

Filed on behalf of: Pharmacyclics LLC

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

**DECLARATION OF MICHAEL J. ECK, M.D., PH.D.
IN SUPPORT OF PATENT OWNER'S RESPONSE**

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I. INTRODUCTION

1. I have been retained by Pharmacyclics LLC (“Patent Owner” or “Pharmacyclics”) to provide my opinion concerning the validity of U.S. Patent No. 11,672,803 (EX1001) (“’803 Patent”). I am being compensated for my work in this matter at my customary hourly rate of \$800 and being reimbursed for reasonable expenses. My compensation is not contingent upon the substance of my opinions or the outcome of this matter.

II. BACKGROUND AND QUALIFICATIONS

2. In 1985, I received my Bachelor’s Degree in Electrical Engineering (B.S.E.E.) from Rice University. I continued my education at the University of Texas Southwestern Medical School and the University of Texas Southwestern Graduate School, earning my Doctor of Medicine (M.D.) degree and Doctor of Philosophy (Ph.D.) degree in Biochemistry, both in 1991. Since completing my M.D. and Ph.D. degrees, I have spent my professional career at Harvard Medical School and affiliated hospitals.

3. From 1991 to 1996, I trained as a Postdoctoral Fellow at Boston Children’s Hospital and the Howard Hughes Medical Institute. In 1994, I was appointed as an Instructor in Pediatrics at Harvard Medical School.

4. In 1996, I joined the faculty of the Department of Cancer Biology at the Dana-Farber Cancer Institute and the Department of Biological Chemistry and

Molecular Pharmacology at Harvard Medical School as an Assistant Professor. I was promoted to Associate Professor in 2003 and promoted to Professor in 2007, the latter of which is my current position.

5. Since completing my degrees and training, I have worked for roughly 28 years in the field of structural biology, studying protein structure and function. In my current position, I direct a research laboratory at the Dana-Farber Cancer Institute. My laboratory studies the three-dimensional structure of proteins and protein complexes, particularly focusing on proteins that play a role in cancer, as my laboratory works in the area of cancer drug discovery. My laboratory uses the techniques of X-ray crystallography and cryogenic electron microscopy to study the three-dimensional structure and function of proteins and protein complexes. In the course of my career, I have studied numerous proteins, including protein kinases such as the tyrosine kinase c-Src, focal adhesion kinase (“FAK”), and epidermal growth factor receptor (“EGFR”). My laboratory has determined the structures of particular kinases and has studied how diverse inhibitors target such kinases. My laboratory uses tools of computational chemistry (molecular dynamics, virtual ligand screening, and docking) in our studies of protein structure and function and in our inhibitor discovery/characterization efforts. I also teach graduate students at Harvard Medical School in courses concerning protein structure and function.

6. Cancer drug discovery is a major focus in my laboratory. With our collaborators, we have developed inhibitors of several kinases including EGFR, HER2, JAK3, and Bruton's tyrosine kinase ("BTK"). A number of these projects involved structure-informed development of irreversible inhibitors that target a cysteine residue near the active site (including EGFR, HER2, JAK3 and BTK).

7. I have authored or co-authored more than 130 peer-reviewed publications, with most relating to the structure and function of proteins, including protein kinases. For example, I was a first-author of a 1994 publication titled "Structure of the regulatory domains of the Src-family tyrosine kinase Lck." The full list of my peer-reviewed publications is included in my *curriculum vitae* ("CV"). Furthermore, I have been a member of the editorial board of the peer-reviewed scientific journal Chemical Biology and Drug Design (2006 - 2010) and a member of the board of reviewing editors for the Journal of Biological Chemistry (2011 - 2016).

8. Moreover, I am a named inventor on at least eight issued U.S. patents—most of which relate to EGFR inhibitors. For example, I am a named inventor of U.S. Patent No. 9,908,884, titled "EGFR inhibitors and methods of treating disorders." As another example, I am a named inventor of U.S. Patent No. 10,385,019, titled "Inhibitors of EGFR and methods of use thereof." In addition, I am a named inventor on at least eleven World Intellectual Property Organization

(“WIPO”) publications. A list of my WIPO publications and issued U.S. patents is included in my CV.

9. I have been a member of numerous professional societies in the course of my career, including the American Crystallographic Association, the American Chemical Society, and the American Association for Cancer Research. Additional professional society memberships are listed in my CV.

10. Throughout my career, my work has been recognized with various awards and honors, including the Scholar Award from the Leukemia and Lymphoma Society (2002) and the National Cancer Institute (“NCI”) Outstanding Investigator Award (2019). Additional awards and honors are listed in my CV.

11. And throughout my career, I have been an invited speaker to numerous regional, national, and international presentations. For example, in 2009, I was an invited speaker to the Sixth International Conference on Inhibitors of Protein Kinases in Warsaw, Poland. As another example, in 2017, I was an invited speaker to the Ninth International Conference on Inhibitors of Protein Kinases – Challenges in Molecular Biology and Biomedicine in Warsaw, Poland. And as an additional example, in 2017, I was an invited speaker to the Kinase Inhibitors in Drug Discovery presentation in Berlin, Germany. A list of these presentations is included in my CV.

12. The above summary is not intended to be exhaustive. A copy of my CV is EX2011, which describes in greater detail my professional experience and qualifications as well as a list of my publications and patents. EX2011 is being served simultaneously with this Declaration and is incorporated here by reference.

III. MATERIALS REVIEWED AND CONSIDERED

13. All of the opinions contained in this Declaration are based on the documents I considered and my education, years of professional experience, and knowledge. In forming the opinions expressed in this Declaration, while drawing on my experience in the field of kinase inhibitors, I considered the following documents. To the extent a document is not listed in the below table or not cited in my Declaration, the document did not affect my opinion or was cumulative to other documents included in the below table.

Ex.	Description
1001	United States Patent No. 11,672,803
1003	Declaration of Hollis D. Showalter, Ph.D.
1036	U.S. Patent Publication No. 2020/0140432
1044	Chiara Brullo, et. al. "Btk Inhibitors: A Medicinal Chemistry & Drug Delivery Perspective", Int'l J. of Molecular Sci. 2021; 22:7641
1049	L. Garuti, et. al. "Irreversible Protein Kinase Inhibitors", Current Medicinal Chem., 2011; 18:2981-2994
1052	Arup K. Ghose, et. al. "Knowledge Based Prediction of Ligand Binding Modes & Rational Inhibitor Design for Kinase Drug Discovery", J. Medicinal Chem. 2008; 51(17); 5149-5171

Ex.	Description
1053	Yunhang Guo, et. al. "Discovery of Zanubrutinib (BGB-3111), a Novel, Potent, and Selective Covalent Inhibitor of Bruton's Tyrosine Kinase", J. Medicinal Chem. 2019; 62:7923-7940
1055	Lee A. Honigberg, et. al. "The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy", PNAS 2010; 107(29):13075-130
1060	Zhengying Pan, et. al. "Discovery of Selective Irreversible Inhibitors for Bruton's Tyrosine Kinase", ChemMedChem 2007; 2, 58-61
1066	Frédérique St-Pierre and Shuo Ma, "Use of BTK Inhibitors in Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma (CLL/SLL): A Practical Guidance", Blood & Lymphatic Cancer: Targets & Therapy 2022; 12:81-98
1072	Fatih M. Uckun, "Clinical Potential of Targeting Bruton's Tyrosine Kinase", Int'l Reviews of Immunology 2008; 27:43-69
1073	Fatih M. Uckun and Sanjive Qazi, "Bruton's tyrosine kinase as a molecular target in treatment of leukemias and lymphomas as well as inflammatory disorders and autoimmunity", Expert Opinion 2010; 20(11):1457-1470.
1075	Rula Zain and Mauno Vihinen, "Structure-Function Relationships of Covalent and Non-Covalent BTK Inhibitors", Frontiers in Immunology 2021; 12:694853
1076	Datong Zhang, et. al. "Recent Advances in BTK Inhibitors for the Treatment of Inflammatory and Autoimmune Diseases", Molecules 2021; 26:4907
1077	Jianming Zhang, et. al. "Targeting cancer with small molecule kinase inhibitors", Nature reviews Jan. 2009; 9:28-39
2001	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) ("Marcotte 2010")
2011	<i>Curriculum Vitae</i> of Michael J. Eck, M.D., Ph.D.

Ex.	Description
2012	Declaration of David A. Scott, Ph.D. (“Scott Decl.”)
2018	Deposition transcript of Hollis Showalter, Ph.D., <i>BeiGene USA, Inc. v. Pharmacyclics LLC</i> , No. PGR2024-00009 (P.T.A.B. July 18, 2024) (“Showalter Dep.”)
2020	Yunhang Guo et al., <i>Discovery of BGB-8035, a Highly Selective Covalent Inhibitor of Bruton’s Tyrosine Kinase for B-Cell Malignancies and Autoimmune Diseases</i> , 66 J. Med. Chemistry 4025 (2023) (Exhibit 2 to the Showalter Dep. (Ex. 2018))
2023	U.S. Patent No. 7,435,820 B2
2024	U.S. Patent No. 10,358,446 B2
2025	U.S. Patent Application Publication No. 2008/0108636 A1
2026	U.S. Patent Application Publication No. 2010/0160303 A1
2027	International Patent Application Publication No. WO 2010/126960 A1
2028	Irini Akritopoulou-Zanze & Philip J. Hajduk, <i>Kinase-Targeted Libraries: The Design and Synthesis of Novel, Potent, and Selective Kinase Inhibitors</i> , 14 Drug Discovery Today 291 (2009)
2029	Misty M. Attwood et al., <i>Trends in Kinase Drug Discovery: Targets, Indications and Inhibitor Design</i> , 20 Nature Revs. Drug Discovery 839 (2021)
2030	Frances C. Bernstein et al., <i>The Protein Data Bank: A Computer-Based Archival File for Macromolecular Structures</i> , 80 Eur. J. Biochemistry 319 (1977)
2033	Philip Cohen, <i>Protein Kinases — The Major Drug Targets of the Twenty-First Century?</i> , 1 Nature Revs. Drug Discovery 309 (2002)
2034	Stephane De Cesco et al., <i>Covalent Inhibitors Design and Discovery</i> , 138 Eur. J. Med. Chemistry 96 (2017)
2035	Richard A. Friesner et al., <i>Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy</i> , 47 J. Med. Chemistry 1739 (2004)

Ex.	Description
2036	Richard A. Friesner et al., <i>Extra Precision Glide: Docking and Scoring Incorporating a Model of Hydrophobic Enclosure for Protein – Ligand Complexes</i> , 49 J. Med. Chemistry 6177 (2006)
2037	<i>Glide 5.5 User Manual</i> , Schrödinger, LLC (2009)
2038	Vijaya Gracias et al., <i>Scaffold Oriented Synthesis. Part 2: Design, Synthesis and Biological Evaluation of Pyrimido-Diazepines as Receptor Tyrosine Kinase Inhibitors</i> , 18 Bioorganic Med. Chemistry Letters 2691 (2008)
2039	Yunhang Guo et al., <i>Supporting Information</i> (pp. S1-S50) to <i>Discovery of Zanubrutinib (BGB-3111), a Novel, Potent and Selective Covalent Inhibitor of Bruton's Tyrosine Kinase</i> , 62 J. Med. Chemistry 7923 (2019) (Exhibit 1053)
2041	Thomas A. Halgren et al., <i>Glide: A New Approach for Rapid, Accurate Docking and Scoring. 2. Enrichment Factors in Database Screening</i> , 47 J. Med. Chemistry 1750 (2004)
2043	Louise N. Johnson, <i>Protein Kinase Inhibitors: Contributions from Structure to Clinical Compounds</i> , 42 Q. Revs. of Biophysics 1 (2009)
2045	Hezekiel Mathambo Kumalo et al., <i>Theory and Applications of Covalent Docking in Drug Discovery: Merits and Pitfalls</i> , 20 Molecules 1984 (2015)
2046	Betty Lam et al., <i>Discovery of TAK-659 an Orally Available Investigational Inhibitor of Spleen Tyrosine Kinase (SYK)</i> , 26 Bioorganic Med. Chemistry Letters 5947 (2016)
2047	Roman A. Laskowski & Mark B. Swindells, <i>LigPlot+: Multiple Ligand — Protein Interaction Diagrams for Drug Discovery</i> , 51 J. Chem. Info. Modeling 2778 (2011)
2048	Laurent Le Corre et al., <i>Synthesis and Biological Evaluation of a Triazole-Based Library of Pyrido[2,3-d]pyrimidines as FGFR3 Tyrosine Kinase Inhibitors</i> , 8 Organic Biomolecular Chemistry 2164 (2010)
2049	Kui Lin et al., <i>An ATP-Site On-Off Switch That Restricts Phosphatase Accessibility of Akt</i> , 5 Sci. Signaling 1 (2012)

Ex.	Description
2050	Qingjie Liu et al., <i>Design and Synthesis of Carbazole Carboxamides as Promising Inhibitors of Bruton's Tyrosine Kinase (BTK) and Janus Kinase 2 (JAK2)</i> , 25 Bioorganic Med. Chemistry Letters 4265 (2015)
2053	Moosa Mohammadi et al., <i>Structures of the Tyrosine Kinase Domain of Fibroblast Growth Factor Receptor in Complex with Inhibitors</i> , 276 Sci. 955 (1997)
2054	Garrett M. Morris et al., <i>AutoDock4 and AutoDockTools4: Automated Docking with Selective Receptor Flexibility</i> , 30 J. Computational Chemistry 2785 (2009)
2055	T. G. Murali Dhar et al., <i>Synthesis and SAR of p38α MAP Kinase Inhibitors Based on Heterobicyclic Scaffolds</i> , 17 Bioorganic Med. Chemistry Letters 5019 (2007)
2056	Albert C. Pierce et al., <i>Docking Study Yields Four Novel Inhibitors of the Protooncogene Pim-1 Kinase</i> , 51 J. Med. Chemistry 1972 (2008)
2057	Krishna P. Ravindranathan et al., <i>Discovery of Novel Fibroblast Growth Factor Receptor 1 Kinase Inhibitors by Structure-Based Virtual Screening</i> , 53 J. Med. Chemistry 1662 (2010)
2058	Robert Roskoski, Jr., <i>Properties of FDA-Approved Small Molecule Protein Kinase Inhibitors: A 2021 Update</i> , 165 Pharmacological Rsch. 105463 (2021)
2061	Scott H. Watterson et al., <i>Discovery of 6-Fluoro-5-(R)-(3-(S)-(8-Fluoro-1-Methyl-2,4-Dioxo-1,2-Dihydroquinazolin-3(4H)-yl)-2-Methylphenyl)-2-(S)-(2-Hydroxypropan-2-yl)-2,3,4,9-Tetrahydro-1H-Carbazole-8-Carboxamide (BMS-986142): A Reversible Inhibitor of Bruton's Tyrosine Kinase (BTK) Conformationally Constrained by Two Locked Atropisomers</i> , 59 J. Med. Chemistry 9173 (2016)
2063	Xuejun Zhang et al., <i>Discovery and Evaluation of Pyrazolo[3,4-d]pyridazinone as a Potent and Orally Active Irreversible BTK Inhibitor</i> , 11 Am. Cancer Soc'y Med. Chemistry Letters 1863 (2020)

Ex.	Description
2111	International Patent Application Publication No. WO 2008/121742 A2

14. I have reviewed the Showalter Declaration (EX1003) and have provided my opinions in response to Dr. Showalter's opinions. While doing so, I have explained various disagreements that I have with Dr. Showalter. My silence on a particular opinion of Dr. Showalter does not mean that I agree with his opinion.

IV. SUMMARY OF OPINIONS

15. I understand that BeiGene USA, Inc. and BeiGene, LTD. ("Petitioner" or "BeiGene") have asserted grounds of unpatentability of claims 1-8, 12, and 20 ("Challenged Claims") of the '803 Patent, including the following two grounds:

- Ground 1: Lack of Written Description of Challenged Claims
- Ground 2: Lack of Enablement of Challenged Claims.

16. I further understand that Petitioner has asserted that the priority non-provisional applications of U.S. Patent No. 11,672,803 including App. No. 13/153,317 (filed June 3, 2011) do not provide adequate written description nor enable the Challenged Claims. I understand that the '803 Patent also claims priority to additional non-provisional patent applications and that these applications were

filed on April 24, 2013, November 26, 2013, September 26, 2017, April 27, 2018, and August 8, 2019.

