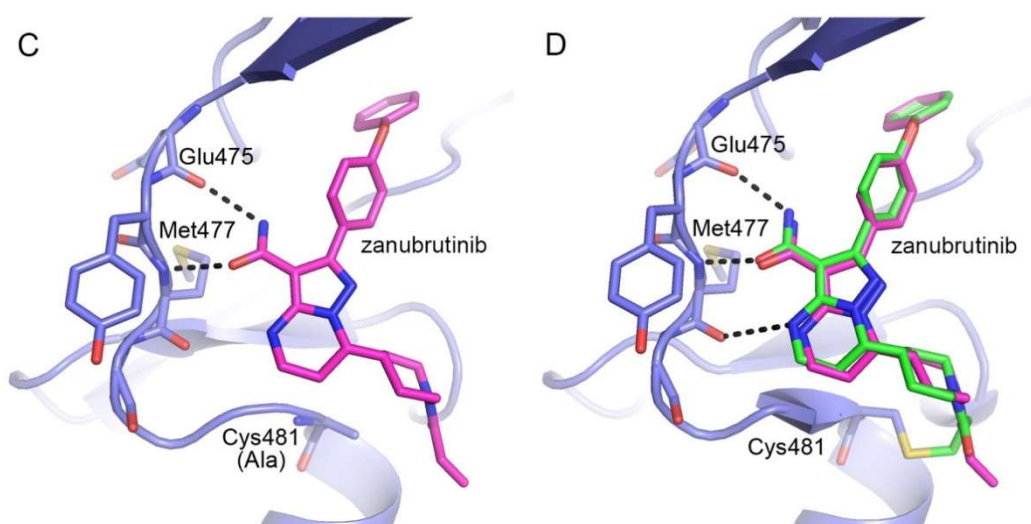
A POSA in 2011 would have been able to “visualize or recognize” the iBTKIs for use in the claimed method, demonstrating the specification sufficiently describes the claims. *Ariad*, 598 F.3d at 1350. Contrary to Petitioner’s assertions, Pet. 67, a POSA’s information is not limited to the structures disclosed in the specification but includes “known structure[s].” *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367-68 (Fed. Cir. 2006). As discussed above, in 2011, a POSA would have known the precise binding mode of ibrutinib-like iBTKIs based on Marcotte and the results in the ’803 Patent. §II.C; EX2010 ¶¶70-71, 111-112. Marcotte provides detailed information about the geometry and specific amino acid interactions between a compound with ibrutinib-like binding and BTK, and the ’803 Patent shows that potent inhibitors with these structural features could be used in the claimed method. EX2001; EX2010 ¶¶70-71, 105, 111-112. This crucial information—completely ignored by Petitioner but known to a POSA—shows exactly how (1) the fixed linker-warhead can project toward BTK’s Cys481, (2) the fixed phenoxyphenyl orients and

binds within BTK's back pocket, and (3) the scaffold hydrogen bonds to the hinge residues. EX2001; EX2010 ¶¶71, 111-112; EX2018, 46:21-47:8 (acknowledging “a POSA would have been aware of [Marcotte] and would have been interested in the [structure]”). A POSA would use software with Marcotte's data to visualize the structures within the claims to recognize the compounds that bind and inhibit BTK. EX2010 ¶¶111-118, 153.

Because the Marcotte structure closely aligns with the common structural features of the claims, a POSA's visualization of the binding of the ibrutinib-like iBTKIs would have been accurate and precise. *Id.* ¶¶112-118. Using software functionality available in 2011 and the data from Marcotte, a POSA would have visualized how ibrutinib-like iBTKIs would bind to BTK. As shown in the figures below, the docking of ibrutinib into Marcotte (A) overlies nearly identically with the crystal structure of ibrutinib bound to BTK (B). *Id.* ¶116.



This precision would not have been limited to ibrutinib's scaffold or the example scaffolds of the specification. A POSA would similarly have been able to visualize compounds having non-aromatic scaffolds, such as that in zanubrutinib. A POSA would be guided by the orientation of the common structural elements in selecting scaffolds and would recognize how to orient non-aromatic, as well as aromatic, scaffolds. As seen in the figure below comparing the docking of zanubrutinib into Marcotte (C) to zanubrutinib's crystal structure (D), docking accurately predicts how zanubrutinib orients and binds within BTK, including the hydrogen bonding to the hinge. EX2010 ¶117.



Rather than acknowledge the importance of Marcotte's teaching, Petitioner's expert did not even mention Marcotte in his declaration, despite admitting that (1) he was aware of it; and (2) that it would have been "helpful" to a POSA. EX2018, 41:21-42:18, 43:20-44:9. It is not surprising Petitioner avoided discussing this significant structural information and the modeling capabilities available to a POSA—(1) its

expert admittedly lacks expertise in structural biology and modeling, preventing him from accurately accounting for the full perspective of a POSA and (2) it undermines Petitioner's argument. *Id.*, 184:3-9. Even Dr. Showalter's cited references repeatedly point to the role of structural biology and computer-aided modeling in analyzing kinase inhibitors. EX1077.006-.007; EX1052.001, .019-.021. Failing to account for these tools is fatal to his analysis.

Contrary to Petitioner's complaints that zanubrutinib's *Z'* was not disclosed, Pet. 63-64, disclosing each potential species is not required: "It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it," particularly where the invention is not the genus of compounds. *In re Kamal*, 398 F.2d 867, 871 (C.C.P.A. 1968). In *Kamal*, the appellate court reversed the §112 rejection for a claim to a combination of novel polymers with a genus of "polyfunctional organic compounds." *Id.* at 868. The court found that the combination was described based on a description of "broad functional groups, broad classes of polyfunctional compounds, thirty-three specific compounds and fifteen working examples," noting that "[t]he fact that appellants' invention is not the polyfunctional organic compound, per se, but resides instead in the *combination* of this class of compounds with the novel [polymer] makes this extensive disclosure adequate." *Id.* at 871.

Like *Kamal*, the same is true here. The invention here is not the ibrutinib-like iBTKIs themselves—Pharmacyclics disclosed these years earlier, EX2111—but how to *use* them to continuously dose through lymphocytosis to effectively treat CLL/SLL patients. The specification provides the “extensive disclosure” the *Kamal* court found sufficient: (1) multiple working examples showing an ibrutinib-like iBTKI effectively treating CLL/SLL patients with continuous dosing through lymphocytosis; (2) describing the mechanism by which it does so; and (3) disclosing the key structural features that predictably drive BTK inhibition for ibrutinib-like iBTKIs to use in the novel method. 398 F.2d at 871.

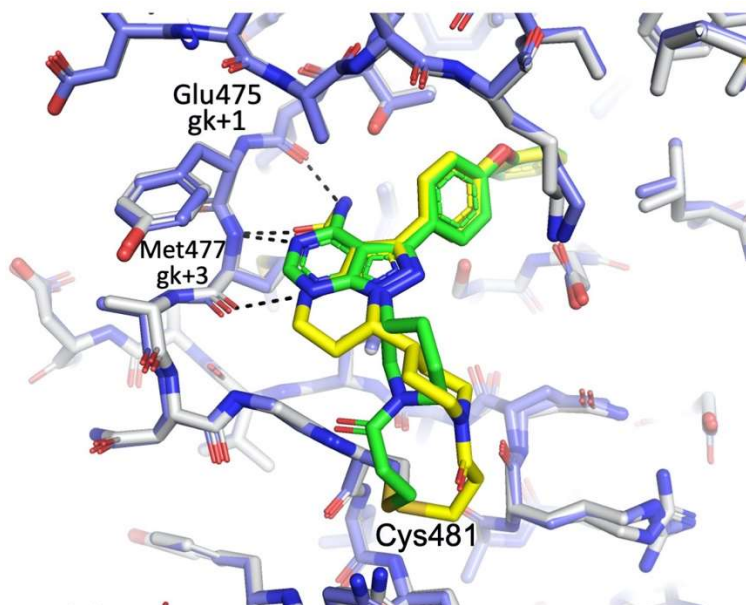
4. Petitioner's Written Description Arguments Are Contrary to the Law and Evidence

Petitioner's arguments conflict with both the law and the evidence.

a. Zanubrutinib Mimics Adenine and Ibrutinib

Petitioner attempts to distance zanubrutinib from ibrutinib and the specification's disclosures, inaccurately asserting that zanubrutinib is not an “adenine-mimetic.” Pet. 13-14, 18-19, 67, 72-73. But a POSA would understand that mimicking adenine reflects a structure's ability to form appropriate H-bonds to the kinase hinge residues. EX2010 ¶¶63, 166-167. As seen below, zanubrutinib (yellow) hydrogen bonds to the same BTK hinge residues as ibrutinib (green)—and adenine—and overlays nearly exactly with ibrutinib in the ATP-binding site.

EX1053.005 (PDB 6J6M; zanubrutinib); EX1076.005-006 (PDB 5P9J; ibrutinib);
EX2010 ¶¶92-102.