17. I have been asked to analyze the '803 Patent and provide my opinion as to whether the compounds in the Challenged Claims of the '803 Patent are adequately described as irreversible inhibitors of Bruton's tyrosine kinase ("BTK") and whether a person of ordinary skill in the art ("POSA"), relying on the '803 Patent and general knowledge in the field, would be able to make and use these compounds.

18. In forming my opinion, I have relied on certain opinions of Dr. David A. Scott, who analyzed chemical structural aspects and pharmacological properties of BTK inhibitors ("BTKIs") and the Challenged Claims.

19. In my opinion, the specification adequately describes the irreversible BTKIs used in the Challenged Claims. I disagree with Dr. Showalter's opinion that the Challenged Claims lack written description because the specification discloses sufficient information such that a POSA would have understood that the inventor possessed the full scope of the compounds used in the Challenged Claims as of the priority date. Specifically, the specification describes common structural features for the claimed irreversible BTKIs for use in the claimed treatment method. Furthermore, the specification provides sufficient blaze marks to the claimed genus of compounds.

20. Additionally, in my opinion, the specification enables the irreversible BTKIs of the Challenged Claims. I disagree with Dr. Showalter's opinion that the Challenged Claims lack enablement because a POSA, having read the specification, could make and use the compounds used in the Challenged Claims without undue experimentation as of the priority date. Specifically, the specification provides guidance and working examples for a POSA to make and use the irreversible BTKIs necessary for the claimed treatment method. Moreover, based on this guidance in the specification, only routine experimentation would have been required to identify the compounds of the Challenged Claims and confirm that they irreversibly inhibit BTK for use in the claimed method.

V. LEGAL PRINCIPLES

21. I have no formal legal training, but I have been advised by counsel for Pharmacyclics of the relevant legal principles relevant to my analysis and opinions.

A. Written Description

22. I understand that to satisfy the written description requirement, the patent specification must reasonably convey to a POSA that the inventor had possession of the claimed subject matter as of the filing date. I understand that the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the patent claims and on the complexity and predictability of the relevant technology. And I understand that to satisfy the

written description requirement, a patent owner can rely on information that is well-known in the art to the extent it informs how a POSA would reasonably understand what is actually described in the specification.

23. I understand that the disclosure must allow a POSA to visualize or recognize the identity of the subject matter purportedly described.

24. I understand that satisfying the written description requirement does not necessitate “*ipsis verbis*” or verbatim disclosure. I understand that the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus establishes the requisite description of a genus. I understand such common structural features must be sufficient for POSA to visualize or recognize the members of the genus. I further understand that while there must be a sufficient correlation between structure and function for such features, there need not be a perfect correspondence.

25. I also understand that when a subgenus is claimed, the written description requirement has alternatively been formulated as “blaze marks” to the claimed subgenus or whether the subgenus is clearly discernible.

26. I further understand that the written description requirement does not demand either examples or an actual reduction to practice.

B. Enablement

27. I understand that the patent's specification must enable the full scope of the invention as defined by its claims, allowing for a reasonable amount of experimentation. And I understand that what is reasonable depends on the nature of the invention and the underlying art. In other words, I understand that the enablement requirement is satisfied when a POSA, having read the specification, could practice the invention without undue experimentation.

28. I understand that a patent need not teach, and preferably omits, what is well known in the art.

29. I understand that the fact that some experimentation may be required for a POSA to practice the claimed invention does not indicate that the enablement requirement is not met. I understand that assessing the reasonableness of experimentation requires weighing not one but many different factual considerations. I further understand that the following *Wands* factors may be considered in determining whether practicing the claimed invention would require undue experimentation: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (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 of the art; and (8) the breadth of the claims.

30. I also understand that the question of undue experimentation is a matter of degree, and that it does not require unduly extensive trial-and-error experimentation. I understand that the focus is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine (*e.g.*, involving repetition of known or commonly used techniques), or if the specification provides a reasonable amount of guidance.

31. I further understand that the enablement requirement does not require actual working examples. I further understand that it is not the function of the claims to exclude inoperative embodiments, particularly where a skilled artisan would understand how to select operative embodiments.

32. I understand that enablement does not require teaching optimum or optimized embodiments. I also understand that meeting FDA approval standards is not required for enablement, even if the claims requiring treating a disease with a “therapeutically effective amount.”

VI. THE '803 PATENT

A. Timeframe

33. Unless otherwise noted below, the discussion of the '803 Patent and related technology is what a POSA would have understood in view of the patent specification and available scientific literature on June 3, 2011. To the extent I reference knowledge in the field “in 2011,” that knowledge would have been

available as of June 3, 2011. My conclusions about the teaching of the patent and knowledge of a POSA would also apply to the filing dates of the non-provisional patent applications to which the '803 Patent claims priority, which I understand to be April 24, 2013, November 26, 2013, September 26, 2017, April 27, 2018, and August 8, 2019. To the extent I address information available after June 2011 it is either indicative of the state of the art in June 2011 or confirms my conclusions that later developments in the field would not change my analysis.

B. Challenged Claims

34. The '803 Patent is directed to methods of treating chronic lymphocytic leukemia ("CLL") or small lymphocytic lymphoma ("SLL") by continuously dosing a therapeutically effective amount of a defined class of irreversible BTKIs wherein lymphocytosis is not considered progression of the CLL or SLL. *See* EX1001.

35. I understand that claims 1 and 8 are independent claims of the '803 Patent and that claims 2-7 and 12 (which depend on claim 1), and 20 (which depends on claim 8) are dependent claims of the '803 Patent. I also understand that the dependent Challenged Claims include all the limitations of the claims from which they depend.

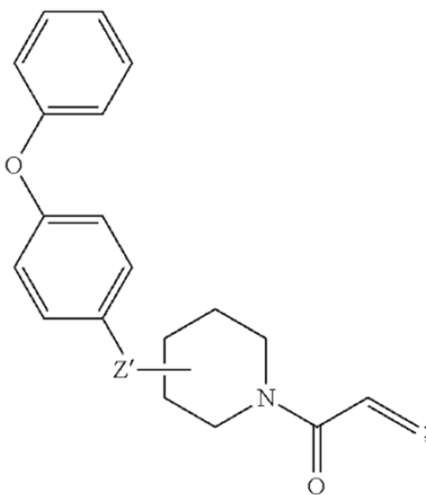
36. Independent claim 1 is reproduced below, and recites:

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 [of] 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.

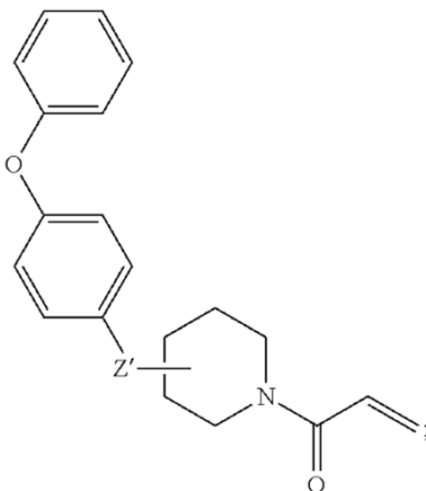
EX1001, 151:33-152:4.

37. Independent claim 8 is similar to independent 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.” EX1001, 152:46-153:23.

38. The dependent Challenged Claims include additional limitations. Claim 2 further requires particular BTK occupancy (>90% of the Btk active sites in the peripheral blood mononuclear cells) at twenty-four hours following administration. EX1001, 152:5-11. Claim 3 further requires that the therapeutically effective dose be determined by measuring the pharmacodynamic parameters of the irreversible BTK inhibitor. EX1001, 152:12-14. Claim 4 further requires that the therapeutically effective dose of the irreversible BTKI be a fixed dose. EX1001, 152:33-35. Claim 5 further requires specific pharmacokinetic results (AUC(0-24) of about >100 ng*h·ml). EX1001, 152:36-38. Claims 6 and 7 further require treating CLL and SLL, respectively, with once daily dosing. EX1001, 152:39-45. Claims 12 and 20 further narrow the BTKI structures to use in the claimed methods, requiring the fused heterocyclic ring system to comprise 3 nitrogen heteroatoms. EX1001, 154:20-21, 156:20-21.

C. Compounds of the Challenged Claims

39. The Challenged Claims recite irreversible BTKIs with the following structure:



wherein Z' is an optionally substituted fused heterocyclic ring system comprising from 2-4 nitrogen heteroatoms (dependent claims 12 and 20 specify 3 nitrogen heteroatoms) and wherein the optionally substituted fused heterocyclic ring system consists of a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom. The class of irreversible BTK inhibitors recited in the claims are “ibrutinib-like”¹ as they

¹ As used here, “ibrutinib-like” means irreversible BTKIs 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 having 2-4 nitrogen heteroatoms, with at least one nitrogen in each ring.

include the structural features of ibrutinib that correlate with the ability to irreversibly inhibit BTK. As explained below, a POSA reading the '803 Patent would have understood that the hinge-binding scaffold of the BTKI—here Z'—would form one to three hydrogen bonds (“H-bonds”) with the kinase hinge region. *See infra* §VI.D.3. Additionally, the compounds recited in the Challenged Claims have two fixed components from ibrutinib: the phenoxyphenyl moiety and the linker-warhead that forms a covalent bond with Cys481 of BTK. *See infra* §VI.D.1-VI.D.2.

D. Overview of the Specification and Related Technology

40. A POSA would understand the '803 Patent specification in June 2011 in the context of the field of protein kinases as therapeutic targets as follows.

41. Protein kinases² were known to catalyze the transfer of a phosphate from an ATP molecule to a protein substrate in the body, usually in order to modulate the protein's activity or interactions with other proteins. *See* EX1077.002. There are over 500 human kinases that mediate diverse cellular processes such as cellular signaling, growth, metabolism, and development. *See* EX1077.001-002; EX2028.0001; EX1052.001. Bruton's tyrosine kinase (“BTK”)

² Unless otherwise noted, in this Declaration, any reference to “kinase” refers to a protein kinase, and I use “kinase” and “protein kinase” interchangeably.

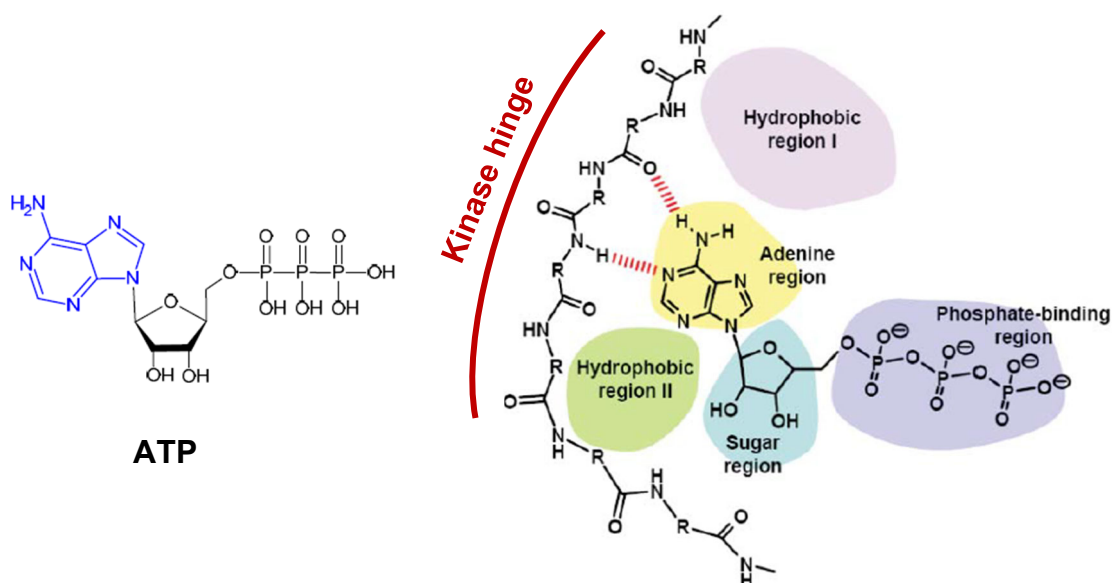
is a protein kinase involved in the development, activation, signaling, and survival of B-cells, including lymphocytes. *See* EX1072.004; EX1066.002.

42. Before 2011, many diseases and disorders were associated with aberrant protein kinase activity. *See* EX1077.001. Accordingly, protein kinases became attractive targets for drug development. *See id.* Starting in the 1980s and 1990s, drug developers had significant interest in inhibitors of protein kinases. *See generally* EX2033. In 2011, there were 13 FDA approved small-molecule drugs targeting the active site of protein kinases. *See* EX2058, Tbl. 1 (.0002-0003); *see also* EX2043, Tbl. 1 (.0004); EX2029, Fig. 1 (.0003). Thus, in 2011, there was long-standing investment and efforts in the study and design of kinase inhibitors. *See* EX2033.0006 (reporting in 2002 that “protein kinases are already the second largest group of drug targets . . . and they account for 20–30% of the drug discovery programmes of many companies”). As one 2009 reference reported, “[p]rotein kinases have rapidly become one of the most important group of drug targets, second only to G-protein coupled receptors (GPCRs). Since the successful launch of Glivec, Iressa, Nexavar and others, ***there are now more than 200 kinase inhibitors in clinical development*** (Prous Science Integrity) and the preclinical target portfolio of nearly every major pharmaceutical company contains a substantial fraction of protein kinases.” EX2028.0001 (emphasis added).

43. The specification of the '803 Patent teaches the structural components for irreversible BTKIs for use in the methods of treating CLL/SLL—namely, the two fixed components (the linker-warhead and the phenoxyphenyl moiety) and the one structurally-constrained component (the hinge-binding central scaffold (Z')). *See* EX1001, 45:32-81:18. The specification of the '803 Patent in particular teaches compounds with components mirroring ibrutinib's structure. *See id.*

44. The specification therefore provided significant guidance about the physical structure and expected characteristics of the compounds encompassed by the genus in the patent claims, particularly in view of what POSA in 2011 would have understood about the structure of the BTK active site.

45. The region of the kinase where ATP binds is commonly referred to as the “active site” of the kinase. *See* EX2018, 100:12-14 (Q. “And the active site of Btk is where ATP binds. Correct?” A. “That’s a well-known fact.”); EX1052.002. In particular, ATP binds to a kinase by making H-bonds to specific residues within a region of the kinase called the “hinge.” Because ATP binding is universal across kinases, the hinge region and its ATP binding interactions are highly conserved across kinases. *See* EX2028.0001 (“[T]he ATP-binding site of the kinase catalytic domain . . . is highly conserved between all protein kinases.”); EX1075.003 (“The ATP binding site is among the most conserved regions.”).



ATP binding to kinase
(EX2048, Fig.1 (.0001) (annotated))

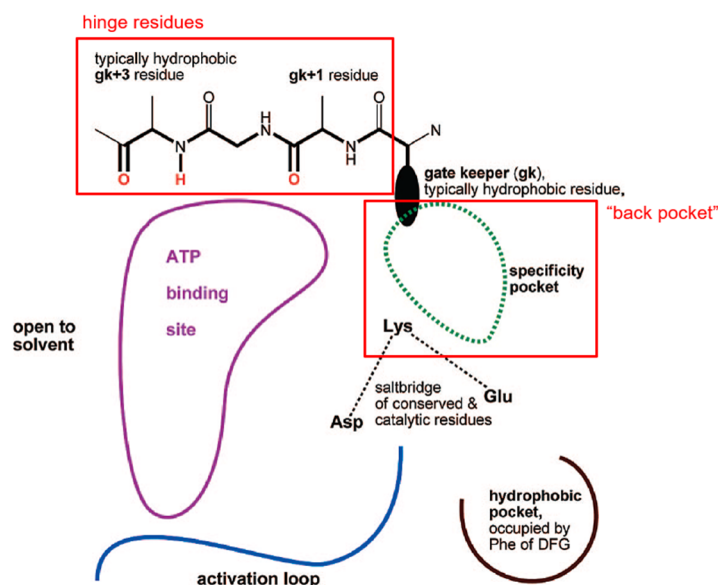
46. The specification—consistent with the art—reflected an advanced understanding of the structure of the kinase active site. By 2011, a large number of protein kinase structures had been determined – approximately 1290 structures of protein kinases with bound ligands were publicly available in the Protein Data Bank (PDB) (including PI-3-kinases and other “atypical” protein kinases).³ Of

³ The Protein Data Bank (PDB) database is a computer archival service established in 1971; it was then managed by the Brookhaven National Laboratory (U.S. Department of Energy, Upton, New York). *See* EX2030.0001 (“The purpose of the Bank is to collect, standardize, and distribute atomic co-ordinates and other data from crystallographic studies.”). By 2011, data from the PDB was freely available

to the public from a small set of partner institutes (*e.g.*, RCSB PDB; <http://rcsb.org>) in multiple formats. Scientists working on the structure-function relationship of kinases and kinase inhibitors, including myself, routinely relied on and contributed to the PDB database. *See also* EX1052.001 (“The current article describes the use of Protein Data Bank (PDB) entries specifically for kinase inhibitor drug discovery. The PDB contains information relating ligand binding in the context of a receptor with protein kinases representing one of the largest known families of enzymes.”). Structures deposited in the PDB are identified and accessed via a 4 character alphanumeric entry code. Each entry contains the atomic coordinates for the structure, and usually the underlying crystallographic structure factor data as well. Each entry is annotated with its deposit date and its release date (the date when the entry became freely available and downloadable for the public at large). As of 2011 and still today, it was common for PDB entries to be deposited prior to publication of a scientific article, but only released upon publication. As of 2011, the PDB database was searchable and freely available at <http://rcsb.org>. For virtually all scientific journals, publication of protein crystal structures requires depositions of those structures in the PDB. Before 2011 and now, I routinely use the PDB in my own work, both depositing structures determined in my laboratory and accessing structures deposited by others.

these, 10 were of BTK itself with diverse ligands. This structural data had led to a developed understanding in 2011 of the basic, conserved regions of the kinase active site. *See, e.g.*, EX1052.002 (describing regions of the kinase ATP binding site and their roles and noting the “high degree of structural similarity of the ATP binding site”); *see also* EX2028.0001 (“The vast majority of known kinase inhibitors bind to the ATP-binding site of the kinase catalytic domain (Figure 1), which is highly conserved between all protein kinases.”); EX1075.003 (“The ATP binding site is among the most conserved regions.”); EX2018, 103:12-17; EX1003, ¶77 (“Btk belongs to the large kinase family known to have conserved active sites.”). A schematic of the active site of protein kinases depicted in Ghose (EX1052) is reproduced below. Dr. Showalter acknowledges that Ghose is “a very important article from 2008.” EX2018, 74:3-10. Ghose’s schematic illustrates key subregions of the kinase active site.

ADAPTED FROM GHOSE FIG. 2 – 2D REPRESENTATION OF THE KINASE ATP BINDING SITE



EX1052, Fig. 2 (.002) (annotated).

1. The Specification Emphasizes Michael Acceptor Linker-Warhead

47. The specification teaches the importance of irreversible binding to BTK's Cys481 residue for selectivity to BTK. *See* EX1001, 45:56-60 ("The Btk inhibitor compounds described herein are selective for Btk and kinases having a cysteine residue in an amino acid sequence position of the tyrosine kinase that is homologous to the amino acid sequence position of cysteine 481 in Btk."). The specification teaches that the linker-warhead forms the covalent bond to Cys481 via a Michael addition reaction. *Id.*, 46:11-12. (explaining that the irreversible BTKI "form[s] a covalent bond with Cys 481 of Btk (e.g., via a Michael reaction)").

48. These structural teachings of the '803 Patent would tell a POSA in 2011 that the strategy for inhibiting BTK involved targeting a relatively rare cysteine near its active site, an approach that they would understand and implement according to the specification and knowledge in the field.

49. A covalent chemical bond requires that two atoms share an electron pair. In the context of ligand-protein interactions, a covalent bond can largely be considered permanent or irreversible. Cysteine is unique among the 20 naturally occurring amino acids in that its side chain contains a thiol group, which can react with certain electrophilic groups to form a covalent bond. *See* EX1077.005; EX1049.001.⁴ This reactive electrophilic group is often colloquially referred to as a “warhead,” and the reaction between the cysteine thiol and warhead is known in the art as a “Michael addition” reaction. *See* EX1001, 20:11-25, 58:26-45; EX1077.005-006; EX1049.001. Pan reports irreversible BTKIs where the warhead was attached to a central scaffold via a “linker” moiety, which, as a POSA would

⁴ Dr. Showalter cited Garuti (EX1049) which was published shortly after the June 3, 2011 priority date. Garuti is a review of irreversible protein kinase inhibitors that was accepted on May 17, 2011. *See* EX1049.014. Therefore, although not available as of the priority date, Garuti reflects the understanding of the POSA as of June 2011.

understand from Marcotte, allows for proper positioning of the electrophile to react with the cysteine. EX1060.002-003; EX2001.0003-0005, .0007.

50. Only a small subset of the approximately 500 protein kinases in the human genome include a cysteine residue in identical locations at or near the kinase active site. *See* EX1060.001-002; EX1077, Box 1 (.007); EX2111, [208]-[209], Fig. 7.

51. Because of the relative uniqueness of these cysteines and their locations, a POSA reading the specification in 2011 detailing ibrutinib's potent irreversible inhibition of BTK would have understood that including a warhead could create "highly potent and selective inhibitors" for kinase inhibitors that included these cysteines. EX1077, Box 1 (.007); *see also* EX1001, 45:56-60 (identifying that the irreversible BTKIs described in the specification "are selective for Btk and kinases having a cysteine residue in an amino acid sequence position of a tyrosine kinase that is homologous to the amino acid sequence position of cysteine 481 in Btk"); EX2111, [208]-[209], Fig. 7.

52. The specification further emphasizes the linker-warhead structure through its preference for ibrutinib, which contains the claimed linker-warhead structure. Specifically, the specification discloses an explicit preference for ibrutinib because ibrutinib is identified as a preferred compound and, as I understand, is the compound used in examples related to CLL/SLL. *See* EX1001,

80:63-65, 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), 147:42-148:56 (Example 15).

53. The specification further discloses the linker and the warhead structures of the claims as these structures appear among a narrow selection of options for such components. *See, e.g.*, EX1001, 52:45-53:19 (disclosing claimed linker structure in four out of eight embodiments), 54:55-55:10 (disclosing claimed warhead structure in one out of five embodiments).

54. Furthermore, the specification teaches that the linker-warhead can approach Cys481 from different directions to form a covalent bond with Cys481 and irreversibly inhibit BTK. Specifically, the specification discloses that ibrutinib and its opposite enantiomer (with a different stereochemistry of the linker-warhead), as well as a racemic mixture of the two, irreversibly inhibit BTK. *See* EX1001, 65:10-25 (ibrutinib), 79:50-65 (ibrutinib), 80:55-57 (compound 13, ibrutinib), 80:63-65 (ibrutinib), 77:5-25 (racemic mixture), 80:38-40 (compound 4, racemic mixture), 80:1-15 (ibrutinib enantiomer); *see also* EX2018, 133:15-134:17 (Dr. Showalter admitting that the specification discloses ibrutinib and its positional and chiral isomers, and despite such differences, all are “potent inhibitors”).

2. The Specification Emphasizes Phenoxyphenyl for Selective Binding to BTK's Hydrophobic "Back Pocket"

55. The specification teaches the importance of the phenoxyphenyl group for selective binding to BTK. Every depicted structure of irreversible BTKIs in the specification contains a phenoxyphenyl moiety that selectively binds within BTK's hydrophobic back pocket. *See* EX1001, 65:10-80:35.

56. The specification further emphasizes the phenoxyphenyl structure through its preference for ibrutinib, which contains the phenoxyphenyl structure.

57. A POSA would understand that this back-pocket-binding phenoxyphenyl group drives selectivity for BTK.

58. A POSA would have understood this importance of the phenoxyphenyl group described in the specification based on the structural knowledge in the field for BTK and kinases. The kinase active site includes hydrophobic pockets that are not accessed or bound by ATP. *See* EX1052.002, Fig. 2 (.002); EX1077.003; EX2028.0002 ("kinase inhibitors . . . gain affinity and specificity by making additional interactions in the ribose and polar region (which are also utilized by ATP) or the extended hinge and ***hydrophobic/specificity pockets (that are not utilized by ATP)***") (emphasis added). While the existence of these hydrophobic pockets is conserved across kinases, these pockets differ between kinases: the pockets can have different sizes or present different accessibility to ligand structures because of non-conserved amino acid residues

located nearby or within the pockets. *See, e.g.*, EX1052.002. Therefore, unlike the ATP-binding site that is shared among protein kinases, the hydrophobic pocket adjacent to the ATP-binding site is more variable and specific for a given kinase—allowing for inhibitors to selectively target particular kinases.

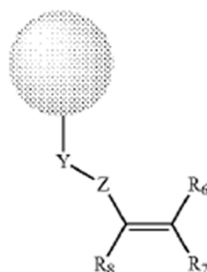
59. The “back pocket” or “specificity pocket” is one of these hydrophobic pockets and is located deep in the active site. *See* EX1052.002; EX2001.0005-0006; EX2028.0002; *see also* EX2018, 104:3-14. It is directly adjacent to an amino acid called the “gatekeeper” residue. EX1052.002. The size/volume of the side chain of the gatekeeper dictates access to the back pocket of a kinase. *See id.* Because the size/volume of the gatekeeper side chain varies across kinases, this pocket is sometimes called the specificity pocket because binding within the pocket will vary across kinases. *See id.* As reflected in the specification’s consistent use of the phenoxyphenyl moiety for the described BTKIs, structures that occupy the back pocket on a kinase inhibitor contribute significantly to the inhibitor’s selectivity and potency for that particular kinase. *See* EX1077.003-004, .009 (“Access to this pocket [(the back pocket)] is important to many kinase inhibitors because hydrophobic interactions in this site are crucial for the binding affinity of the inhibitor.”); EX1052.002 (“The size/volume of the gatekeeper’s side chain dictates access to the hydrophobic pocket located behind the gatekeeper, thereby ***defining the potential inhibitor selectivity*** of the ATP site” (emphasis added));

EX2028.0002 (“kinase inhibitors . . . *gain affinity and specificity by making additional interactions* in the ribose and polar region (which are also utilized by ATP) or the *extended hinge and hydrophobic/specificity pockets* (that are not utilized by ATP)” (emphases added)).

3. The Specification Emphasizes Binding to the Kinase Active Site, Which Requires Binding within the Kinase Hinge Region

60. The specification emphasizes that the compounds for use in the claimed method bind to the BTK active site. In particular, Formula E (included below) provides a structure, represented as an orb, that “binds to the *active site* of a kinase, including a tyrosine kinase[.]” EX1001, 61:65-62:17 (emphasis added).

Formula (E)



wherein:

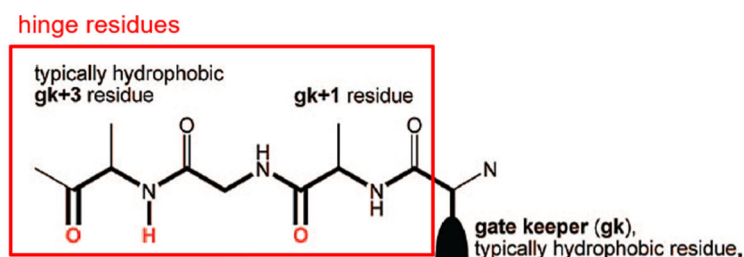
wherein $\odot$ is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

Because, as I explain below, a POSA reading the '803 Patent would have understood that ATP-competitive kinase inhibitors make one to three H-bonds with specific amino acid residues of the kinase hinge region to effectively bind to the kinase active site, a POSA would have understood that the orb disclosed by

Formula E is an element that makes the appropriate H-bonds with the hinge region while appropriately orienting the fixed substituents.

61. A POSA's understanding of this disclosure in 2011 is consistent with the illustration of hinge binding in Ghose, describing specific H-bonds known to form between adenine and adenine analogs in kinase inhibitors and specific hinge amino acid residues. At the top of the Ghose schematic are the residues of the active site hinge region, or "hinge residues." *See* EX1052, Fig. 2 (.002) (schematic included below). The hinge get its name because it is the connection between the two lobes of the protein. *See* EX1052.002; EX1077.002. In 2011, the adenine of the kinase's native ligand ATP was known to form key H-bonds with the kinase hinge region. *See* EX1052.003, .007 (entry 1 of table 2, showing that as of 2008, structures of 40 unique kinases have this same binding to an adenine scaffold);⁵ EX2028.0002; EX2048, Fig. 1 (.0001); *see also* EX2018, 111:5-10 (Dr. Showalter admitting that it was "well established" by 2011 that the adenine of the kinase's ligand ATP forms hydrogen bonds with the kinase hinge region).

⁵ The 40 kinases cited by Ghose appear to be an undercount as I notice at least two examples from my own work are not listed: Src (PDB: 2SRC) and EGFR (PDB: 2ITV).



EX1052, Fig. 2 (.002) (excerpted and annotated).

62. As depicted in the annotated version of the figure from Ghose above, two amino acid residues of the hinge, named for their distance from the so-called “gatekeeper” residue of the kinase active site, are available to form these H-bonds: GK (gatekeeper) +1 (*i.e.*, the amino acid one position away from the gatekeeper) and GK+3 (*i.e.*, the amino acid three positions away from the gatekeeper). *See* EX1052.002. GK+1 presents a potential to form one H-bond and GK+3 presents the potential to form two H-bonds. *See id.* The locations for these potential H-bonds are shown in red atoms in the Ghose figure above. GK+1 includes an H-bond acceptor and GK+3 includes one H-bond donor and one H-bond acceptor. *See id.* (“The hinge region usually has one hydrogen donor flanked by two hydrogen acceptors derived from the protein backbone.”); *see also* EX2018, 105:10-106:22, 114:4-10.

63. The specification’s disclosures as to the hinge-binding central scaffold (Z’) is consistent with a POSA’s understanding in 2011 that ATP competitive kinase inhibitors typically mimicked adenine’s contacts with the hinge, making one to three H-bonds with these hinge residues. *See* EX1077.003

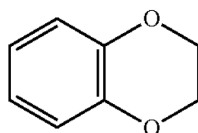
(“Most kinase inhibitors discovered to date are ATP competitive and present one to three hydrogen bonds to the amino acids located in the hinge region of the target kinase, thereby mimicking the hydrogen bonds that are normally formed by the adenine ring of ATP.”); EX2028.0002 (“The backbone atoms of the hinge region contain the critical hydrogen bond donor and acceptor atoms that anchor ATP-binding . . . [and] the vast majority of kinase inhibitors make at least one hydrogen bonding interaction with the hinge region . . .); EX1052.020 (describing the “availability of three hydrogen bond forming moieties in the hinge region of kinases” and the observation that “one, two, or all three are engaged by various ligands,” *i.e.*, inhibitors).

64. H-bonds are one type of non-covalent interaction that can contribute to the binding of a small-molecule ligand to its protein-binding partner. An H-bond is an electrostatic attraction between a hydrogen atom (H) that is covalently bonded to an electronegative **donor** atom, often N or O, and another electronegative atom, the **acceptor** atom (again, often N or O), which has a lone pair of electrons. As confirmed by the analysis of Dr. Scott, the H-bond donor/acceptor potential of a given chemical moiety is readily understood and dictated by chemical **structure**. See EX2012, ¶26; see also *id.*, ¶¶21-25, 27-28. In other words, a chemist can look at a Z'-scaffold for use in the claimed ibrutinib-like irreversible BTKIs and identify which atoms are capable of serving as H-bond donors and acceptors. See *id.*, ¶26.

65. The specification discloses examples of hinge-binding heterocyclic scaffolds that can serve as the orb structure (●) of Formula E. *See* EX1001, 62:44-63:20. Dr. Showalter opines that a POSA would have understood that the hinge-binding heterocyclic scaffolds are limited to “substituted fused biaryl” scaffolds because the specification uses “biaryl” when introducing the scaffold examples. *See* EX1003, ¶115 & n.2; EX1001, 62:44-45 (“In some embodiments, ● is a substituted fused biaryl moiety selected from . . .”). I disagree with Dr. Showalter. In my opinion, a POSA would have understood that the specification’s use of “biaryl” in introducing the BTKI scaffold examples does not reflect an intent to strictly limit the composition of the scaffolds to be used in the claimed methods.