In fact, the art, Dr. Showalter (despite his sworn declaration to the contrary, EX1003 ¶¶51-52), and *Petitioner itself* recognize that ibrutinib and zanubrutinib mimic adenine and have similar H-bond interactions with the BTK hinge. At deposition, Dr. Showalter admitted zanubrutinib made “similar” “hydrogen bond donor interactions with the hinge region as ATP.” EX2018, 84:20-85:21. Further, a review cited by Dr. Showalter notes that all ibrutinib-like iBTKIs, including ibrutinib and zanubrutinib, “mimic” the interactions of adenine: “To *mimic* the intermolecular interactions between ATP adenine and the hinge region, *all BTK inhibitors* possess a heterocycle core to maintain *similar interactions with hinge residues*.” EX1076.005, .011 (Tbl. 1). Petitioner’s own publication admits the same:

“Moreover, five approved BTK inhibitors [including zanubrutinib] *all have similar hinge binding to ATP.*” EX2020.0002; EX2018, 83:11-84:4 (agreeing with EX2020’s characterization that all approved BTK inhibitors have similar hinge binding). These pre-litigation characterizations reflect how a POSA actually understands mimicking adenine interactions—by replicating the H-bonds to the hinge residues. EX2010 ¶¶93, 167.

Petitioner fixates on the difference in aromaticity between ibrutinib and zanubrutinib. *See* Pet. 10-11. Aromaticity is again the wrong analysis. A POSA in 2011 would understand Z'-scaffolds need to properly orient the fixed structural components and form H-bonds with the hinge. EX2010 ¶¶168-171; EX2012 ¶¶25-28. Once the fixed and H-bonding components are properly placed, a POSA would have known that the remaining parts of the Z'-scaffold can be flexibly selected. EX2010 ¶¶168-171. A POSA would have been aware of numerous hinge-binding elements, including those with non-aromatic (i.e., partially saturated and non-planar) portions. *Id.* ¶¶168-175; EX1052.003, .012-.013 (partially saturated scaffolds 30, 31, 33, 37, 39); EX2028.0004, Fig. 5 (disclosing a “highly potent, novel inhibitor[]” with partially saturated scaffold); EX2023, 2:1-6 (kinase inhibitors with 5:6 heterocyclic scaffold having saturated 6-membered ring); EX2026, cls. 1, 10 (BTKIs with partially saturated hinge-binding scaffold); EX2055; EX2038.0001, Fig. 1; EX2053.

Petitioner also points to other differences between ibrutinib and zanubrutinib that it contends leads to unpredictability of the Z'-scaffold: differences in heteroatom patterns, placement of the phenoxyphenyl and linker-warhead substituents, and how the linkers connect the Z'-scaffolds and the warheads. *See* Pet. 10-13. These differences do not determine whether a Z'-scaffold would predictably bind to the hinge. EX2010 ¶¶176-179. The specification itself teaches examples of hinge-binding scaffolds with different heteroatom patterns, EX1001, 62:44-63:21, and the B43 compound in Marcotte—shown bound to BTK—has a different heteroatom placement from ibrutinib. EX2010 ¶177. Further, the numeric designation for the placement of the linker-warhead and phenoxyphenyl groups and the chirality of the linker attachment do not determine how the ibrutinib-like iBTKI would be expected to bind to BTK. *Id.* ¶¶178-179. When focusing on the actual analysis a POSA would conduct, a POSA in 2011 would have been able to recognize the Z'-scaffolds that form appropriate H-bonds with the hinge region and orient the fixed components from ibrutinib toward BTK's Cys481 and back pocket. *Id.* ¶¶145-153, 170.

Furthermore, examples with partially-saturated scaffolds or various heteroatom patterns are not required to find written description for the genus of ibrutinib-like iBTKIs of the Challenged Claims. *See Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, 93 F.3d 1572, 1582 n.7 (Fed. Cir. 1996) (“If [the inventor] did not consider the precise location of the [feature] to be an element of his invention,

he was free to draft [the claims] broadly (within the limits imposed by the prior art) to exclude the [feature's] exact location as a limitation of the claimed invention.”). For example, in *Medtronic, Inc. v. Teleflex Innovations S.à.r.l.*, the Federal Circuit found adequate written description for claims to catheters with side openings outside a rigid segment despite the specification only describing side openings within the rigid segment because “the precise location of the side opening was not an element of the invention[.]” 69 F.4th 1341, 1353-54 (Fed. Cir. 2023). Likewise, here, the precise structure of the Z'-scaffold is **not** an inventive element of these claims. Rather, a POSA would have understood based on the specification's teaching in Formula E that the fixed linker-warhead and phenoxyphenyl groups of ibrutinib could be attached to numerous diverse Z'-scaffolds with H-bond acceptors and donors arranged in the proper geometry to form the appropriate H-bonds with the hinge to inhibit BTK, treat CLL/SLL patients, and induce lymphocytosis. EX2010 ¶¶145-153.

b. Petitioner Ignores the Full Context of the Ibrutinib-Like iBTKIs of the Claims

Petitioner argues that the claims include “potentially billions of structurally diverse species[.]” such that a POSA could not visualize or recognize the iBTKIs in the claims. Pet. 57. Petitioner's arguments focus on the breadth of the possible Z'-scaffolds **in isolation**—leading to an improper inflation of the compounds for use in the claims. Petitioner and its expert ignore the full context of the ibrutinib-like

iBTKIs in the claims that include the fixed linker-warhead and the phenoxyphenyl substituents on Z'. In 2011, a POSA would have understood that these required substituents, their orientations, and the steric limitations that allow for binding to the BTK hinge would limit the scope of Z'-scaffolds for use in the claims. EX2010 ¶¶180-182.

Petitioner and its expert took none of these limitations into account in performing their hyperbolic calculations. Initially, Dr. Showalter claims that his Appendix A structures were found in “textbooks” or “online searching” but failed to cite any such references he consulted to generate his voluminous list. EX2018, 148:13-149:6. In addition to shielding the foundation of his analysis from cross-examination, Dr. Showalter admits he did not consider whether any of his proposed Z'-scaffolds would allow for productive binding to BTK when appended to the fixed substituents of the claims or even whether any had ever been used for kinase inhibitors. *Id.*, 151:11-20, 163:8-17. He further admitted that he has no expertise in structural biology to opine on the modeling capabilities available to a POSA. *Id.*, 184:3-9. As such, Dr. Showalter's Appendix A is uncorroborated speculation and admittedly divorced from the actual claim limitations. *TQ Delta, LLC v. Cisco Sys. Inc.*, 942 F.3d 1352, 1358-61 (Fed. Cir. 2019) (“Conclusory expert testimony does not qualify as substantial evidence.”).

Dr. Showalter's analysis is further substantively unreliable. He admits that a POSA would approach identifying ibrutinib-like iBTKIs using "common sense" and "wouldn't want to make something that would not ... be active." EX1003 ¶176; EX2018, 160:3-161:1. Yet to arrive at his inflated calculations, Dr. Showalter alleges that a POSA would individually substitute *each and every* available position on Z'. EX1003 ¶¶167-169. But such an approach defies common sense, and even he admits that a POSA would have "hung their hat onto" the well-known Lipinski drug design principles, including a desire to "maintain lower molecular weight compounds[]" and "wouldn't want to generate every compound in the universe." EX2018, 146:10-147:2, 158:6-15, 161:2-9; EX2010 ¶182; EX2012 ¶¶41-46. Further, such excessive substitutions ignore the probability for steric clash within the BTK active site that would hinder or prevent the compound from binding and inhibiting BTK as required by the claims. EX2010 ¶¶181-182; EX2012 ¶¶41-46.

The law does not require the specification to describe known inoperative embodiments. *See In re Smythe*, 480 F.2d 1376, 1385 (C.C.P.A. 1973) (holding that broad claim language encompassing species that "would be predictably inoperative in the invention and thus would never be selected by one skilled in the art[]" satisfies written description requirement); *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005) ("It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided

that the effect is sufficiently demonstrated to characterize a generic invention.”). Yet a vast number of Petitioner’s proposed compounds encompass such “predictably inoperative” species that a POSA would eliminate based on knowledge from Marcotte of how the Z'-scaffold would orient the phenoxyphenyl and linker-warhead moieties. EX2010 ¶¶181, 209; EX2012 ¶¶42-46. Dr. Showalter suggests extensive trial-and-error testing would be required, but he ignores (and admittedly lacks the expertise to comment on), the role of structural biology and modeling within a POSA’s knowledge. EX2018, 184:3-9. Because of the well-developed structure-function relationship available from Marcotte between the common structural elements of the claims and predictable binding to BTK, a POSA would have been able visualize the operative species within the claimed genus that inhibit BTK. EX2010 ¶181.

c. Petitioner’s Cited Evidence Contradicts Its Unpredictability Assertions

Petitioner cites Ghose (EX1052), Garuti (EX1049), Pan (EX1060), Honigberg (EX1055), '432 Publication (EX1036), Brullo (EX1044), and Zhang 2021 (EX1076) as evidence of the supposed unpredictability of Z'-scaffolds binding to BTK. *E.g.*, Pet. 16-20, 67-68; EX1003 ¶¶60, 65, 76, 240, 242, 254-256, 279. These references do not support its arguments. Instead, Petitioner and its expert distort and selectively ignore the teachings of their cited references, which demonstrate the *predictability*

and *sophisticated knowledge* of hinge-binding and kinase inhibitor design in 2011, particularly when viewed in conjunction with the '803 Patent.