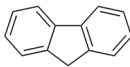
66. As an initial matter, the scaffold examples are heteroaryls, rather than “aryls,” which the specification defines as limited to structures containing only carbon atoms and would thus exclude the nitrogen-containing examples for Formula E. EX1001, 15:4-5, 62:44-63:20. This indicates the specification’s use of “biaryl” was not intended as a literal narrowing of the examples. Moreover, although the specification does not define “biaryl,” the specification’s definitions of “aryl” and “non-aromatic heterocycle” provide guidance as to how a POSA would have understood the use of “biaryl” here. *See* EX1001, 15:4-12, 15:66-16:62, 17:30-18:33. These definitions do not strictly differentiate between aromatic and non-aromatic structures. *See id.* For example, the “aryl” definition

includes “fluorenyl,” which has a central non-aromatic ring (*i.e.*, a partially saturated portion).⁶ *See* EX1001, 15:4-12. Accordingly, a POSA would have understood that the specification’s use of “aryl” does not exclude structures that are partially non-aromatic. *See id.* As an additional example, the “non-aromatic heterocycle” definition, *id.*, 17:30-18:33, includes a structure with an aromatic portion: a phenyl fused to a dioxane ring (structure included below):



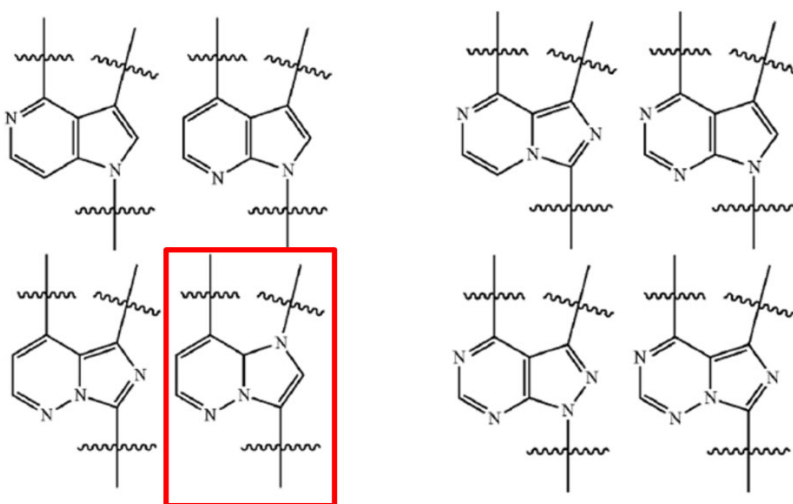
EX1001, 18:20-25. Therefore, in the context of these disclosures, a POSA would have understood that the specification’s use of “biaryl” in introducing the BTKI scaffold examples does not strictly limit the types of structures that could be used.

67. A POSA’s knowledge of the field in June 2011 is entirely consistent with the understanding that the possible Z’-scaffolds that could be used in the ibrutinib-like irreversible BTKIs for the claimed methods would not be limited to biaryl structures. In June 2011, a POSA would have understood that diverse heterocyclic core scaffolds—including partially saturated scaffolds—are capable

⁶ Fluorene has the following structure: . As Dr. Showalter agrees, fluorene has a central ring that is not aromatic. *See* EX2018, 140:1-142:1.

of forming the appropriate H-bonds to the conserved hinge of protein kinases. *See infra* §§VII.A.4, X.A.2.a, X.A.3.b(2). Accordingly, a POSA would have understood that the specification's use of "biaryl" in introducing the BTKI scaffold examples was not intended to be limiting.

68. The examples of 5:6 fused heterocyclic cores disclosed by the specification are shown below. These cores include both unsaturated and partially saturated cores:



EX1001, 62:44-63:20 (annotated). As shown in the above example hinge-binding scaffolds disclosed in the specification, the scaffold with an annotated red box is a partially-saturated scaffold and therefore not a biaryl scaffold, which Dr. Showalter concedes. *See* EX1003, ¶115 & n.2. The addition of this partially-saturated scaffold in the list of examples was an additional signal to a POSA that the specification's use of "biaryl" in introducing the BTKI scaffold examples was not intended to be

limiting. I disagree with Dr. Showalter that a POSA would have considered this structure a mistake because of the specification's reference to "biaryl" in introducing the example structures. *See id.* Rather, as discussed above, the specification's loose characterization of structures as aryl or non-aromatic reflects that these terms should not be strictly applied and does not support Dr. Showalter's suggestion that a POSA would disregard an example structure from the specification.

E. Priority Date

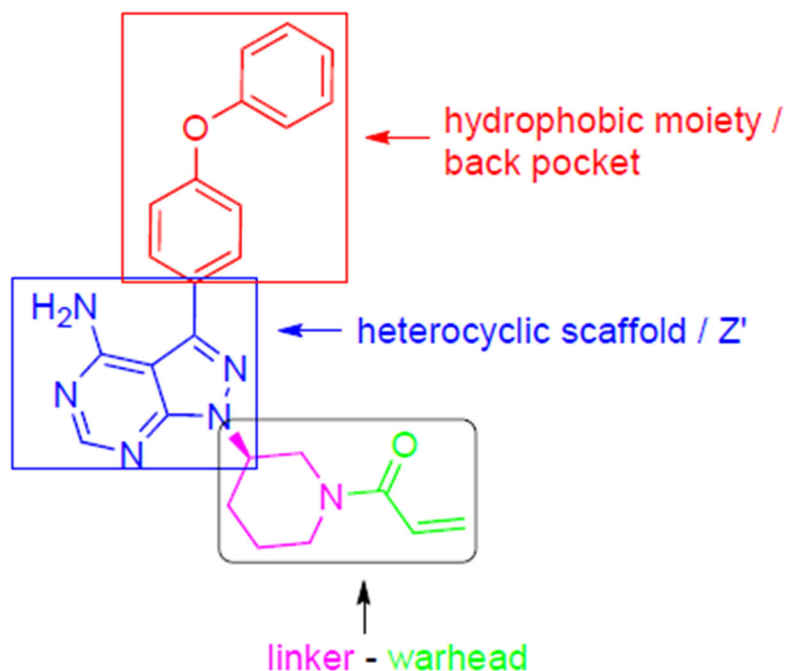
69. I understand that the specification of the '803 Patent is identical in substance to a non-provisional application (U.S. Patent Application No. 13/153,317 ("317 Application")) filed on June 3, 2011. EX1001.002. Because the specification describes and enables the Challenged Claims as I explain below, I understand that the priority date of the '803 Patent is at least June 3, 2011 (the filing date of the non-provisional '317 Application).

VII. BACKGROUND OF THE TECHNOLOGY

A. The '803 Patent Is Grounded in a POSA's Understanding of the Structure-Function Relationship for Ibrutinib-Like BTKIs

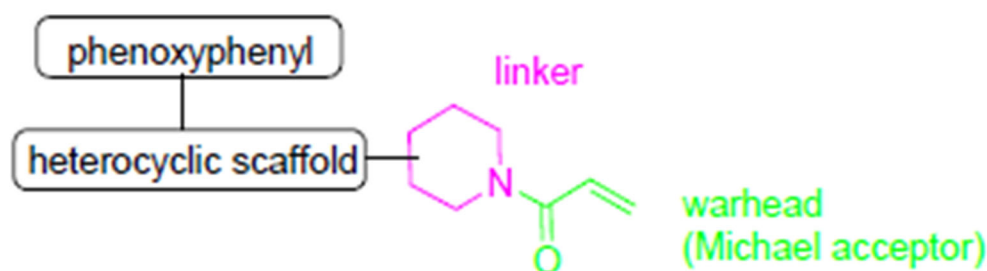
70. As I have explained, BTK is a protein kinase involved in the development, activation, signaling, and survival of B-cells. *See* EX1072.004; EX1066.002. In 2011, a POSA reading the '803 Patent would have been aware of numerous structures reported to inhibit BTK. As reflected in the '803 Patent,

scientists, some of whom later joined Pharmacyclics, had designed selective irreversible inhibitors of BTK having particular structures with a linker-warhead and phenoxyphenyl attached to a central scaffold. *See* EX1060; EX2025; EX2111, [453]-[454]; EX1001, 47:25-80:65. From this research, one lead compound that was developed was ibrutinib; the '803 Patent describes ibrutinib's activity in irreversibly inhibiting BTK and treating CLL/SLL patients. Ibrutinib has three primary components: (i) a linker connected to a terminal warhead (purple and green structures below); (ii) a hydrophobic phenoxyphenyl moiety (red structure below), and (iii) a heterocyclic core. *See* EX1060.001-004; *see also* EX2018, 62:16-64:8.



71. The '803 Patent describes ibrutinib effectively occupies and irreversibly inhibits BTK. EX1001, 137:9-26, 138:33-43. Knowing this, a POSA would understand based on the art how the structural features of ibrutinib correlate with this activity. In 2011, a detailed crystal structure of a compound (B43) having ibrutinib-like binding to BTK was available in the PDB ("Marcotte"). EX2001.0003-0005 (PDB: 3GEN); EX2018, 43:20-46:11. The Marcotte structure provided detailed information about the geometry of this ligand in the BTK active site as well as specific amino acid interactions such as hydrogen-bonds between the inhibitor and the BTK hinge. *See* EX2001.0003-0005. This information allowed a POSA reading the '803 Patent to understand not only the effective conformation of ibrutinib for inhibiting BTK but also informed them of how related molecules could be recognized as irreversible BTKIs for use in the claimed methods.

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



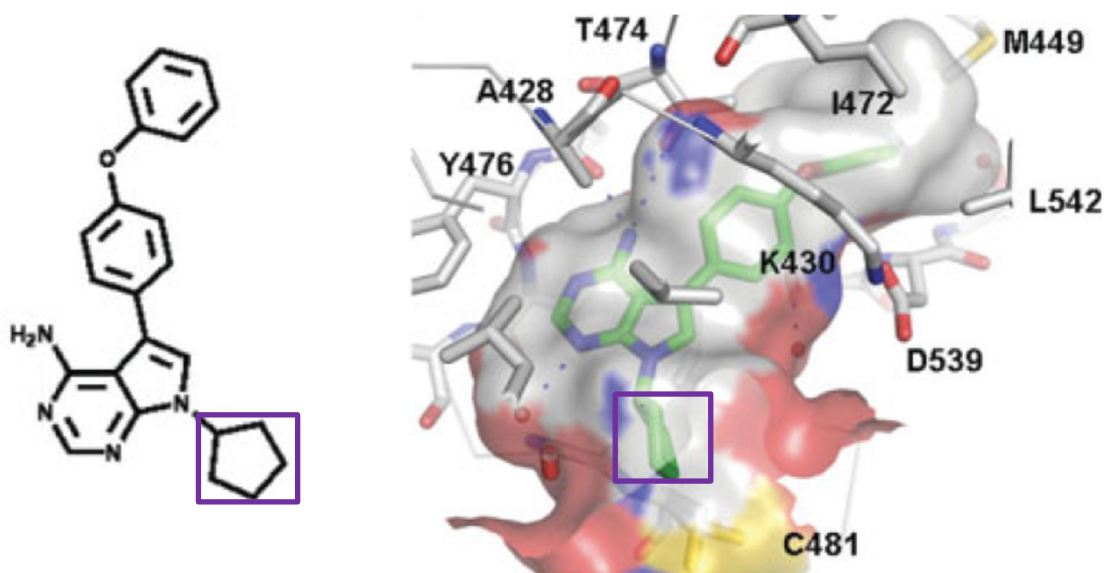
72. As I have explained, in 2011, a POSA would have understood from the '803 Patent's teachings that the linker-warhead structure covalently binds to

the Cys481 residue of BTK's active site, thereby causing irreversible inhibition of BTK. *See supra* §VI.D.1. Ibrutinib exploits the existence of Cys481 in BTK to create a selective, irreversible BTK inhibitor. Pan, which was authored by the inventors of ibrutinib, suggests that Cys481 in BTK is "a nucleophilic site, which could potentially form a covalent complex between Btk and an electrophilic inhibitor." EX1060.001. It was known that only ten of the approximately 500 kinases have a cysteine at this position.⁷ EX1060.001-002; *see also* EX1055.001, .004; EX1049.001; EX1077, Box 1 (.007). Understanding the irreversible inhibition activity of ibrutinib from the '803 Patent and the ibrutinib-like binding mode from Marcotte, a POSA would have understood from Pan that BTK's Cys481 could be targeted with various linker-warheads for covalent binding to selectively and irreversibly inhibit BTK. EX1060.001-002 (Pan reporting that compounds with different warheads and linkers for covalently bonding Cys481 "were highly potent inhibitors"); EX1060.002 (Pan "confirm[ing] the irreversibility" using two methods: "1) after recombinant Btk was pretreated with compounds, its activity was not recovered by multiple washings with inhibitor-free medium; and 2) a major peak was observed by mass spectrometry corresponding

⁷ It was later appreciated that there are 11 kinases, rather than 10 kinases, with a cysteine residue at this position.

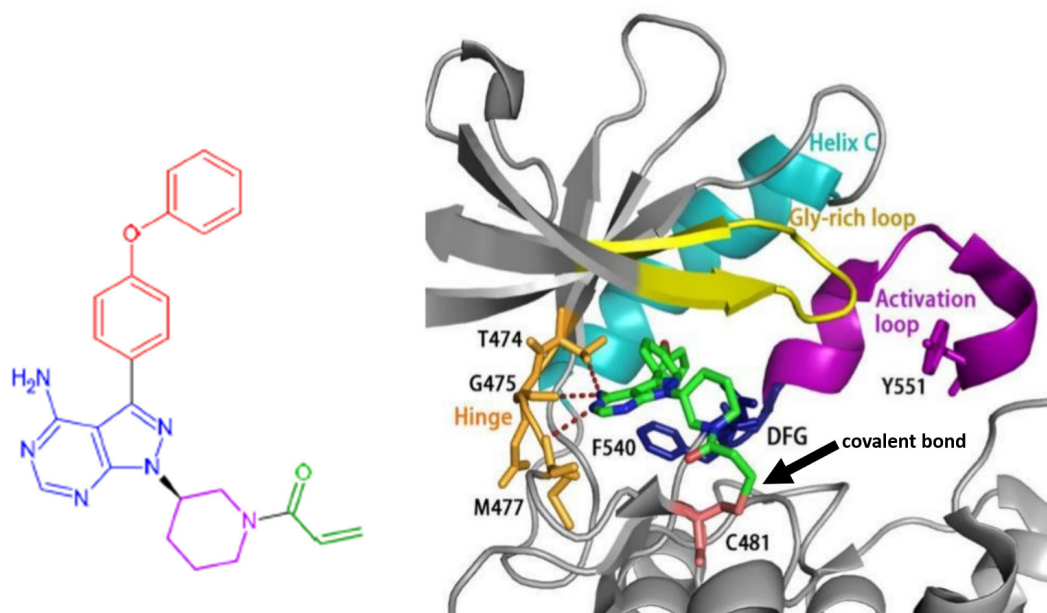
to the molecular weight of a 1:1 covalent complex between compound 4 and Btk.”); EX1077.005-006, Box 1 (.007) (“[S]caffolds with moderate potency and selectivity can be converted to highly potent and selective inhibitors by the judicious introduction of an electrophile that can target unique cysteine residues.”); EX2018, 60:18-62:6.

73. A POSA would have understood the specification’s description of ibrutinib’s irreversible inhibition activity in light of the Marcotte structure. B43, the compound in Marcotte, has the same phenoxyphenyl group as ibrutinib, a similar heterocyclic scaffold, and a cyclopentyl group in the same position as ibrutinib’s linker. The linker-like cyclopentyl group in Marcotte is oriented towards Cys481. EX2001, Fig. 2D (.0003); *see also* EX2001.0007 (“Cys481 in the active site of BTK-KD [kinase domain] could also be exploited to gain kinase selectivity in which a small molecule may be irreversibly bound to this cysteine via a covalent bond.”). Figure 2 (included below) depicts a portion of the crystal structure of the BTK kinase domain complexed with B43 (BTK-KD/B43, PDB: 3GEN) and shows the cyclopentyl substituent (purple box) oriented towards Cys481 (“C481”).