First, Ghose describes observations about hinge binding substructures that expressly inform those in the field how to *predict* hinge binding. EX2010 ¶¶154-155. Dr. Showalter cites Ghose as allegedly “show[ing] changing the substitution pattern of the Z'-scaffold of a kinase inhibitor can *unpredictably* affect” an inhibitor's orientation within the kinase. EX1003 ¶65 (citing EX1052.002-.010). But the *text* of Ghose directly refutes these assertions, stating that it is “straightforward to identify” hinge-binding structures and that “one can anticipate the binding mode” within the hinge. EX1052.019-.020, .002; EX2010 ¶155; EX2018, 121:15-125:8. Applying Ghose to the '803 Patent disclosure teaches precisely what Petitioner contends would be unpredictable. EX2010 ¶¶154-155.

Copying out-of-context figures from Ghose, Petitioner's expert asserts that “substitution pattern” can unpredictably affect hinge-binding and “present distinct orientations” within the hinge region. EX1003 ¶65. In doing so, he misrepresents the full context of Ghose's analysis. “[D]istinct orientations” are not due to “subtle changes in the substitution pattern,” *id.*, but rather the result of *structural differences among different kinases*. EX2010 ¶¶156-157. Ghose does not suggest the binding is unpredictable, but rather concludes that the binding data would allow a POSA to “*anticipate the binding mode.*” EX1052.002; EX2010 ¶157. At deposition, Dr.

Showalter admitted that Ghose taught “making estimates or guesses on a candidate molecule based on known ligand [] hinge region interactions.” EX2018, 125:3-6. Contrary to Petitioner's unpredictability assertions, Ghose reveals the significant structural information known to a POSA about how numerous scaffolds orient and bind within the hinge region. EX2010 ¶¶155-157, 165.

Second, Garuti details how to select an appropriate structure to allow for covalent bonding with a cysteine near the kinase active site. Garuti teaches “the corrected orientation of the Michael acceptor toward the cysteine and a short distance” to the cysteine side chain are “important parameters.” EX1049.001; EX2010 ¶158. It states hinge-binding interactions “place the [warhead] in the right position to react with [the] cysteine.” EX1049.001. While noting that “[v]arious scaffolds have been used for this type of inhibitor[]” and that “many of [which] are heterocyclic systems,” nowhere does Garuti suggest these hinge binding interactions and orientation toward the reactive cysteine would be unpredictable with respect to identifying ibrutinib-like iBTKIs that would work in the claimed method. *Id.* Rather, as described above, the art, including Ghose, teaches that identifying hinge-binding modes is straightforward. *E.g.*, EX1052.002; EX2010 ¶155.

Third, Petitioner's expert cites two references published by ibrutinib inventors before 2011—Pan (EX1060) and Honigberg (EX1055)—as allegedly supporting “limited understanding of the structure-function relationship, including the covalent

bonding between the Michael acceptor and Cys481 and the hydrogen bonding between the scaffold and residues located in the hinge region.” EX1003 ¶240. But as Marcotte later confirmed, Pan suggests ibrutinib's linker-warhead engages Cys481 and irreversibly inhibits BTK. EX1060.001-.002; EX2010 ¶160. Further, nothing in Honigberg reports anything about a “limited understanding of the structure-function relationship[]” of BTK inhibition with ibrutinib-like structures. EX1003 ¶240 (citing EX1055.004); EX2010 ¶¶160-161.

Fourth, Petitioner's cited '432 Publication, a 2020 patent publication describing BTK/ITK inhibitors, shows that structures falling within the genus of the claims are iBTKIs, with IC₅₀ ranging from 1-30 nM, which even Dr. Showalter admits a POSA would consider “highly potent.” EX1003 ¶76 (summarizing EX1036); EX2018, 131:17-132:8; EX2010 ¶159. Thus, these structures demonstrate the common structural features of the genus impart the claimed function.⁸

⁸ At deposition, Dr. Showalter attempted to identify “inactive” compounds within the claims that he failed to include in his declaration. EX2018, 12:11-15:12. These compounds further confirm the robust structure-function relationship for ibrutinib-like iBTKIs. Based on docking, a POSA would have recognized the compounds that would not appropriately orient within BTK's active site, explaining their higher IC₅₀

Fifth, Petitioner relies on two additional post-priority references, Brullo (EX1044) and Zhang 2021 (EX1076), to argue that the crystallography data for BTK-ibrutinib and BTK-zanubrutinib shows that “Btk inhibition involves complicated interactions that are highly unpredictable.” EX1003 ¶240; *see also id.* ¶¶59, 70; Pet. 19-20. But neither describes the interactions as unpredictable. They simply summarize the crystal structure. EX2010 ¶162. Indeed, Brullo notes that “[o]n the basis of the crystallographic data available, ibrutinib and zanubrutinib share ***similar bioactive conformations*** within the wild-type Btk binding site ... [and the] two complexes are mainly stabilized by similar interactions.” EX1044.003. And Petitioner’s expert’s interpretation of Brullo’s data conflicts with Brullo’s ***own interpretations*** of the “similar bioactive conformations” for ibrutinib and zanubrutinib within the BTK active site that are “stabilized by similar interactions.” *Cf.* EX1003 ¶63; EX1044.003; *see also* EX2010 ¶162. Software intended to allow comparison of binding between crystal structures confirms just how identical the interactions of ibrutinib and zanubrutinib with BTK are. EX2010 ¶¶96-102, 162-164.

values compared to compounds reported to have potent inhibition. EX2010 ¶¶183-185.

Lastly, Petitioner's expert cites no support for his theory that "a POSA would not have been able to predict how other Z'-scaffolds, including other possible combinations of the fused heterocyclic ring systems and substitutions, that do not mimic adenine would interact with the hinge region of Btk." EX1003 ¶¶66. Again, the evidence contradicts Petitioner's conclusory assertions, where using the Marcotte structure—which Petitioner completely ignores—a POSA would have been able to predict the binding of ibrutinib and zanubrutinib with remarkable accuracy. EX2010 ¶¶116-118, 164; §IV.C.3. Petitioner's expert further fails to address how his own cited reference presents diverse fused heterocyclic ring systems that productively bind within the hinge. EX1052.003, Tbl. 3 (scaffolds 30, 31, 33, 37, 39 are partially saturated); *see also* EX2010 ¶165.

d. Petitioner's Cited Cases Are Readily Distinguishable

Petitioner relies on written description case law with readily distinguishable facts. Petitioner's cited cases deal with functional genus claims where there was no structure-function relationship. As detailed below, the facts here align much more closely with *UroPep* than Petitioner's cited cases. *Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629 (E.D. Tex. 2017), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018).

First, Pharmacyclics disclosed ibrutinib and the ibrutinib-like iBTKIs found in the '803 Patent years before. EX2025; EX2111. In addition, Marcotte provided

detailed information about the binding and geometry of the fixed components of the ibrutinib-like iBTKIs in the '803 Patent and the expected hydrogen bonding to the BTK hinge. EX2001.0003-.0005; EX2010 ¶¶71, 111-112. Thus, in 2011, a POSA would have had a mature, sophisticated understanding of the structure-function relationship for ibrutinib-like iBTKIs based on *Marcotte*. EX2010 ¶¶70-89, 147, 153-165, 223-229; §II.C. Like *UroPep*, such information allowed a POSA to recognize the compounds for use in the claims. 276 F. Supp. 3d at 653; EX2010 ¶¶111-118, 153; §IV.C.3. Therefore, unlike the fields in Petitioner's cited cases, ibrutinib-like iBTKI design in 2011 was not "in its infancy" and "unpredictable." *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1159 (Fed. Cir. 2019); *Juno*, 10 F.4th at 1341 (finding "unpredictability of an scFv's binding ability[]" is "relevant" to the lack of written description); *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014) (finding antibody field "highly unpredictable"); *Ariad*, 598 F.3d at 1354 (same); *Amgen II*, 598 U.S. at 601 (same).