EX2001, Figs. 2A & 2D (.0003) (annotated).

74. The crystal structure of BTK complexed with ibrutinib confirms what a POSA would have expected based on the teachings of the '803 Patent: that the ibrutinib linker-warhead orients toward and covalently binds to BTK's Cys481 to irreversibly inhibit BTK. The relevant region of the ibrutinib crystal structure (PDB: 5P9J) is illustrated below, which I have annotated to indicate the covalent bond.



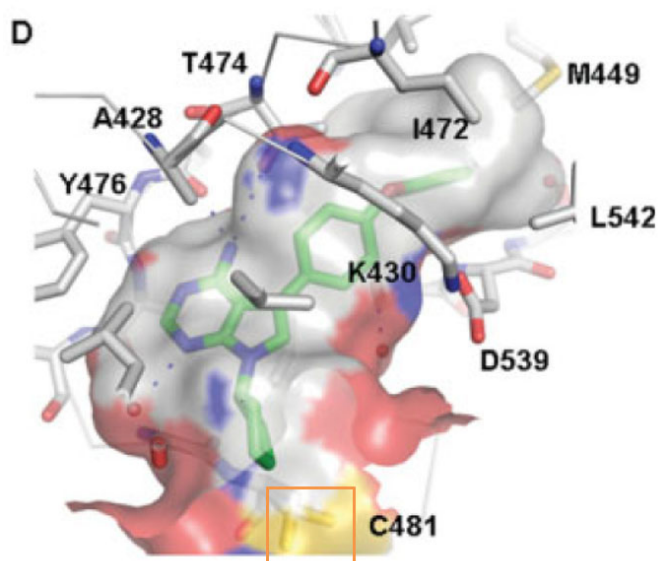
EX1076, Fig. 3a (.006) (annotated).

75. This structural information aligns with the '803 Patent disclosure demonstrating that ibrutinib occupies and irreversibly inhibits BTK in patients. *See* EX1001, 138:33-37 (describing “all” patients administered with ibrutinib “demonstrate complete occupancy of Btk” by ibrutinib after 4 hours and complete inhibition of BTK dependent cellular process up to 24 hours). I understand from Dr. Spurgeon that occupancy of BTK treats CLL/SLL patents through irreversibly inhibiting BTK.

2. The Linker-Warhead Can Approach Cys481 of BTK from Different Trajectories

76. As I have explained, based on the disclosures in the specification, a POSA would have understood that the linker-warhead could approach and

covalently bond with BTK's Cys481 from different trajectories. *See supra* §VI.D.1. The specification teaches ibrutinib and its enantiomer (which has a different orientation for the linker-warhead), as well as a racemic mixture of the two, both form a covalent bond with Cys481 and potently and irreversibly inhibit BTK. EX1001, 65:10-25 (ibrutinib), 79:50-65 (ibrutinib), 80:55-57 (compound 13, ibrutinib), 80:63-65 (ibrutinib), 77:5-25 (racemic mixture), 80:38-40 (compound 4, racemic mixture), 80:1-15 (ibrutinib enantiomer); *see also* EX2018, 133:15-134:17 (Dr. Showalter admitting that the specification discloses ibrutinib and its positional and chiral isomers, and despite such differences, all are “potent inhibitors”). A POSA would have further understood this teaching in the context of Marcotte. Marcotte teaches that Cys481 is solvent-exposed, meaning there are fewer steric hindrances such that a linker-warhead could approach Cys481 from a variety of directions. EX2001, Fig. 2D (.0003). Marcotte further explicitly shows that the Cys481 side chain (“C481”) (orange box) of BTK adopts two orientations, indicating that it is rotatable.



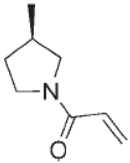
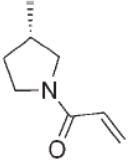
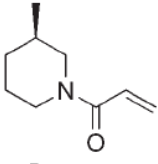
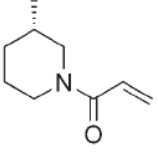
EX2001, Fig. 2D (.0003) (annotated).

77. Examination of crystallographic coordinates and corresponding electron density maps made available in the PDB by Marcotte (PDB: 3GEN) would further confirm for a POSA that the sidechain of Cys481 of BTK adopts two orientations, with approximately equal “occupancy.” That is, about half of the BTK molecules in the crystal have Cys481 oriented in one direction and half in the other direction.

78. A POSA would therefore have been able to select ibrutinib-like irreversible BTKIs for use in the claimed method based on the knowledge from Marcotte that Cys481 can rotate and is solvent-exposed, indicating that it could be targeted with different linker-warhead trajectories. That is, one specific and precise angle of approach to the cysteine thiol would not be required. A POSA reading the

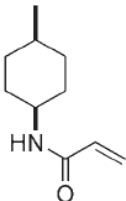
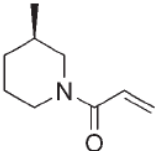
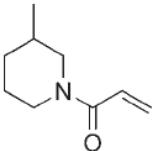
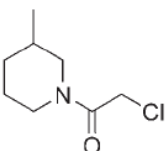
'803 Patent would also understand that Pan reports irreversible BTKIs using warheads with different orientations were potent irreversible inhibitors.

79. For example, Pan reports that inverting the stereochemistry of the linker only modestly changed potency. EX1060, Tbl. 3 (.003) (compare compounds 11 vs. 12, 13 vs. 14, in Table 3 excerpt below); *see* EX2018, 96:1-97:18 (Dr. Showalter admitting that Pan's data comparing compounds 11 versus 12 and compounds 13 versus 14 shows that "the stereochemical orientation [of the linker-warhead] does not have a major impact" on BTK inhibition of the compounds); *see also* EX2018, 60:18-62:6 (Dr. Showalter admitting that the compounds in Pan's Table 3 have "good to excellent potency").

Table 3. Assay data for irreversible inhibitors.			
Compd	R	Btk IC ₅₀ [nM]	Ramos Cell Ca Flux IC ₅₀ [nM] ^[a]
11		1.6	24
12		1.9	90
13		< 0.5	10
14		1.4	7

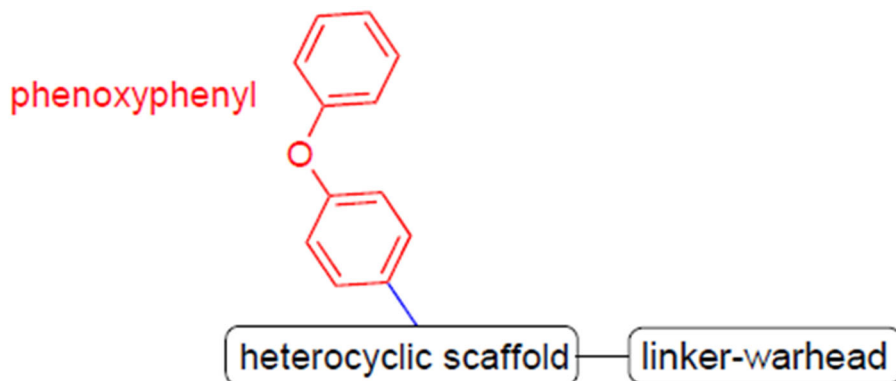
EX1060, Tbl. 3 (.003) (excerpted).

80. Pan further reports similar potency could be obtained with different linkers (compare compounds 10 vs. 13, in Table 3 excerpt below) or with different warhead chemistry that results in a covalent adduct that is “shorter” by one carbon-carbon bond length (compare compounds 4 vs. 6, where the chlorine in compound 6 will be eliminated upon reaction with the target cysteine, in Table 3 excerpt below). EX1060, Tbl. 3 (.003); *see also* EX2018, 60:18-62:6 (Dr. Showalter admitting that the compounds in Pan’s Table 3 have “good to excellent potency”).

Table 3. Assay data for irreversible inhibitors.			
Compd	R	Btk IC ₅₀ [nM]	Ramos Cell Ca Flux IC ₅₀ [nM] ^[a]
10		0.58	3
13		< 0.5	10
4		0.72	10
6		0.52	92

EX1060, Tbl. 3 (.003) (excerpted).

3. Hydrophobic Phenoxyphenyl Moiety Binds within BTK's "Back Pocket"

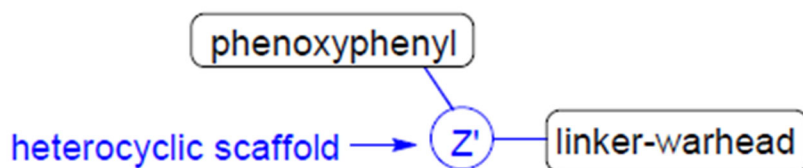


81. As I have explained, in 2011, a POSA would have understood from the '803 Patent's teachings that an ibrutinib-like BTKI must orient its hydrophobic phenoxyphenyl moiety to bind within BTK's "back pocket," contributing to potency and selectivity in BTK binding. *See supra* §VI.D.2. Consistent with the specification's teachings, Marcotte confirmed that the phenoxyphenyl of B43 binds within BTK's hydrophobic back pocket. EX2001.0004-0005 (PDB: 3GEN) ("The distal phenyl group of the phenoxyphenyl . . . enters a hydrophobic pocket composed of only hydrophobic residues . . . Phe540 of this motif forms a face-to-edge pi-stacking interaction with the phenoxyphenyl group of B43."); *see also* EX1052.002, Fig. 2 (.002) (describing the known "specificity pocket" adjacent to the hinge region that furthers inhibitor selectivity).

82. Pan also reports that irreversible inhibitors that include this phenoxyphenyl moiety have potent and selective inhibition of BTK. EX1060.001-

003 (“[W]e describe the discovery of a selective, irreversible Btk inhibitor and its efficacy in a mouse RA model.”), Tbl. 3 (.003).

4. Hinge-Binding Scaffold Makes Predictable H-Bonds to BTK



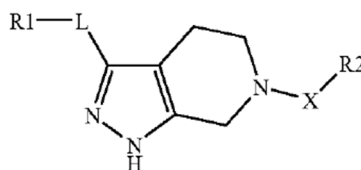
83. In 2011, a POSA reading the '803 Patent would have understood that the heterocyclic scaffold of the ibrutinib-like irreversible BTKIs for use in the claimed method bind within BTK's highly conserved hinge region. *See supra* §VI.D. In particular, as I have explained, in 2011, a POSA would have understood from the '803 Patent's teachings that the Z'-scaffolds make H-bonds with the hinge region, and that typically such scaffolds make one to three H-bonds with specific amino acid residues of the kinase hinge region in order to effectively bind to the kinase. *See supra* §VI.D.3; *see also* EX2028.0002-0004.

84. Importantly, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have known that hinge-binding elements can exhibit structural diversity because a defining attribute of a hinge-binding element is its ability to have H-bond acceptors/donors arranged in a suitable geometry to form one to three H-bonds with specific amino acid residues of the hinge. EX2028.0002-0003. A POSA would have understood from the

specification's Formula E that Z'-scaffolds that bind to the highly conserved hinge region (while maintaining the fixed groups of ibrutinib: the linker-warhead and phenoxyphenyl) are fungible and predictable. EX1001, 61:66-63:20. Specifically, as reflected in the description of Z' in the '803 Patent, a POSA would have understood that diverse heterocyclic core scaffolds are capable of making the hinge interactions. *See* EX1077.004; EX2028.0003-0004; EX2023 ("820 Patent"), Formula I (1:65-2:6), Formula II (2:29-37), Formula III (2:56-65), 53:1-103:38 (reporting 85 example structures and corresponding inhibition activity against two kinases); EX2026 ("303 Publication"), claim 1, claim 10, [0023], [0076], [Abstract]; EX2027 ("960 Publication"), Examples 16(1), 16(2), 16(3), 21, 21(1), 25(1), 32, 32(1)); *see also* EX2018, 138:9-139:5 (Dr. Showalter acknowledging that there were many hinge-binding scaffolds known in the literature).

85. The '820 Patent, titled "SUBSTITUTED TETRAHYDRO-1H-PYRAZOLO [3,4-C]PYRIDINES COMPOSITIONS COMPRISING THEM, AND USE," issued on October 14, 2008 and reports "novel tetrahydro-1H-pyrazolo-[3,4-c]pyridines" and their use as kinase inhibitors for the treatment of cancer. EX2023, 1:16-25. The '820 Patent describes a series of compounds as kinase inhibitors that have the same 5:6 fused scaffold for hinge binding, where the scaffold's 5-membered ring is aromatic with two nitrogen heteroatoms and the

6-membered ring is saturated with one nitrogen heteroatom, as exemplified below in Formula I:



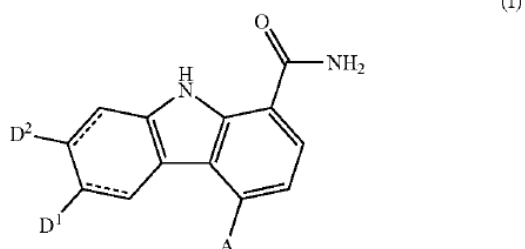
Id., 1:65-2:6. The '820 Patent describes 85 specific structures having this partially saturated scaffold with varying substituents and reports the inhibition of two kinases, Tie-2 and KDR, for the example structures. *Id.*, 53:1-103:38. Therefore, in 2011, a POSA reading the '803 Patent would have been aware of these structures with partially saturated scaffolds for hinge binding.

86. The '303 Publication, titled "CARBAZOLE CARBOXAMIDE COMPOUNDS USEFUL AS KINASE INHIBITORS," reports diverse heterocyclic scaffolds that a POSA reading the '803 Patent would have understood as capable of making these hinge interactions with BTK and modulating activity. *See* EX2026.0001-0002. The '303 Publication was assigned to Bristol-Myers Squibb Company and is directed to "fused carbazole carboxamide compounds useful as kinase inhibitors, including the modulation of Bruton's tyrosine kinase (Btk) and other Tec family kinases such as Itk." EX2026, [0002]. The '303 Publication claims formulas (I), (Ia), and (Ib) (all included below), which contain

tricyclic scaffolds, including scaffolds with a saturated non-aromatic ring fused to the core (formulas (I) and (Ia)):

What is claimed is:

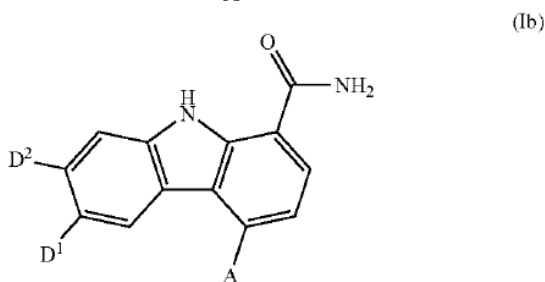
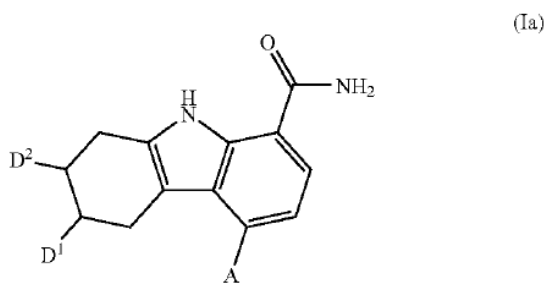
1. A compound according to formula (I):



or a salt thereof, wherein

the dashed lines are either single or double bonds;

10. The compound of claim 9, wherein a compound of formula (I) is (Ia) or (Ib)



EX2026, claims 1, 10; *see also id.*, [0023], [0076], [Abstract]. Because these compounds are described as kinase inhibitors for BTK, a POSA reading the '803 Patent in 2011 would have understood that these structures hydrogen bond to the

BTK hinge. A later publication confirms that the tricyclic scaffold disclosed in the '303 Publication makes the appropriate H-bonds with the hinge region (below figure on the right containing the same tricyclic scaffold as formulas (I) and (Ib) of the pre-priority '303 Publication):

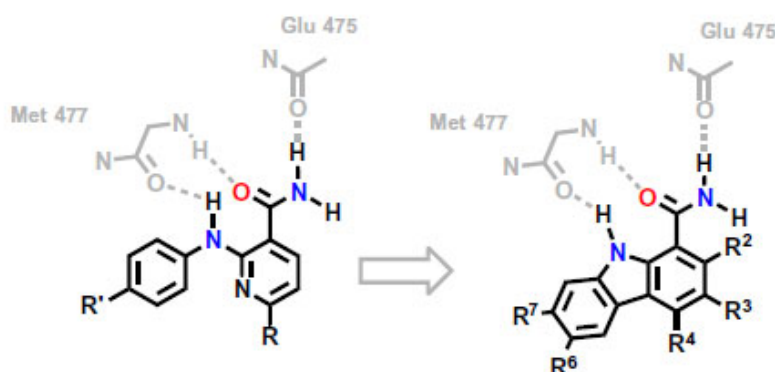
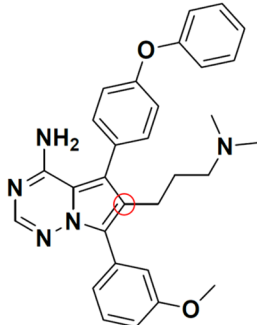
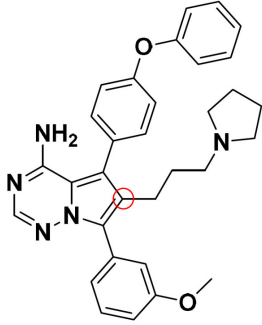
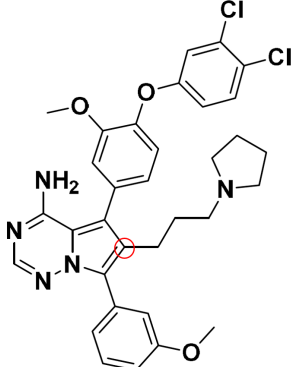


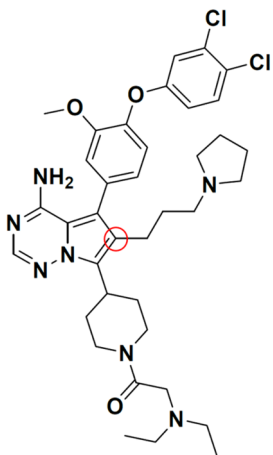
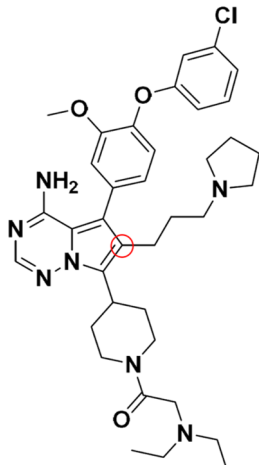
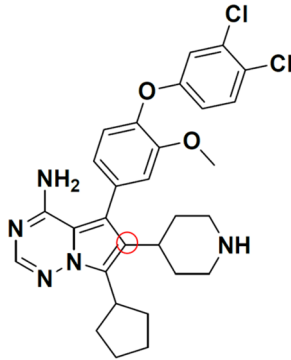
Figure 2. Constraining the nicotinamide to form a carbazole.

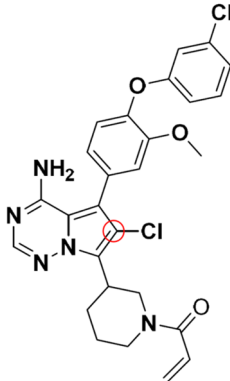
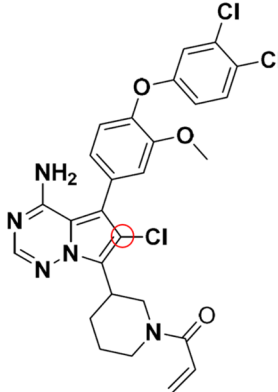
EX2050, Fig. 2 (.0002). Figure 2 further confirms what a POSA would have understood in 2011: that the hydrogen bonding elements of kinase inhibitor scaffolds are fungible and appropriate H-bonds with the hinge region can be made by differing atoms and functional groups.

87. The '960 Publication, titled "PYRROLOTRIAZINE COMPOUNDS," reports diverse heterocyclic scaffolds that a POSA reading the '803 Patent would have also understood as capable of making the appropriate hinge interactions in BTK. EX2027, Examples 16(1), 16(2), 16(3), 21, 21(1), 25(1), 32, 32(1). The '960 Publication is directed to "pyrrolotriazine compounds

useful as tyrosine kinase inhibitors, particularly Bruton's tyrosine kinase (Btk) inhibitors." EX2027.0002. The '960 Publication discloses Examples 16(1), 16(2), 16(3), 21, 21(1), 25(1), 32, 32(1), each of which is a compound with a fourth substitution on the scaffold that showed BTK inhibition, as shown in the below table:

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

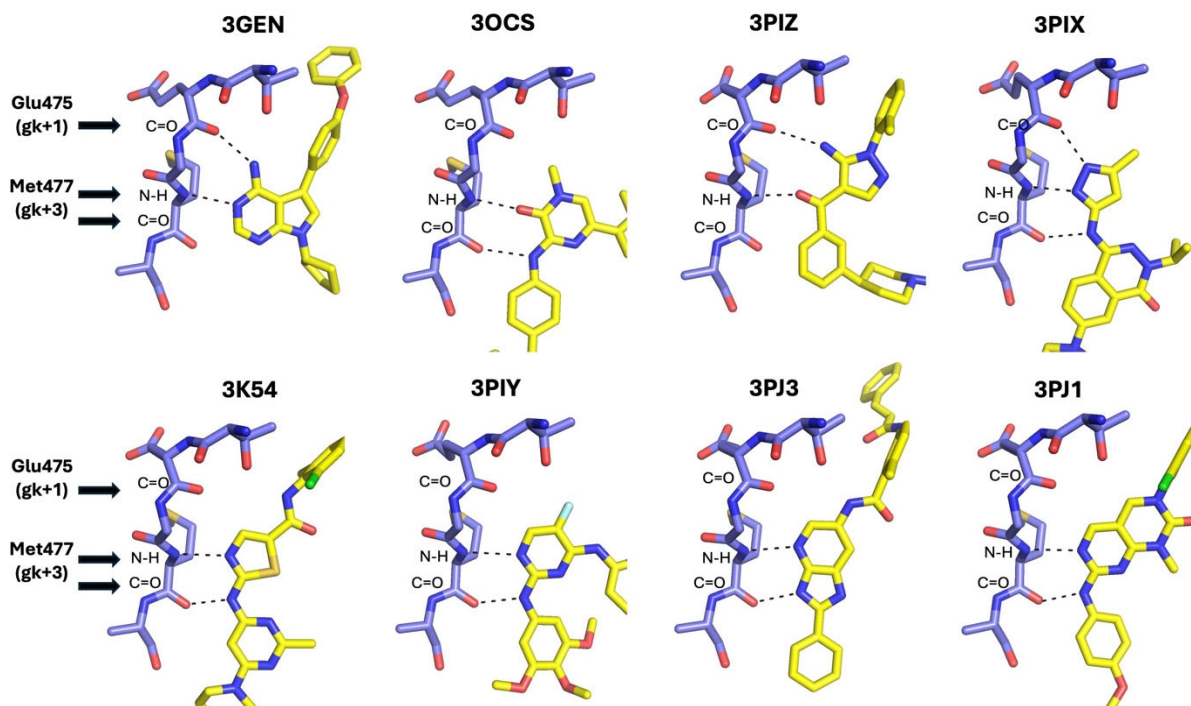
Example	Name	Structure	IC50 (nM)
21	1-(4-(4-amino-5-(4-(3, 4-dichlorophenoxy)-3-methoxyphenyl)-6-(3-(pyrrolidin-1-yl)propyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-1-yl)-2-(diethylamino)ethanone		16
21(1)	1-(4-(4-amino-5-(4-(3-chlorophenoxy)-3-methoxyphenyl)-6-(3-(pyrrolidin-1-yl)propyl)pyrrolo[2,1-f]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

Example	Name	Structure	IC ₅₀ (nM)
32	1-(3-(4-amino-6-chloro-5-(4-(3-chlorophenoxy)-3-methoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-1-yl)prop-2-en-1-one		2
32(1)	1-(3-(4-amino-6-chloro-5-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidin-1-yl)prop-2-en-1-one		2

EX2012, ¶43; EX2027.0063-0064 (Examples 16(1), 16(2), 16(3)), .0066 (Examples 21, 21(1)), .0068-0069 (Example 25(1)), .0073-0075 (Examples 32, 32(1)), .0091 (disclosing IC₅₀ values).

88. As noted above, in June 2011, there were 10 crystal structures of BTK bound to diverse ligands available in the PDB. Consistent with Formula E in the '803 Patent, these structures show the diversity of scaffolds capable of forming hinge H-bond interactions in BTKIs. As illustrated below, which of the three potential hydrogen bonds are made can vary, as can the specific atoms/substituents

of the inhibitor that make those H-bond interactions.⁸ These ten structures exhibit eight distinct hinge-binding elements in structurally diverse BTKIs.



89. Other post-priority publications further confirm what a POSA with the '803 Patent in hand would have understood as of June 2011: consistent with the '803 Patent's Formula E, diverse heterocyclic core scaffolds are capable of making these important hinge interactions, including with a non-aromatic heterocyclic ring. For example, Watterson et al. reported a "highly potent and

⁸ These figures, and similar figures in this Declaration, have been generated in PyMol, an industry-standard software for viewing crystal structure data.

selective” BTKI (compound 14f) (PDB: 5T18) (shown below) that has a saturated non-aromatic ring fused to the core:

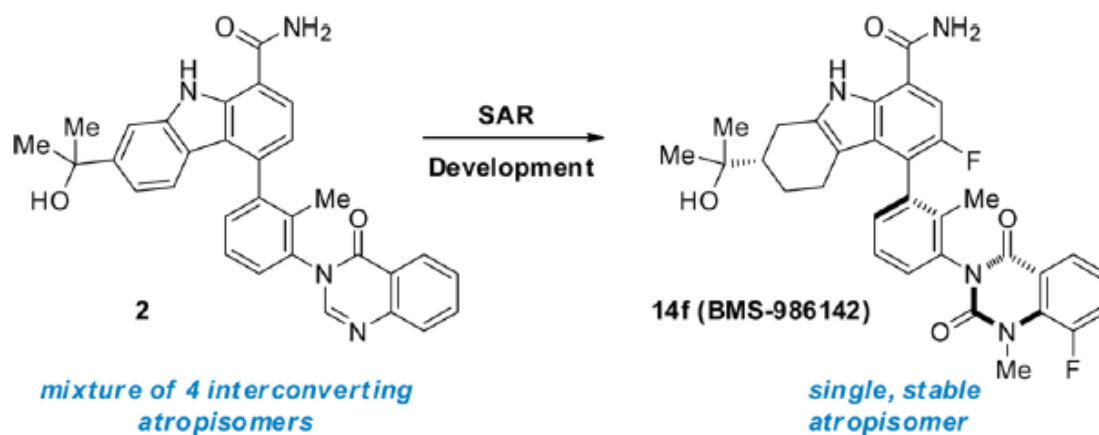


Figure 3. Compound 14f as a single, stable atropisomer.

EX2061, Fig. 3 (.0003). Watterson reported the crystal structure of compound 14f binding to BTK's kinase domain and making the appropriate H-bonds to the hinge region (shown below):

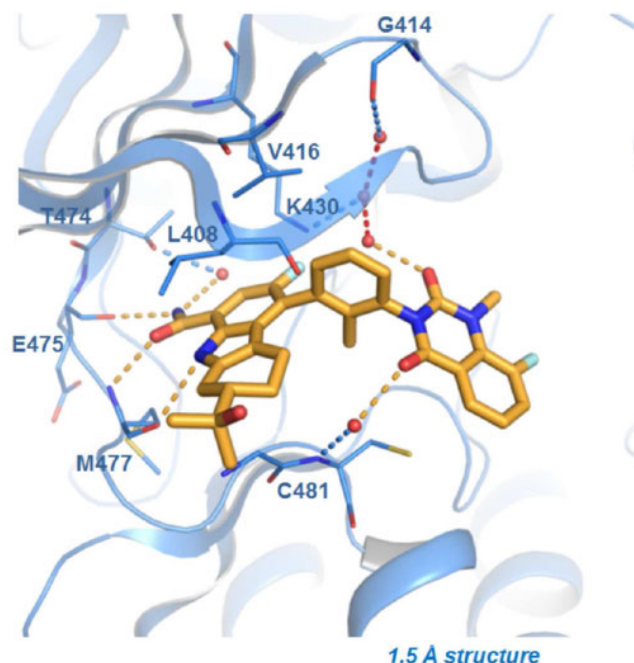


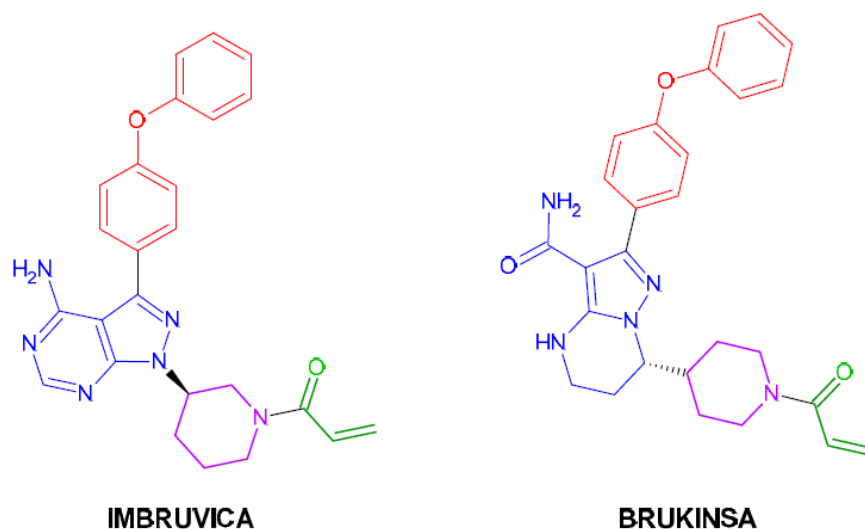
Figure 12. X-ray crystal structure of 14f bound to the kinase domain of BTK (1.5 Å structure) (PDB ID: 5T18).

EX2061, Fig. 12 (.0012).

5. Zanubrutinib Affirms the Key Structural Features Taught in the Patent

90. Although not expressly disclosed in the '803 Patent, zanubrutinib's structure follows the expectations of a POSA in 2011 by incorporating the key structural features of ibrutinib to a central scaffold that makes H-bonds to the BTK hinge. Indeed, the zanubrutinib 5:6 heterocyclic scaffold has similar structural features (aromatic 5-membered ring fused to a non-aromatic 6-membered ring) as the scaffold from the '820 Patent which a POSA would have known as a hinge-binding scaffold in 2011. *See* EX2023, 1:65-2:6. Petitioner's zanubrutinib affirms the key structural features taught in the '803 Patent.

91. First, as Dr. Showalter illustrates (shown below), zanubrutinib copies ibrutinib's phenoxyphenyl moiety (red) and linker-warhead (purple and green, respectively).



EX1003, ¶39; *see also* EX2018, 66:11-67:5, 67:19-68:19.

92. Second, ibrutinib and zanubrutinib bind to BTK in the same way from a structural perspective: the heterocyclic scaffolds of ibrutinib and zanubrutinib make the key H-bond interactions with BTK residues that adenine makes. As shown below, zanubrutinib forms the same H-bonds with the hinge of BTK as ibrutinib and adenine.

Ligand	BTK Residue	
	GK+3 Met477 (NH, H-bond donor)	GK+1 Glu475 (C=O, H-bond acceptor)
Adenine	Ring N (H-bond acceptor)	-NH ₂ amine substituent (H-bond donor)
Ibrutinib	Ring N (H-bond acceptor)	-NH ₂ amine substituent (H-bond donor)
Zanubrutinib ⁹	-C=O of amide substituent (H-bond acceptor)	-NH ₂ of amide substituent (H-bond donor)

⁹ Zanubrutinib also makes a third H-bond to the third available H-bond interaction in the BTK hinge: H-bond acceptor of GK+3 residue Met477. *See* EX1053.005 (PDB: 6J6M). Based on the distance between the hydrogen bond donor and acceptor (3.34Å), this is likely a relatively weak hydrogen bond, but this nevertheless aligns with the understanding from the '803 Patent and state of the art regarding the standard one to three H-bonds formed with specific residues of the protein kinase hinge. *See supra* §§VI.D.3, VII.A.4; EX1077.003; EX2028.0001-0002; EX1052.020.