Second, the common structural features of the claims are based on ibrutinib and reflect the defined structure-function relationship for the binding of ibrutinib-like iBTKIs as demonstrated in '803 Patent and confirmed in *Marcotte*. §II.C; EX2010 ¶¶111-112, 131-153. This is in contrast to *Idenix*, where the Federal Circuit faulted the challenged patent for providing only "lists or examples of supposedly

effective” compounds, without “explain[ing] what makes them effective, or why.” 941 F.3d at 1164. In that case, the claims were not limited by any particular enzyme function. *Id.* at 1158-59. Here, the claims require compounds that irreversibly inhibit BTK. Indeed, the specification expressly teaches that irreversibly inhibiting BTK treats CLL/SLL in patients and induces lymphocytosis. EX1001, 28:32-41, 34:42-50; EX2014 ¶¶78-84; §IV.B.1. Further, the specification specifically teaches the mechanism for why the described ibrutinib-like iBTKIs induce lymphocytosis: “likely a consequence of the inhibitory effects of a Btk irreversible inhibitor on lymphocyte homing to the nodal and splenic compartments.” EX1001, 135:30-36; EX2014 ¶¶91-92. Thus, the common structural features align with the known structure-function relationship and the disclosed mechanism behind the claimed method of treating CLL/SLL.

Third, in 2011, there were numerous known structures relevant to the ibrutinib-like iBTKIs of the method claims. Petitioner attempts to limit the known BTKI structures to only those in clinical development. Pet. 94-95. But clinical development and FDA approval is not the written description standard. *See United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1370 (Fed. Cir. 2023); ID 9-10. Indeed, *UroPep* found hundreds of disclosed ***preclinical*** compounds part of the “very large” scope of known compounds within the “mature area.” 276 F. Supp. 3d at 639, 645-46. Similarly, here there were numerous known heterocyclic

scaffolds that bound to the “highly conserved” kinase hinge. EX2010 ¶¶83-89, 147-148; §II.C.3; EX1077.003-.004; EX2028.0002-.0004; EX1052.003-.018; EX2023, 2:1-6; EX1073.009, Tbl. 2 (BTKIs); EX2026, cls. 1 & 10, [0023], [0076] (BTKIs); EX2027, Examples 16(1), 16(2), 16(3), 21, 21(1), 25(1), 32, 32(1) (BTKIs). As taught in the specification's Formula E, a POSA would understand heterocyclic scaffolds make predictable interactions with the kinase hinge. EX2010 ¶¶83-89, 147-148; EX1052.002; EX2028.0001-.0005. Further, a POSA would have access to Marcotte to predict how a heterocyclic scaffold, when combined with the fixed phenoxyphenyl and linker-warhead structural features of the claims, would bind with BTK's hinge. EX2010 ¶¶71, 111-112, 153. Indeed, a POSA in 2011 would have been able to accurately dock zanubrutinib into the BTK active site to recognize it as an ibrutinib-like iBTKI. §IV.C.3; EX2010 ¶¶117-118. The robust structural information for the compounds of the claims known in 2011 stands in stark contrast to the fields in Petitioner's cited cases, where few or no known structures were available to a POSA. *Juno*, 10 F.4th at 1341 (finding “at most” five known CD19-specific scFvs); *Ariad*, 598 F.3d at 1356-57 (at most a single inhibitor known); *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 928 & n.7 (Fed. Cir. 2004) (no disclosure of “even a single” selective COX-2 inhibitor).

Fourth, Petitioner's zanubrutinib copies the key structural features of ibrutinib that convey its BTK activity. Thus, instead of being “conspicuously absent” as the

Idenix court found, 941 F.3d at 1165, Petitioner's product aligns exactly with the specification's disclosure of structures that irreversibly inhibit BTK to treat CLL/SLL in patients and induce lymphocytosis. §§IV.C.1-3. Petitioner attempts to undermine the specification's teaching related to the Z'-scaffold but fails to appropriately consider a POSA's full knowledge of predictable hinge-binding elements, the known structural binding mode for ibrutinib, and the common use of available docking tools. EX2010 ¶¶70-71, 145-153; EX2001; §II.C-D. Indeed, a POSA in 2011 would have been able to predict the binding of zanubrutinib to BTK with remarkable accuracy, refuting Petitioner's assertion the specification provided no guidance for a POSA to recognize zanubrutinib as an ibrutinib-like iBTKI. *E.g.*, Pet. 78; EX2010 ¶¶117-118; *see also UroPep*, 276 F. Supp. 3d at 652-53 (adequate written description even though the "disclosure [did] not expressly discuss the common structural features of PDE5 inhibitors[]" because a POSA would recognize shared features based on knowledge in the art and PDE5 inhibitors disclosed in the specification).

D. The Specification Provides Sufficient Blaze Marks to the Claimed Genus

The specification provides blaze marks to the genus of ibrutinib-like iBTKIs for use in the claimed method. As the Board appropriately noted, "[t]here is no dispute that the Specification describes the phenoxyphenyl hydrophobic moiety and the linker-warhead" of ibrutinib—*i.e.*, the fixed substituents. ID 25. The

specification provides blaze marks to the fixed linker-warhead because the structures appear among a narrow selection of options for these components. EX1001, 52:45-53:20 (claimed linker structure in four out of eight embodiments), 54:55-55:10 (claimed warhead structure one out of five embodiments); EX2010 ¶188. Further, the specification provides blaze marks to the fixed phenoxyphenyl moiety of the claims because *every* example species in the specification uses phenoxyphenyl attached to a hinge-binding scaffold, markedly identifying a preference for this structural element for binding to the active site of BTK. *See* EX1001, 65:9-80:35; EX2010 ¶187. Moreover, as the Board correctly recognized, the specification's preference for ibrutinib also provides blaze marks to the combination of the fixed claimed phenoxyphenyl moiety and fixed claimed linker-warhead because ibrutinib itself combines these two fixed features. *See* ID 25; EX1001, 80:63-65, 134:26-136:13, 139:48-144:41, 146:6-148:56; EX2010 ¶¶186-187, 189-190. Further support for such blaze marks rests in the examples showing that the specific combination of the phenoxyphenyl moiety and linker-warhead in ibrutinib effectively inhibits BTK, resulting in the treatment of CLL/SLL patients and inducing lymphocytosis. *See* EX1001, 134:26-136:13 (Example 6), 139:48-140:25 (Example 10), 140:28-143:36 (Example 11), 143:38-144:41 (Example 12), 146:6-147:40 (Example 14); §IV.B.

As for the Z'-scaffold, Formula E describes that the linker-warhead can be attached to a variable scaffold that binds to the BTK active site and provides specific examples of the types of hinge-binding scaffolds that could be used. *See* EX1001, 61:65-62:66; EX2010 ¶191. The specification's specific examples of potential hinge-binding scaffolds are *all* substituted 5:6 fused heterocycles—including partially saturated and aromatic 5:6 fused heterocycles—guiding the POSA to select exactly the types of hinge-binding scaffolds recited in the claims. *See* EX1001, 62:44-63:20; EX2010 ¶191. And Dr. Showalter expressly admits that this structure is “typical[]” for ibrutinib-like iBTKIs. EX1003 ¶32. The specification's disclosure of a variety of hinge-binding scaffolds to use to bind within the BTK active site aligns with a POSA's sophisticated understanding in 2011 of the permissiveness and variability for hinge-binding structures. *See* §II.C.3; §IV.C.3; EX2010 ¶¶192-193. In 2011, a POSA would have known of numerous diverse structures that could make the appropriate H-bonds to bind to the BTK hinge—including partially saturated scaffolds similar to the one used in zanubrutinib. *See* §IV.C.3; EX2010 ¶¶192-193; EX2023, 2:1-6.

Relying on the specification's introduction of the example scaffolds as “biaryl,” Petitioner improperly tries to limit the disclosure to fully aromatic scaffolds. Pet. 33, n.1. But a POSA reading the specification would understand that the use of “biaryl” does not narrow the description of Z'-scaffolds. EX1001, 62:44-

45. Initially, the example structures are not “aryl,” which the specification limits to aromatic rings containing only carbon atoms, but would be “heteroaryl” because they contain nitrogen. EX2010 ¶¶65-66. Further, although “biaryl” is not defined, the definitions of “aryl” and “heterocycle” reflect a permissive use of the terms and do not indicate any intention to strictly differentiate between aromatic and non-aromatic structures. *See* EX1001, 15:4-12, 15:66-16:62; EX2010 ¶66. For example, the definition of “aryl” does not exclude structures that are partially non-aromatic, as it includes “fluorenyl,” which has a central non-aromatic ring (*i.e.*, a partially saturated portion). *See* EX1001, 15:4-12; EX2010 ¶66. As another example, the definition of “non-aromatic heterocycles” includes a structure with an ***aromatic*** portion (phenyl fused to dioxane ring). *See* EX1001, 17:30-18:33; EX2010 ¶66. The specification's disclosure of diverse possible scaffolds for use in ibrutinib-like iBTKIs reflects the understanding in the field in 2011 that numerous different structures—including partially saturated ones—had been shown to form H-bonds to the hinge in different kinase inhibitors and that these structures could be docked using Marcotte. *See* §II.C.3; EX2010 ¶¶67, 153.

In arguing that there are insufficient blaze marks to the Z'-scaffolds that satisfy the claims, Petitioner analogizes to the “laundry list disclosure of different moieties for every possible side chain or functional group[]” in *Regents of the University of Minnesota v. Gilead Sciences, Inc.*, 61 F.4th 1350, 1357 (Fed. Cir.

2023). Pet. 69. However, *Minnesota* is inapposite. Here, the specification does not disclose an exhaustive “laundry list” of “every possible side chain or functional group” for hinge-binding scaffolds from which there was a “lack of direction” to the claimed structural features with no discussion of structure-function relationship or any mechanistic understanding. 61 F.4th at 1357-58. Rather, the specification describes clear preferences for fixed key components of the ibrutinib-like iBTKIs for use in the claims—ibrutinib’s phenoxyphenyl moiety and linker-warhead—leaving as partially generic in the claim only the Z’-scaffold with specific structural constraints (5:6 fused ring requiring certain heteroatoms). These structural constraints fall directly from the specification’s teaching of a variable, permissive structure for the hinge-binding scaffold and 5:6 fused heterocycles to exemplify the types of structures to be used. EX1001, 61:65-63:21. Such disclosure directs a POSA to the claimed structural features for Z’. EX2010 ¶¶191-192. These claimed features are entirely consistent with how a POSA in 2011 would understand the specification in light of the known diversity, variability, and structure-function relationship of hinge-binding structures. *See* §§II.C.3, IV.C.3; EX2010 ¶¶191-193.

The Federal Circuit’s decisions in *Invitrogen Corp. v. Clontech Laboratories, Inc.* and *Falko-Gunter* are instructive. 429 F.3d 1052 (Fed. Cir. 2005); 448 F.3d 1357 (Fed. Cir. 2006). In *Invitrogen*, the Federal Circuit found sufficient written description for a claim to a modified reverse transcriptase (RT) peptide that retained

certain native activity (DNA polymerase) but substantially reduced other native activity (RNase H). 429 F.3d at 1071-74. The court agreed there was “sufficient structure” from the DNA sequence in the specification and “within the knowledge of one of ordinary skill in the art[.]” to support claiming peptides with no explicit structural disclosures. *Id.* at 1073. The specification disclosed a DNA sequence for only one representative embodiment, but “at the time of the invention, the sequences of RT genes were known and members of the RT gene family shared significant homologies from one species of RT to another[.]” and the art “established a sufficiently known correlation” between gene structure and function. *Id.* at 1072-73.

Similarly, in *Falko-Gunter*, the Federal Circuit found adequate written description for claims to vaccines using defective poxviruses despite a limited disclosure of poxviruses in the challenged patent’s specification because “essential genes for poxvirus were well-known in the art.” 448 F.3d at 1365-68. The claims were to vaccines “comprising ... a defective poxvirus that lacks a function imparted by an essential region of its parental poxvirus,” while the specification and examples therein focused on a different class of virus (herpesviruses) and included only passing references to poxvirus and no disclosure—or incorporation by reference—of the DNA sequence of the poxvirus genome and the locations of the “essential regions.” *Id.* at 1360-61, 1364-65, 1367-68. Because “articles describing essential genes for poxvirus were well-known in the art[.]” a POSA would “have been readily

able to choose an essential vaccinia [poxvirus] gene” based on these references. *Id.* at 1366. A POSA would also be able to consider the “well-known” differences between the herpesviruses and poxviruses. *Id.* at 1365.

Here, as in *Invitrogen* and *Falko-Gunter*, in 2011, there was a “well known” or “sufficiently known correlation” between heterocyclic scaffold structure and hinge-binding function that would have been understood in view of the specification’s teaching. *See* §§II.C.3, IV.C.3; EX2010 ¶¶192-193. In view of a POSA’s sophisticated understanding of this correlation and the breadth of hinge-binding heterocyclic scaffolds to use, a POSA would have understood that the specification identifies the flexibility for the hinge-binding heterocyclic scaffold where the fixed phenoxyphenyl moiety and linker-warhead attach to bind BTK. *See* §§II.C.3, IV.C.3; EX2010 ¶¶191-193. Accordingly, the specification provides blaze marks to the specific genus of iBTKIs for use in the claimed method.

V. Ground 2: The Specification Enables the Challenged Claims

Like the written description analysis, the enablement of the Challenged Claims is supported by the clear teaching of the relationship between the structures in the claims and their function. Like written description, Petitioner’s cited cases do not resemble the facts here. Petitioner cites cases where a POSA would be required to essentially start over from scratch, performing trial-and-error testing of random sequences to identify additional molecules having the desired function. But here, the

teaching in the specification, the knowledge in the art, and the structural features built into the claimed method allow a POSA to practice them without undue experimentation.

A. Legal Standard

A patent's "specification must enable the full scope of the invention as defined by its claims[.]" allowing for "a reasonable amount of experimentation." *Amgen II*, 598 U.S. at 610-12. "What is reasonable in any case will depend on the nature of the invention and the underlying art." *Id.* at 612. In other words, "[t]he enablement requirement is met where one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012); *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998) (stating that it is "imperative" to consider enablement from the perspective of a POSA).

Undue experimentation can be assessed by considering factors outlined in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988): (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. The test for undue experimentation is "not merely quantitative, since a considerable amount of

experimentation is permissible[.]” *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996); *see also Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1339 (Fed. Cir. 2013) (“[A] considerable amount of experimentation is permissible, if it is merely routine[.]”); *Johns Hopkins*, 152 F.3d at 1360 (same).

B. A POSA Can Practice The Full Scope of the Claimed Method

The specification teaches a POSA that irreversibly inhibiting BTK treats CLL/SLL and induces lymphocytosis and instructs how to determine therapeutically effective doses by monitoring BTK occupancy from a straightforward assay. Following the structural features of ibrutinib recited in the claims, a POSA reading the '803 Patent would have recognized compounds for use in the claimed method because of the then well-understood structure-function relationship for ibrutinib-like iBTKIs. Using the compounds within the claims, a POSA would have needed only reasonable experimentation following the specification's teaching to identify a therapeutic dose that occupies BTK and treats CLL/SLL. The claims are more than enabled in view of the teaching of the specification and the POSA's sophisticated understanding of predictable binding of ibrutinib-like iBTKIs based on Marcotte.

1. The Specification Provides Guidance and Working Examples (Wands Factors 2-4)

The specification provides significant guidance for a POSA to practice the full scope of the claimed method, disclosing examples showing ibrutinib irreversibly inhibits BTK, treats CLL/SLL patients, and induces lymphocytosis. Examples 6, 10,

11, and 14 describe how irreversibly inhibiting BTK with ibrutinib results in the treatment of CLL/SLL patients and induces lymphocytosis. EX1001, 134:26-136:14 (Example 6), 139:48-140:25 (Example 10), 140:28-143:36 (Example 11), 146:6-147:40 (Example 14); §IV.B.1; EX2014 ¶118. Petitioner and its expert agree that ibrutinib-like iBTKIs treat CLL/SLL patients by irreversibly inhibiting BTK, as the specification teaches. EX1012.022 (Petitioner's FDA-approved labeling describing zanubrutinib's "Mechanism of Action" as a "small-molecule inhibitor" of BTK); EX2021, 36:6-8; EX2014 ¶122. The specification further describes the mechanism for lymphocytosis, explaining that it is a class effect for the claimed ibrutinib-like iBTKIs. EX1001, 11:16-22, 135:30-36, 143:27-31; EX2014 ¶118. The field—including the governing treatment guidelines, Petitioner, and its expert—adopted the specification's teaching that irreversibly inhibiting BTK results in lymphocytosis. EX2014 ¶¶ 64-65, 92-94, 118, 123; EX2003.0010 (revising treatment guidelines to reflect lymphocytosis is an effect of inhibiting BTK); EX1012.008 (Petitioner admitting lymphocytosis is a "known effect of BTK inhibition"); EX2022.0003 (Rosen publication acknowledging lymphocytosis "is likely due to the unique impact of Btk inhibition").

Contrary to Petitioner's assertions, Pet. 88-89, the specification further guides a POSA to the structural features of the claimed ibrutinib-like iBTKIs responsible for irreversibly inhibit BTK. The examples demonstrate ibrutinib's efficacy in

treating CLL/SLL patients and inducing lymphocytosis, emphasizing that ibrutinib's linker-warhead and phenoxyphenyl are critical structures that convey irreversible BTK inhibition and utility in the claimed method. EX2010 ¶¶198-199. The specification further informs a POSA that the Z'-scaffold is selected to bind within the "active site" of BTK, which a POSA would understand to require appropriate hydrogen bonds with BTK's hinge residues. EX1001, 61:65-62:17; EX2010 ¶¶200-202. Petitioner and its expert fail to view the specification's guidance regarding Z' from the perspective of a POSA having the mature understanding in 2011 of structures that bind BTK's active site. EX2010 ¶¶200-202; §II.C.3, IV.C.3. With that proper context, the guidance from the specification in light of a POSA's understanding of the field teaches the full scope of the claimed ibrutinib-like iBTKIs.