Notably, Dr. Showalter incorrectly describes this H-bond interaction, opining that the NH on the 6-membered ring of zanubrutinib is an H-bond *acceptor* to Met477. EX1003, ¶61. The NH on the 6-membered ring of zanubrutinib is an H-bond *donor* to Met477. I understand that Dr. Showalter later corrected this error. *See* EX2018, 17:18-18:20, 113:15-20; *see also id.*, 112:12-113:5 (Dr. Showalter explaining that zanubrutinib has two H-bond donors and one H-bond acceptor). Zanubrutinib's

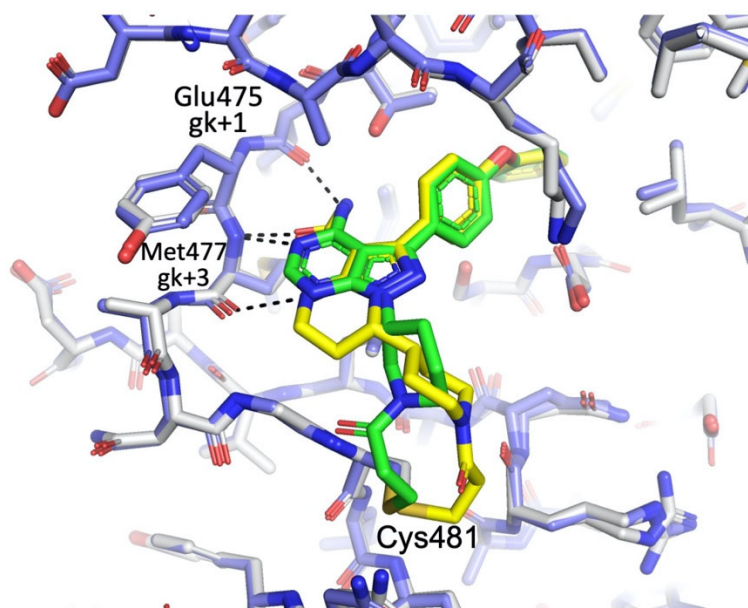
See EX1052.003, Fig. 2 (.002) (adenine); EX2048, Fig. 1 (.0001) (adenine); EX1076.005-006 (ibrutinib) (PDB: 5P9J); EX1053.005-006 (zanubrutinib) (PDB: 6J6M), Fig. 3 (.005), Fig. 4b (.006); *see also supra* §VI.D.3.

93. In fact, both ibrutinib and zanubrutinib are recognized to be adenine mimics, *including by Petitioner*. In a 2023 publication, Petitioner admitted that the “*five approved BTK inhibitors all have similar hinge binding to ATP.*” EX2020.0002; *see also* EX1076.005 (“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.” (emphasis added)), Tbl. 1 (.011) (including zanubrutinib in review). Dr. Showalter admitted the same, explaining that both ibrutinib and zanubrutinib have “similar hinge binding patterns to ATP.” EX2018, 82:10-84:4; *see also id.*, 84:13-85:21 (Dr. Showalter conceding that zanubrutinib showed “similar” H-bond interactions with the hinge region as ATP); *id.*, 115:12-116:15 (Dr. Showalter admitting that ibrutinib and zanubrutinib have “similar[]” binding patterns); *id.*, 93:7-20 (Dr. Showalter admitting that the five approved BTK inhibitors, including ibrutinib and

additional interaction does not change that ibrutinib and zanubrutinib have similar H-bond interactions with the hinge region of BTK and that both inhibitors mimic adenine.

zanubrutinib, “all form interactions with the hinge region, and those interactions include binding to the g[k]+1 [residue] and g[k]+3 [residue]” of BTK).

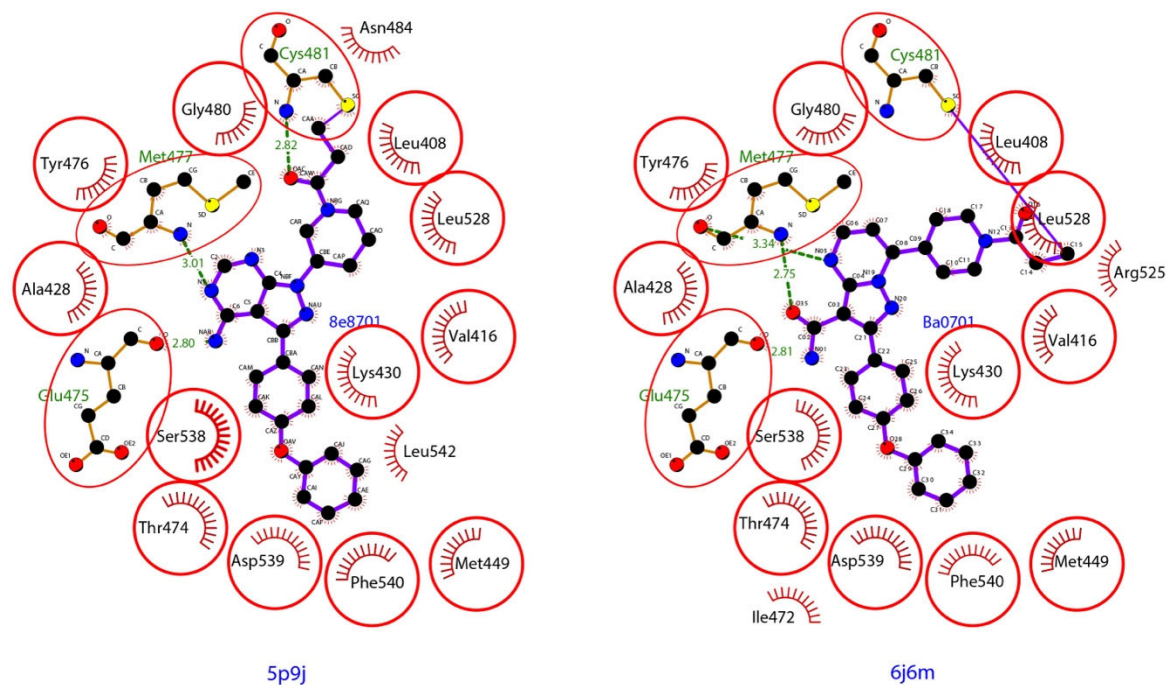
94. Additionally, as shown in the below overlay of BTK-ibrutinib (PDB: 5P9J) and BTK-zanubrutinib (PDB: 6J6M), ibrutinib and zanubrutinib have largely overlapping placement in three-dimensional space, further confirming that the two inhibitors bind to BTK in the same way from a structural perspective. Ibrutinib is shown with carbon atoms colored green, and zanubrutinib is shown with carbon atoms colored yellow.



95. The precise maintenance of hydrogen bond interactions in zanubrutinib as compared with ibrutinib also allows zanubrutinib to position the phenoxyphenyl substituent exactly as in ibrutinib, preserving the overall structure-function relationship in binding to BTK. The precise correspondence of these

interactions is especially striking in light of the comparative diversity of interactions evident in BTKI structures available in June 2011. *Compare* figure showing overlay of ibrutinib-BTK and zanubrutinib-BTK (*see* ¶94) *with* other BTKI structures bound to BTK (*see* ¶88).

96. I have compared the interactions between BTK and ibrutinib and between BTK and zanubrutinib using the program Ligplot+, a successor to the original version of the program Ligplot. Ligplot+ offers a useful additional feature: the ability to display the interaction diagrams of two related protein-ligand complexes side-by-side and in a consistent orientation with interactions that are conserved highlighted. *See generally* EX2047. This feature therefore provides an automated, unbiased tool for comparing the interactions of ibrutinib and zanubrutinib with BTK. The resulting analysis is shown in the figure below.



97. As the figure shows, almost *all* of the interactions with BTK are the same for ibrutinib (left, PDB: 5P9J) and zanubrutinib (right, PDB: 6J6M) (with areas of conserved interactions highlighted with red circles). Moreover, ibrutinib and zanubrutinib have the same linker-warhead that orients toward and binds to BTK's Cys481 and have the same phenoxyphenyl group that orients toward and binds within BTK's hydrophobic back pocket. The extensive conserved interactions between ibrutinib and zanubrutinib is not surprising given that zanubrutinib copies the same phenoxyphenyl and linker-warhead from ibrutinib.

98. Additionally, ibrutinib and zanubrutinib both have a heterocyclic scaffold that forms the key H-bonds with the GK+3 Met477 and GK+1 Glu475 hinge residues of BTK. Specifically, the heterocyclic scaffold of ibrutinib donates

a hydrogen bond to the carbonyl of Glu475 and receives a hydrogen bond from the mainchain amide of Met477. Likewise, the heterocyclic scaffold of zanubrutinib donates a hydrogen bond to the carbonyl of Glu475 and receives a hydrogen bond from the mainchain amide of Met477.¹⁰ As I have explained, a POSA in 2011 would have understood from the teachings of the '803 Patent and consistent prior art that hydrogen bonding to the hinge region is a key part of the structure-function relationship for the ibrutinib-like irreversible BTKIs for use in the claimed method. *See supra* §§VI.D.3, VII.A.4.

99. In all, ibrutinib and zanubrutinib make the same corresponding interactions with 18 out of the 19 BTK residues shown in the figure. Only one interacting residue is unique to the inhibitors in the figure (the Arg525 residue interacts with the acrylamide of zanubrutinib only, but that interaction would not

¹⁰ As I have explained, zanubrutinib also donates a hydrogen bond to the carbonyl of Met477, but based on the distance between the hydrogen bond donor and acceptor (3.34Å), this is likely a relatively weak hydrogen bond. And as I have also explained, this third H-bond aligns with the understanding from the '803 Patent and state of the art regarding the standard one to three H-bonds formed with specific residues of the protein kinase hinge. *See supra* §§VI.D.3, VII.A.4; EX1077.003; EX2028.0001-0002; EX1052.020.

be expected to contribute significantly to binding given its positioning on the solvent-exposed surface of BTK).¹¹

100. Furthermore, by default, Ligplot+ does not include water-mediated interactions. Enabling that option reveals an additional binding interaction that is essentially identical between ibrutinib and zanubrutinib: a water molecule that is coordinated between the sidechain amine of Lys430 and the nitrogen in the five-membered ring of the heterocyclic scaffold.

101. While there is significant overlap in interactions between ibrutinib and BTK and between zanubrutinib and BTK, there are some differences in interactions. A water-mediated interaction is observed between the side chain of

¹¹ Certain interactions are present in both ibrutinib and zanubrutinib but are not included in the figure because the distance between interacting atoms falls just outside Ligplot+'s default cutoff (3.9Å) for identifying an interaction. Inspection of ibrutinib and zanubrutinib indicates that the Asn484 and Leu542 residues that appear to only be present for ibrutinib in the figure also make the corresponding interaction with zanubrutinib (with distances of 4.0Å and 4.2Å, respectively). Similarly, the Ile472 residue that appears to only be present for zanubrutinib in the figure also makes the corresponding interaction with ibrutinib (with a distance of 3.91Å).

Asn484 and the carbonyl oxygen of zanubrutinib's warhead, but the corresponding carbonyl in ibrutinib hydrogen bonds with the mainchain amide of Cys481. However, this difference is not essential to the structure-function relationship because as I have explained, a POSA in 2011 would be aware that highly potent covalent BTK inhibition can be accomplished with differing linker-warhead geometries. *See supra* §§VI.D.1, VII.A.1. Furthermore, these solvent-exposed and solvent-mediated interactions are expected to contribute very little to binding. In particular, the geometry of the water-mediated hydrogen bond with Asn484 for zanubrutinib is far from optimal, indicating a very weak interaction.

102. In sum, overall, the structure-function relationship of ibrutinib is preserved in zanubrutinib, and the vast majority of interactions made by the two inhibitors with BTK are the same.

B. A POSA Reading the '803 Patent Would Have Known How to Use Ibrutinib and Available Modeling/Docking Software to Create Additional Ibrutinib-Like BTKIs with Different Z'-Scaffolds

1. The '803 Patent Taught Scaffold Swapping for Ibrutinib-Like BTKIs for Use in the Claimed Method

103. As I have explained, the specification's Formula E recognizes that the substructures that bind to the highly conserved hinge region are fungible and predictable (while maintaining the fixed groups of ibrutinib: the linker-warhead and phenoxyphenyl). EX1001, 61:66-63:21; *supra* §VII.A.4. In 2011, consistent with the specification, a POSA reading the '803 Patent would have identified Z'-

scaffolds for ibrutinib-like irreversible BTKIs by leveraging structural information regarding the binding of ibrutinib and other known hinge-binding elements of kinase inhibitors. *See* EX1077.007 (describing the use of “structure-informed design” to “facilitate inhibitor discovery and optimization” including by using “crystal structures . . . to design hybrid compounds in which a portion of one inhibitor is grafted onto a portion of another, guided by superimposition of the bound structures”), .009 (explaining that “[k]inase inhibitor design has benefited immensely from crystallography in the elucidation of binding modes” and that “much of current kinase inhibitor discovery takes place through rational drug design . . . and empirical optimization on the basis of structure–activity relationships”); EX1052.019-020 (describing the process for lead/scaffold swapping activities of aligning a scaffold of interest to a known active compound and “follow[ing] the topology of the active compound to add/modify structural moieties in the chosen scaffold” including automated 3D versions of this approach); *see also* EX2018, 171:18-173:16, 173:19-174:15.

104. A POSA following the '803 Patent would have expected this approach to yield potent ibrutinib-like BTKIs for use in the claimed method for two reasons. First, as reflected in the specification's Formula E calling for structures that bind to BTK's active site to couple with the linker-warhead structure to target BTK's Cys481 to irreversibly inhibit BTK, a POSA in 2011 would have

understood that a hinge-binding substructure from a known ligand is likely to make similar interactions with the highly conserved hinge in a different kinase. *See* EX1001, 61:65-62:17. A POSA reading the '803 Patent would have understood that all active protein kinases must bind ATP (their nucleotide substrate), and they do so in a conserved manner. *See, e.g.*, EX1052.003, .007 (entry 1 of table 2, showing that crystal structures of 40 unique kinases reveal the same mode of binding to adenine). Second, for the highly conserved ATP binding site, a POSA would have been aware of numerous kinase-ligand structures to allow for swapping of scaffolds that make productive interactions with the kinase hinge in view of the known structure of ibrutinib and its binding to BTK and the '803 Patent disclosure. There are approximately 500 protein kinases with a conserved ATP-binding site, and in 2011, there were over 400 publicly available kinase structures in the Protein Data Bank with at least 53 distinct scaffolds bound in the ATP-site and kinase hinge region. *See generally* EX1052. And as I have explained, in June 2011, approximately 1290 structures of protein kinases with bound ligands were publicly available in the Protein Data Bank. *See supra* §VI.D.

105. Thus, in 2011, a POSA could generate additional inhibitors from ibrutinib, whose structure the '803 Patent taught resulted in potent inhibition of BTK in patients. *See* EX2028.0004-0005 (describing a “powerful approach” to generate additional kinase inhibitors by “scaffold swapping” wherein “the hinge-

binding element of a given kinase lead is replaced, based on structural information, with the novel scaffold”); *see also* EX1052.019-020, Fig. 7 (.020).