Contrary to Petitioner's assertion, the specification's teaching regarding ibrutinib is sufficient to enable the claims because the specification discloses the "general quality" of the class—irreversibly inhibiting BTK based on the ibrutinib structural features that convey that function—that "gives [the class] a peculiar fitness for the particular purpose[]" and thus "reliably enable[s] a [POSA] to make and use all of what is claimed." *Amgen II*, 598 U.S. at 611; *United States v. Telectronics, Inc.*, 857 F.2d 778, 786 (Fed. Cir. 1988) (finding "one embodiment" "along with the general manner" of its fitness for use in the claims enabled a POSA to practice "other permutations of the invention" "without undue experimentation"). Here, ibrutinib's

features represent the features of the genus within the claims, with the fixed common structural elements that impart the ability to treat CLL/SLL patients and induce lymphocytosis by irreversibly inhibiting BTK. EX2010 ¶¶198-202; EX2014 ¶¶118-120.

The specification further guides a POSA in recognizing therapeutically effective doses for ibrutinib-like iBTKIs for use in the claimed method by measuring occupancy. EX2014 ¶¶105, 119-120. Example 7 teaches the use of BTK occupancy and BCR biomarker assays to assess BTK inhibition. EX1001, 136:28-31. This novel approach to track the inhibition of BTK allows for a straightforward confirmation that the administered ibrutinib-like iBTKI occupies BTK and affects its downstream activity, providing a measure of the effectiveness of the administered dose. EX2014 ¶120; EX2021, 235:9-236:5. The examples confirm that, even at the lowest doses administered, ibrutinib occupied and inhibited BTK, which the specification teaches results in clinical responses. EX1001, 138:40-43, 139:48-140:25; EX2014 ¶120.⁹ Petitioner itself used Pharmacyclics's inventive method to

⁹ Although the claims do not require any particular level of safety, the specification teaches that irreversibly inhibiting BTK with ibrutinib “was well tolerated” with low grade adverse events and does not report identifying a maximum tolerated dose. EX2014 ¶101. Because therapeutic effects were observed at doses below the

track BTK occupancy in assessing the therapeutic doses for zanubrutinib, corroborating the significance of the guidance provided. EX1043.002; EX2014 ¶121.

2. Quantity of Experimentation Would Be Reasonable (*Wands* Factors 1 and 8)

a. Only Routine Experimentation Needed to Confirm Irreversible Inhibition of BTK

A POSA in 2011, having the clinical results of the '803 Patent, would have been able to leverage Marcotte as well as significant knowledge of hinge-binding elements and commonly used tools for virtual docking to readily recognize ibrutinib-like iBTKIs for use in the claimed method. EX2001.0003-.0005; EX2010 ¶¶203-211, 215-219; §II.D. The specification taught that ibrutinib's structural features convey irreversible inhibition of BTK that results in treating CLL/SLL patients. §IV.B.1. Virtual docking with Marcotte would have allowed a POSA to visualize compounds within the claims expected to bind and irreversibly inhibit BTK like ibrutinib and screen structures that would not be accommodated. EX2010 ¶¶203-

maximum tolerated dose, ibrutinib's reported safety would have provided a POSA guidance regarding the ability to identify therapeutic doses of other ibrutinib-like iBTKIs that would not induce significant safety concerns, particularly in view of the comparative toxicity of alternative treatment options. *Id.* ¶124.

211, 215-219; §II.D. Indeed, available docking tools in 2011 would have accurately predicted the binding in Marcotte of both ibrutinib and zanubrutinib—highlighting the precision of a POSA's ability to visualize binding of ibrutinib-like iBTKIs in 2011. EX2010 ¶¶116-118; §IV.C.3. This stands in stark contrast to Dr. Showalter's unsupported assertions regarding the use and power of virtual docking as of 2011. EX1003 ¶¶238-240. It is not surprising this analysis lacks substance; Dr. Showalter admits he lacks structural biology and modeling expertise: "I am not informed as to the capabilities ... of these [modeling] programs." EX2018, 183:7-184:9.

Contrary to Petitioner's assertion that "a POSA would need to synthesize and screen the billions of candidates," Pet. 83, a POSA reading the '803 Patent would identify compounds that productively bind to BTK based on modeling using Marcotte. Extensive trial-and-error screening would not be required. EX2010 ¶¶203-211. At deposition, Dr. Showalter admitted that, although he lacked the expertise to comment on modeling, a POSA would be able to use modeling "to winnow down" the compounds within the claims. EX2018, 171:3-14.¹⁰ A POSA would recognize

¹⁰ Dr. Showalter alleges it would take "months, years, decades of synthesis[]" to test the compounds of the claims. EX2018, 170:3-171:2; *id.*, 168:11-170:2. Yet again his assertions lack any support and are too conclusory to give any weight,

these ibrutinib-like iBTKIs by taking the full context of the structure and claim into account—not focusing on Z' in isolation as Dr. Showalter does. EX2010 ¶¶208-210, 216-219.

Initially, a POSA would recognize from the '803 Patent's teaching that the claimed iBTKIs require orienting the phenoxyphenyl toward BTK's back pocket, orienting the linker-warhead toward Cys481, and forming the required hydrogen bonds with BTK's hinge. EX1001, 26:23-31; EX2010 ¶¶208, 218. Such structures would be confirmed by modeling with Marcotte to visualize their binding to BTK. *Id.* ¶¶207-210, 217-219; EX2018, 178:15-179:9 (admitting that “one would use that [crystal structure] information to look at other candidate ligands toward making a new inhibitor[]”).

Consistent with how a POSA would approach recognizing ibrutinib-like iBTKIs in 2011, Petitioner itself used virtual docking in Marcotte for a zanubrutinib analog to confirm binding. EX2039.0003-.0004, Fig. 1; EX2010 ¶210. Working within the known structural constraints from Marcotte, a POSA would have been able to eliminate inoperative species and identify where possible substitutions could be introduced on Z', focusing on areas that are solvent-exposed and avoid

particularly as he admittedly lacks the necessary expertise to comment on the scope of compounds a POSA would recognize using modeling based on Marcotte.

interference with BTK-binding. EX2010 ¶¶207-210, 217-219, 221; EX2012 ¶¶42-46. Dr. Showalter's suggestion that a POSA would have indiscriminately substituted Z' defies the actual perspective of a POSA to identify compounds that bind within the well-defined structure of BTK's active site. EX2010 ¶¶218-219, 221; EX2012 ¶¶41-46; EX2018, 160:12-161:9 (admitting that "a POSA wouldn't want to make something that would not ... be active" in a kinase assay).

The claims' requirement that the ibrutinib-like iBTKI be orally administered would additionally limit the candidate structures. In considering ibrutinib-like iBTKIs for use in the claimed method, a POSA would be guided by well-known principles to optimize a structure's oral bioavailability, including constraints on molecular weight, lipophilicity, and H-bond donors and acceptors. EX2012 ¶¶31-36, 46. Petitioner's suggestion that a POSA would have "infinitely" substituted Z' defies common sense. Petitioner identifies no example of any BTK inhibitor, kinase inhibitor, or any drug that is substituted in the way Petitioner suggests. As Dr. Rosen concedes, his opinion that excessive experimentation would be required "relies on [his] understanding that there would be billions of compounds to test[.]" EX2021, 224:20-225:5; EX1003 ¶243; EX2018, 171:3-17 (Showalter admitting that "part of [his] analysis" was based on how long it would take to make the full scope of compounds within the claims). But, the "understanding" that there are "billions" of compounds requires ignoring the perspective of a POSA in 2011 and their full

knowledge of ibrutinib-like iBTKI binding by the complete structure in the claims, use of virtual docking in Marcotte, and practical drug design principles. EX2010 ¶¶216-222; EX2012 ¶¶41-46; *Bayer Healthcare LLC v. Baxalta Inc.*, 989 F.3d 964, 982 (Fed. Cir. 2021) (stating that undue experimentation “***must be viewed*** from the perspective of” a POSA).

As the Supreme Court has recognized, enablement is not based on “the cumulative time and effort it takes to make every embodiment within a claim[.]” *Amgen II*, 598 U.S. at 615. Petitioner’s suggestions to the contrary are irrelevant and contrary to law. Pet. 83-84. Far from excessive experimentation, once candidate ibrutinib-like iBTKIs are recognized to bind to BTK in Marcotte’s structure, standard experiments for IC₅₀ measurements can confirm their activity in irreversibly inhibiting BTK. EX2010 ¶¶212-213; EX1060.002. The specification outlines these routine assays, noting that they can be performed in commercially available high throughput assays, as Petitioner’s expert agrees. EX1001, 45:55-46:35; EX2021, 223:13-224:9; EX2010 ¶212; EX2014 ¶¶125, 127, 131, 133; *see UroPep*, 276 F. Supp. 3d at 659-60 (acknowledging that drug companies “‘routinely’ screen” inhibitors for selectivity and potency and that the patent specification taught such “common and [] commonly used” methods). For any given candidate, such IC₅₀ testing would be routine and minimal. EX2010 ¶212.

b. No Undue Experimentation Would Be Needed to Identify a Therapeutically Effective Amount

The specification teaches a POSA to use a novel method to identify therapeutic doses using BTK occupancy to confirm BTK binding and irreversible inhibition. §V.B.1; EX2014 ¶¶128-129. Such assays can be conducted on readily accessible patient blood samples, allowing prompt feedback that a particular dose inhibits BTK in a patient and confirm its therapeutic effect as required by the claims. EX2014 ¶128. The specification's teaching of ibrutinib's properties would guide a POSA's understanding of what dose would be therapeutically effective for another compound within the claims. *Id.* ¶¶128-129. Further, the specification teaches ibrutinib occupied BTK at even the lowest doses tested, providing a POSA reasonable confidence to identify doses for other ibrutinib-like iBTKIs that would effectively occupy and inhibit BTK in patients. *Id.* ¶129. Given the specification's teaching to use occupancy as a direct measure of BTK inhibition, a POSA would know how to apply this approach to identify therapeutic doses for compounds within the claims. *Id.* ¶¶129-133; *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 923 (Fed. Cir. 2011) ("Enablement is not negated if a reasonable amount of experimentation is required to establish dosages and formulation of an active ingredient."). "[T]he fact that a clinician's involvement may be necessary to determine effective amounts [for use in the claims] does not itself constitute undue experimentation[,]" and "repetition of known or commonly used techniques[]" is not

undue experimentation. *Cephalon*, 707 F.3d at 1338 (citing *Ortho-McNeil Pharm., Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1365-66 (Fed. Cir. 2008)) (finding “extensive or ‘undue’ tests” not required “even if clinical trials informed” the effective dose).

Petitioner and its expert identify various preclinical tests, animal models, and extensive clinical trials that they allege would be required to practice the claims as evidence of alleged undue experimentation. Pet. 84-88; EX1005 ¶¶235-254. As Dr. Rosen admits, these tests are standard for any compound intended to be administered to humans. EX2021, 221:1-223:20; EX2014 ¶125. Further, much of this testing is not directly related to practicing the claimed method but rather reflect regulatory requirements for human safety. EX2014 ¶126; EX1005 ¶247. But the claims here do not require efficacy (or safety) sufficient to meet such regulatory requirements. §V.B.4.a. Instead, the claims here require only continuous dosing of a therapeutically effective dose of an ibrutinib-like iBTKI that irreversibly inhibits BTK in the patient and thereby treats CLL/SLL patients and induces lymphocytosis. As discussed above, because the specification taught ibrutinib irreversibly inhibited BTK and treated CLL/SLL patients, identifying a therapeutic dose for another ibrutinib-like iBTKI would require only reasonable experimentation using the specification's direction to measure BTK occupancy and track inhibition. EX2014 ¶¶126-133.

Petitioner and its expert allege different ibrutinib-like iBTKIs would have unpredictable properties requiring undue experimentation to identify a therapeutic dose, pointing to differences between the potency, pharmacological properties, adverse events, and approved doses of zanubrutinib and ibrutinib. Pet. 21; EX1005 ¶¶65, 68-79. None support finding undue experimentation here. The claims do not require optimized efficacy or doses, and the specification teaches that numerous doses achieve BTK occupancy. EX1001, 136:15-25, 138:33-43 (Example 7 describing “complete occupancy” and inhibition of BTK-dependent cellular processes at 2.5 mg/kg); EX2014 ¶¶97, 128-129. As Dr. Rosen acknowledged at deposition, differences in potency, selectivity, and bioavailability can be addressed by adjusting the dose. EX2021, 135:5-137:9. Moreover, the specification’s teaching that ibrutinib effectively treated CLL/SLL patients despite its poor pharmacological properties would have provided a POSA confidence that other ibrutinib-like iBTKIs would have sufficient bioavailability to identify therapeutically effective doses. EX2012 ¶¶29, 37, 40; EX2014 ¶¶129, 131. Further, although the claims do not require any level of safety, both zanubrutinib and ibrutinib are effective to treat CLL/SLL despite characteristic adverse events of ibrutinib-like iBTKIs. EX2014 ¶130; EX2021, 154:21-155:21 (agreeing that ibrutinib and zanubrutinib exhibit the same adverse events).

3. A POSA Would Have Been Highly Skilled and State of the Art Was Sophisticated and Predictable (*Wands* Factors 5-7)

There is no dispute that the POSA would be highly skilled. EX1003 ¶253; EX1005 ¶265; EX2010 ¶223; EX2014 ¶134. But despite acknowledging the sophistication of a POSA, Petitioner ignores Marcotte's teaching regarding the ibrutinib-like binding to BTK. Pet. 90-92. In ignoring (and mischaracterizing) the wealth of structural information available to a POSA in 2011 reading the '803 Patent, Petitioner and its experts present a fatally flawed analysis that fails to account for the perspective of a POSA. *Bayer*, 989 F.3d at 982 (enablement “*must be viewed* ‘from the perspective of’” a POSA).

Contrary to Petitioner's claim that “little was known” regarding BTK, Pet. 90, in 2011, the structure-function relationship for ibrutinib-like iBTKIs was well-understood, having been taught in the specification that an ibrutinib-like iBTKI treats CLL/SLL patients and further defined by Marcotte showing precisely how the fixed phenoxyphenyl orients in BTK's back pocket and the linker projects toward BTK's cysteine. EX2014 ¶¶135, 137; EX2010 ¶¶224-226; §II.C. A POSA would have been able to leverage the known binding mode from Marcotte to accurately predict binding of other ibrutinib-like iBTKIs to recognize structures that bind and irreversibly inhibit BTK. EX2010 ¶¶224-226; EX2014 ¶¶136-137; §IV.C.3. Further, contrary to Petitioner's characterization, a POSA reading the '803 Patent had significant understanding of the structure-function relationship for hinge-binding

elements that made predictable hydrogen bonds to the conserved kinase hinge. EX2010 ¶227; §II.C.3; *cf.* EX1003 ¶¶254-257. Petitioner's own cited references exhaustively detail that hinge-binding elements were "straightforward," "empirical," "predictable," and could be "anticipat[ed]." EX1052.002, .019, .020; EX2010 ¶¶228-229.

Petitioner fails to support its assertions of unpredictability in practicing the claimed method. First, citing prior statements by Pharmacyclics, Petitioner alleges that cancer treatment is unpredictable and that "[y]ou have no idea until you actually try it." EX1005 ¶266. But the inventors here *already tried it* and showed in the specification that irreversibly inhibiting BTK with an ibrutinib-like iBTKI treated CLL/SLL patients and induced lymphocytosis. §IV.B.1-2; EX2014 ¶¶138-139. Second, Petitioner cites long development timelines and drug development failures as evidence of unpredictability. EX1005 ¶267. But the claims here do not require a successfully developed drug, and even a drug that fails to achieve (or does not pursue) regulatory approval may still treat CLL/SLL patients. EX2014 ¶140; EX2021, 144:12-15, 188:2-6; *see* §V.B.4.a. Third, Petitioner claims that it was unpredictable whether an ibrutinib-like iBTKI that inhibits BTK would treat CLL/SLL patients and induce lymphocytosis. EX1005 ¶¶65-80, 99-100. But Dr. Rosen admitted these were "theoretical" concerns and does not identify any example of an ibrutinib-like iBTKI failing to have these functions. EX2021, 95:7-97:2,

219:12-18, 226:19-227:14; EX2014 ¶¶122. Moreover, the specification teaches—and Petitioner and its expert agree—that inhibiting BTK leads to treating CLL/SLL patients and lymphocytosis. EX2014 ¶¶123, 136-137, 139, 143; EX1012.008, .012; EX2022.0003; EX2021, 39:1-8 (admitting that a compound that occupies and inhibits BTK “presumably, it would lead to killing[]” CLL/SLL cells).

4. Petitioner's Non-Enablement Arguments Are Contrary to Law and Evidence

a. Enablement Does Not Require Meeting FDA Regulatory Standards for Safety and Efficacy

As the Board correctly noted in the ID, regulatory approval is not the standard for enablement, even for claims requiring a “therapeutically effective” dose. ID 29; *United Therapeutics*, 74 F.4th at 1370 (noting that failed safety study “may be an issue for the FDA[,]” but it is not an issue for enablement of a “therapeutically effective” dose); *UroPep*, 276 F. Supp. 3d at 662 (“FDA approval is not required to enable a patent claim to a medicinal compound or a method of treatment.”); *see also In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) (“FDA approval ... is not a prerequisite for finding a compound useful within the meaning of the patent laws.”). As discussed above, much of Petitioner's evidence of alleged non-enablement fails because Petitioner attempts to invoke and import optimized efficacy and safety standards necessary for clinical development and regulatory approval, but not required by the claims.

b. Enablement Does Not Require Excluding Inoperative Species or Optimal Activity

Enablement does not require teaching optimum or optimized embodiments. *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338-40 (Fed. Cir. 2003) (enablement does not demand “mak[ing] and us[ing] a perfected, commercially viable embodiment absent a claim limitation to that effect”); *Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991) (finding “enablement requirement is met if the description enables any mode of making and using the claimed invention”). Much of Petitioner's evidence of alleged non-enablement fails because Petitioner merely points out that some ibrutinib-like iBTKIs of the claims may have better performance than others, rather than establishing an inability to meet claim requirements. §V.B.4.c.

Petitioner incorrectly assumes that if inoperative species meet the structural requirements of the claims, the claims are not enabled. Pet. 83. But simply because one could hypothesize inoperative embodiments does not render the claim invalid; rather, given the specification's teaching of ibrutinib's therapeutic activity in CLL/SLL patients and the sophisticated level of understanding of the structure-function relationship of ibrutinib-like iBTKIs in 2011, a POSA would understand how to identify the operative embodiments. “It is not a function of the claims to specifically exclude ... possible inoperative substances” *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984) (explaining

claims are not invalid “[e]ven if some of the claimed combinations were inoperative[]” where “one skilled in the art would know which [components of the claims] would work in a given system”); *Capon*, 418 F.3d at 1359 (“It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention.”). In *Atlas*, the Federal Circuit agreed that the specification for a patent claiming emulsion blasting agents need not “list all operable emulsions and exclude the inoperable ones[]” because “one skilled in the art would know how to select” certain required components and then would apply a “basic principle of emulsion chemistry” in order “to determine the proper emulsifier.” 750 F.2d at 1576-77. Here, the claims require and the specification teaches the inclusion of the linker-warhead and phenoxyphenyl fixed components with a Z’ that must bind to the BTK active site. §II.A-II.B.2. Because of the sophisticated understanding of the structure-function relationship, including the precise structural data for the binding mode for ibrutinib-like iBTKIs, a POSA reading the ’803 Patent would be able to readily exclude plainly inoperable embodiments using common sense, well-understood drug-design guidelines, and virtual docking. §II.C-II.D; EX2010 ¶¶209, 219; EX2012 ¶¶41-46.

The ability of a POSA to avoid inoperative species here confirms the claimed genus is enabled. For example, in *In re Smythe*, the CCPA found that a method claim

requiring an “inert fluid” was not invalid despite the broader claim term “fluid” including certain “liquids” which would render the method inoperative. 480 F.2d at 1382-85. The court explained that such liquids “would be predictably inoperative in the invention and thus would never be selected” by a POSA. *Id.* at 1385. Similarly, in *In re Marzocchi*, the CCPA reversed an enablement rejection after determining that the disclosure of a single polyethyleneamine enabled the full scope of the genus because the class of compounds possessed similar adhesion enhancing properties for use in the claims. 439 F.2d 220, 223-24 (C.C.P.A. 1971). Despite the potential for certain compounds to lose this “essential” property, the CCPA found the single species enabling because there was “no basis to conclude that the ready avoidance” of inoperative species “would not be within the level of ordinary skill in this art.” *Id.* at 224. The same is true here. As discussed above, a POSA would recognize the compounds to use in the claimed method because of the predictable structure-function relationship for binding of ibrutinib-like iBTKIs. §IV.C.3.

The '803 Patent claims appropriately do not recite exclusions that would be well-known to a POSA in identifying compounds for use in the method. The CCPA has referred to specifying “inoperative substances or ineffective reactant proportions[]” in the claims as “unnecessary limitation[s]” where there is “[d]isclosure in the specification sufficient to enable practice of the invention by” a POSA, including modifications of the specification's specific examples. *In re Dinh-*

Nguyen, 492 F.2d 856, 858-59 (C.C.P.A. 1974). Here, a POSA reading the '803 Patent would recognize which Z'-scaffolds with attached linker-warhead and phenoxyphenyl substituents from ibrutinib achieve the BTK inhibition required by the claims. EX2010 ¶¶208-209, 219; EX2012 ¶¶20, 42-46. Detailing the choices a POSA would *not select* is not required.

c. Petitioner Points to Irrelevant Differences Among Species Suitable for Use in the Claimed Method

Petitioner identifies irrelevant differences among ibrutinib-like iBTKIs that do not show that they are not useful for the claimed continuous dosing method. Specifically, Petitioner argues that differences in measured preclinical potency and selectivity, side effects, and dosage schedules between compounds within the claimed genus suggest the claims are not enabled; but as discussed above, these differences do not evidence that the compounds do not work in the claimed method and thus do not support finding the claims not enabled. Pet. 20-24; §V.B.3; *CFMT*, 349 F.3d at 1338-40; *Engel*, 946 F.2d at 1533; *United Therapeutics*, 74 F.4th at 1370; *UroPep*, 276 F. Supp. 3d at 662.

Petitioner and its expert cite variation in preclinical selectivity and potency of compounds within the genus in the claims. But these compounds all have measurable nanomolar potency. Pet. 19-20; EX1003 ¶¶71-73; EX2010 ¶¶230-231. And Petitioner has cited no evidence that these potent compounds could not be dosed to

treat CLL/SLL as taught in the specification and recited in the claims. EX2021, 254:16-255:6; EX2014 ¶¶136, 140.

Petitioner additionally cites to clinical data and experience with zanubrutinib and tolebrutinib as allegedly demonstrating lack of enablement. Pet. 22-24. But each of these examples **support** enablement of the claims, showing that the compounds of the genus are able to irreversibly inhibit BTK and/or treat CLL/SLL in patients. Petitioner relies on the alleged superiority of zanubrutinib over ibrutinib, as shown in the ALPINE trial. *Id.* 22; EX1005 ¶¶75-77. This simply confirms the efficacy of zanubrutinib to treat CLL/SLL and the specification's enablement of the class of iBTKIs for this method. EX2014 ¶140. And while Petitioner invokes differences in safety profiles of the two drugs, both are FDA-approved for treating CLL/SLL, demonstrating their therapeutic efficacy. Pet. 23-24; EX1005 ¶¶87-96. Moreover, these differences do not demonstrate that the compounds of the claims are unsafe. Indeed, ibrutinib is FDA-approved to treat CLL/SLL and is a safe and effective therapy today. EX2021, 68:4-6; EX2014 ¶¶130, 140. Further, ibrutinib-like iBTKIs are safer and more effective than the prior art standard of care of chemotherapy and chemoimmunotherapy. EX2014 ¶¶52, 60, 141. In addition, despite the attempts to separate the side effects of ibrutinib from zanubrutinib, Petitioner's cited side effects are **class effects**, shared to at least some degree by reported iBTKIs. *Id.* ¶¶59-60, 142; EX2021, 154:11-155:21.

Finally, while Petitioner argues that the partial hold for tolebrutinib in multiple sclerosis clinical trials evidences non-enablement by demonstrating “[t]he unpredictable nature of a BTKI’s safety,” this assertion distorts both the legal standard for enablement and the facts. Pet. 23; EX1092; §V.B.4.a. FDA approval is not required to enable the claims (much less FDA approval for a different (unclaimed) indication). §V.B.4.a. Further, the claims do not recite a safety component, making Petitioner’s reliance on tolebrutinib inapposite. §III.A. Rather, in fact, the advanced clinical development of tolebrutinib demonstrates that compounds within the claimed genus irreversibly inhibit BTK. Pet. 23; EX1092; EX2014 ¶110.

VI. Grounds 3 and 4: Petitioner’s Asserted References Are Not Prior Art

The specification filed in June 2011 fully describes and enables the challenged claims for all the reasons described above. Thus, the claims are entitled to at least the June 2011 priority date. Because Byrd published in 2013 and the IMBRUVICA label published in 2016, after the June 2011 priority date, Petitioner’s references are not prior art and cannot anticipate or render obvious the challenged claims.

VII. Conclusion

For the reasons set forth above, the Board should find the challenged claims not unpatentable.

Respectfully submitted,

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

I hereby certify that this Patent Owner's Response complies with the word count limitation of 37 C.F.R. § 42.24(b)(2) because the Patent Owner's Response contains 18,575 words using Microsoft Word's counting feature, excluding the cover page, signature block, and the parts of the Patent Owner's Response exempted by 37 C.F.R. § 42.24(b)(2).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 7th day of August, 2024, a true and correct copy of the foregoing **Patent Owner's Response and all Exhibits** were served by electronic mail on Petitioner's lead and backup counsel at the following email addresses:

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