GHOSE FIG. 7 – BASIC CONCEPT OF GENERATING CROSS-BRED LIGANDS

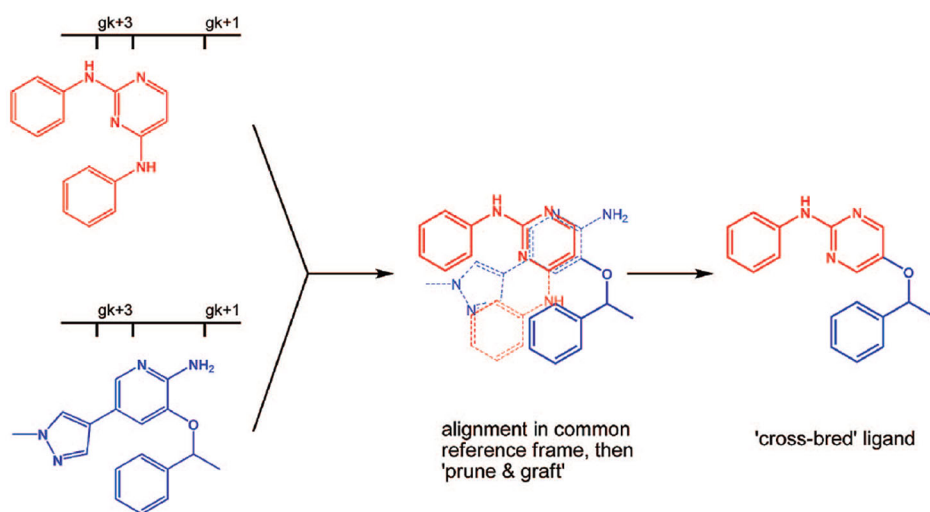
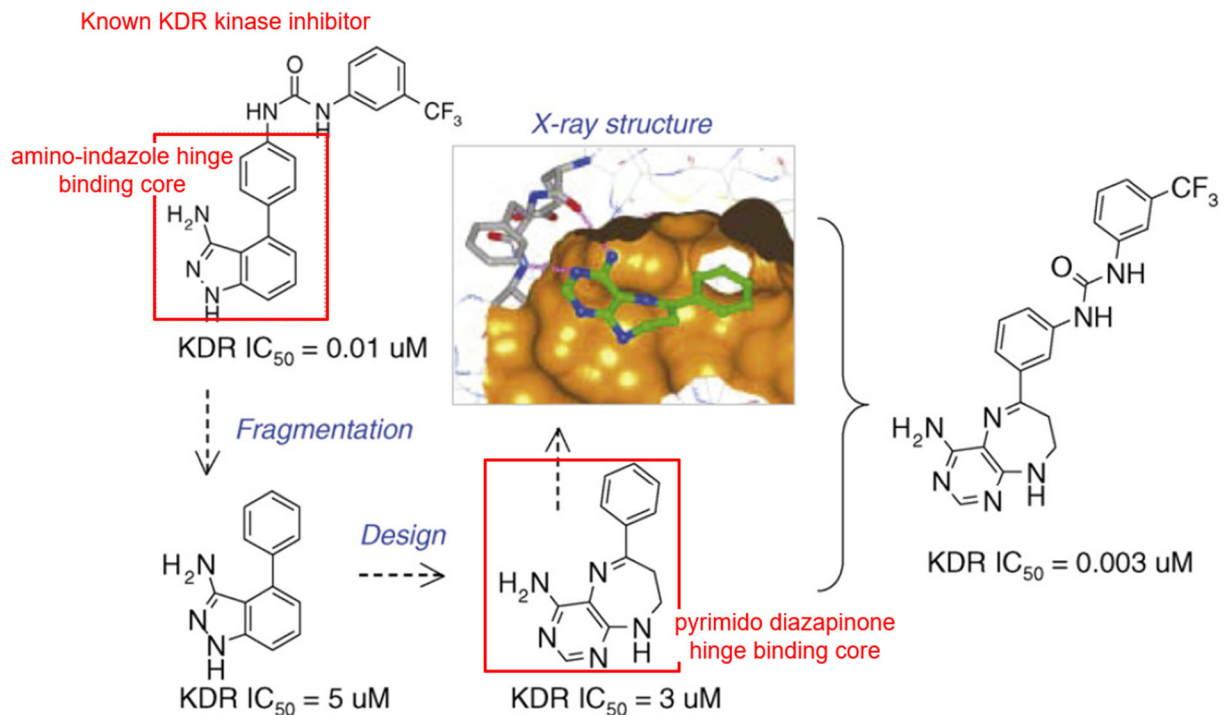


Figure 7. Basic concept of generating cross-bred ligands: (1) ligand–protein structure complexes have been aligned into a common reference frame; (2) the position of their hydrogen bond forming moieties relative to the gk+3 and gk+1 residues of the hinge orient the scaffolds such that fragmentation and reconnection points can be identified (either computationally or manually); (3) hybrid structures, containing portions from both scaffolds, are generated.

EX1052, Fig. 7 (.020).

106. Moreover, consistent with the '803 Patent's direction to use Z'-scaffolds that bind the BTK active site, the art provided examples of successful swaps. EX2028.0004-0005 (scaffold swapping to replace the amino-indazole core of a known KDR kinase inhibitor with a pyrimido-diazapinone analog); EX2038, Fig. 1 (.0001) (describing similar scaffold swapping).

ADAPTED FROM AKRITOPOULOU-ZANZE FIG. 5 – SCAFFOLD SWAPPING



EX2028, Fig. 5 (.0004) (annotated).

107. The '803 Patent specification's Formula E invokes this approach of scaffold-swapping in calling for the use of structures that bind to the highly conserved BTK active site. EX1001, 61:65-62:17. A POSA reading this teaching would have recognized the applicability of scaffold-swapping of kinase hinge-binding elements across kinase inhibitor programs to attach substituents shown to result in productive inhibition of the kinase target. EX2028.0005 ("This concept of scaffold swapping is, in principle, applicable to virtually every kinase inhibitor program, provided that structural information can be generated on both the original series and the scaffolds of interest.").

2. Specific Application to BTK/Irreversible BTKIs

108. Because of available detailed structural information from Marcotte showing how a reversible inhibitor with ibrutinib-like binding bound to BTK, a POSA reading the '803 Patent would have understood this inhibitor class was a strong candidate for inhibitor scaffold-swapping to use alternate hinge-binding structures, as the '803 Patent specification taught.

109. Indeed, a POSA in 2011 would have understood that Pan revealed significant structural information about how ibrutinib-like BTKIs interact with BTK. Having the structural information from Marcotte about ibrutinib's binding mode, a POSA would have understood that Pan reports irreversible BTKIs, including ibrutinib, that covalently bind to and irreversibly inhibit BTK's Cys481. EX1060.001-004; *see also* EX2018, 54:4-13, 55:12-60:6. The '803 Patent further confirms that ibrutinib irreversibly inhibits BTK, reporting its occupancy of BTK in patients in clinical trials. *E.g.*, EX1001, 138:33-36.

110. A POSA in 2011 would have readily appreciated the structural features of the irreversible BTKIs reported in Pan, with the phenoxyphenyl interacting with the back pocket and the linker-warheads interacting with and binding Cys481. EX1060.001-003.

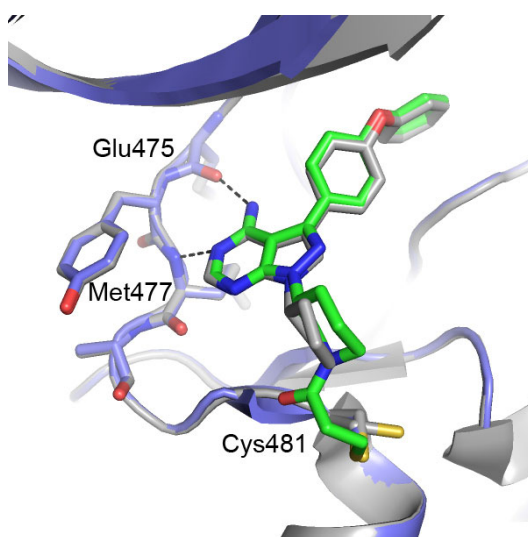
111. The structural information of Marcotte (PDB: 3GEN) would have provided a POSA in 2011 with data for use in virtual docking and modeling of the

ibrutinib-like irreversible BTKIs of the claims. Marcotte provides information on key interactions between structural features of ibrutinib and BTK.

112. For example, Marcotte shows how the phenoxyphenyl enters the BTK hydrophobic “back pocket” and also participates in a pi-stacking interaction with the phenylalanine in the kinase DFG-motif. *See* EX2001.0003-0005. Marcotte also details the H-bond interactions of heterobicyclic scaffold of the inhibitor with the BTK hinge region. *See id.* Finally, Marcotte shows how the cyclopentyl ring of the inhibitor occupies the space generally occupied by ATP ribose, in close proximity to Cys481, indicating the general positioning of the linker-warhead of ibrutinib and related compounds. *See* EX2001.0003-0004. A POSA in 2011 would have had significant data from Marcotte and the '803 Patent to recognize the scaffolds from other known kinase hinge-binding elements that could productively orient ibrutinib's phenoxyphenyl and linker-warhead to irreversibly inhibit BTK and treat CLL/SLL patients as the '803 Patent specification taught. Indeed, Dr. Showalter admitted that Marcotte would have been “helpful” in developing an irreversible BTK inhibitor as taught by the '803 Patent. *See* EX2018, 43:20-44:9; *see also id.*, 46:21-47:19. Dr. Showalter further admitted that in 2011, “a POSA, based on x-ray crystal structures, would [have] be[en] able to make some guesses based on the binding patterns to the hinge region . . . as to maybe which compounds yet to be discovered would bind in the same fashion to the hinge region.” EX2018, 117:10-

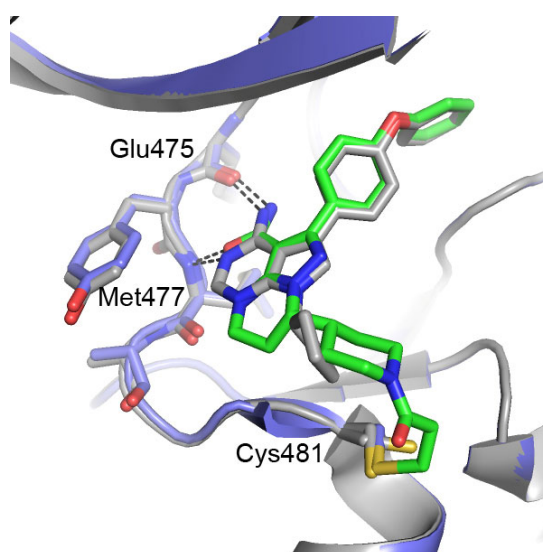
21; *see also id.*, 168:2-170:2 (Dr. Showalter admitting that in 2011, a POSA may have used Pan's type of modeling), 177:10-179:9 (Dr. Showalter admitting that "to the extent that there was information regarding homology models, and there was in the Pan article, one would use that information to look at other candidate ligands toward making a new inhibitor").

113. The applicability of Marcotte's structural information to ibrutinib-like irreversible BTKIs was later confirmed in both the crystal structures of ibrutinib and zanubrutinib. A superposition of the B43 compound of Marcotte bound in the BTK active site (PDB: 3GEN) and BTK-ibrutinib (PDB: 5P9J) is shown below. Both structures have largely overlapping placement in three-dimensional space, and make adenine-mimicking hydrogen bonds to hinge residues Glu475 and Met477. Ibrutinib is shown with carbon atoms colored green, B43 is gray.



114. Similarly, zanubrutinib and compound B43 of Marcotte also bind in a closely analogous manner to BTK. A superposition of the B43 compound of

Marcotte, bound in the BTK active site (PDB: 3GEN) and BTK-zanubrutinib structure (PDB: 6J6M) is shown below. Both compounds have largely overlapping placement in three-dimensional space, and make adenine-mimicking hydrogen bonds to the hinge at Glu475 and Met477. Zanubrutinib is shown with carbon atoms colored green, B43 is gray.



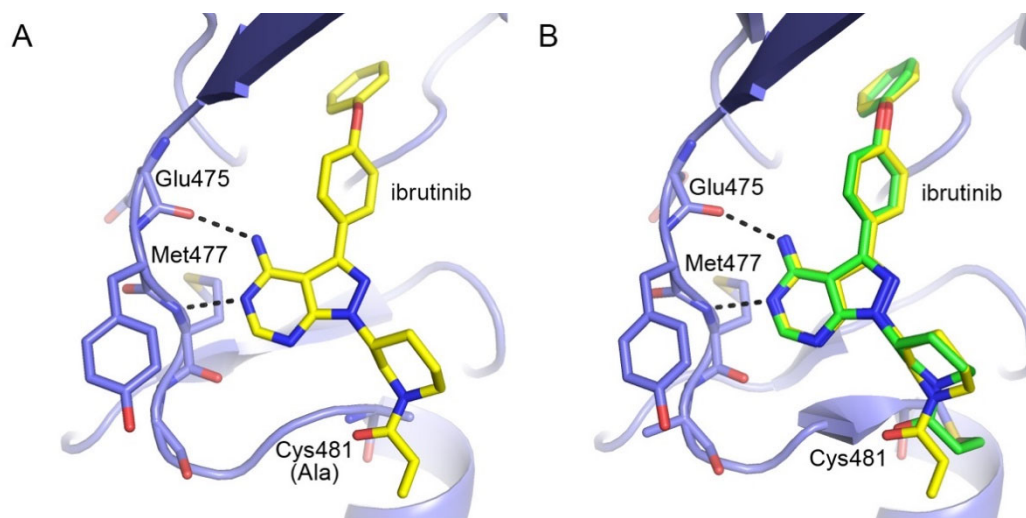
115. A POSA reading the '803 Patent to select additional ibrutinib-like irreversible BTKIs for use in the claimed methods would have been aware of computational tools for docking of ligands into target protein structures that were widely available and widely used. *See, e.g.,* EX2035; EX2036; EX2037; EX2041. In my experience, every major drug discovery program as of June 2011 had a computational/modeling component for fully assessing the properties of proposed compounds. These tools were an integral part of inhibitor design, used to visualize binding modes and prioritize compounds for synthesis and potential further

preclinical development. Dr. Showalter agrees, admitting that “a POSA would likely be working with specialists in molecular docking[,] . . . x-ray crystallography[,] or computational modeling[.]” EX2018, 143:11-19; *id.*, 143:19-22 (Dr. Showalter explaining that such a “specialist[.]” would have been “one of th[e] members of the team.”). In fact, as Dr. Showalter’s cited reference acknowledges, binding models based on crystal structures, like Marcotte, would be used to assess analogs that “modulate potency, selectivity and pharmacological properties. Isosteric replacements are used to improve these properties while preserving the stereo electronic contacts responsible for binding to the kinase.” EX1077.006-007. This is consistent with my experience and what a POSA would have known about the use of structural information to inform prioritization and selection of candidate inhibitors in 2011 where crystal structure data is available, like Marcotte, for ibrutinib-like irreversible BTKIs and where the ’803 Patent provided functional and clinical data validating the mechanism.

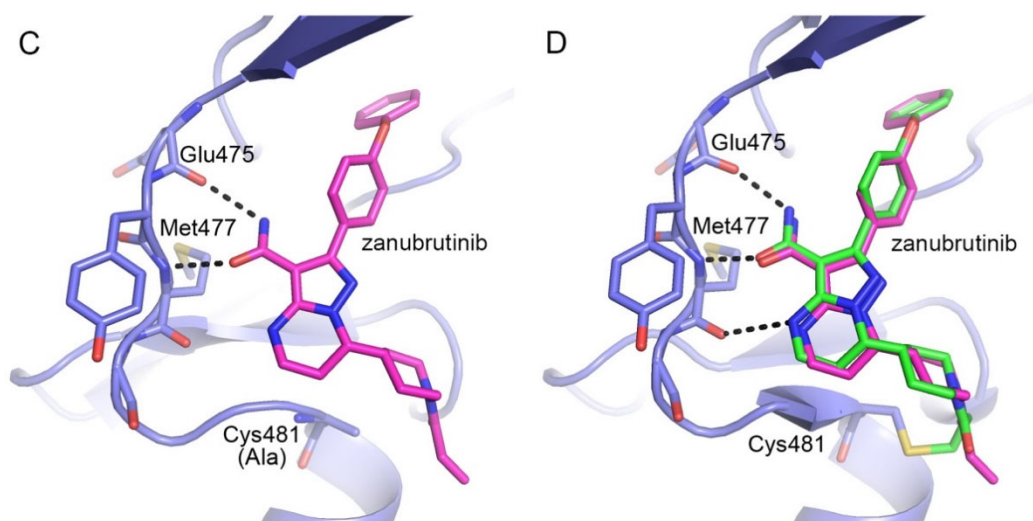
116. Using a docking program available in June 2011 and the 3GEN crystal structure of Marcotte, a POSA would have been able to confidently and accurately predict the expected binding mode of ibrutinib-like BTKIs, as taught by the specification. Using Glide docking within the Maestro (Schrödinger) modeling environment, I docked ibrutinib (figures below). The target receptor for docking was the BTK portion of the Marcotte (3GEN) crystal structure, prepared for

docking using the “protein prep” functionality within Maestro. The B43 ligand in 3GEN was used to define the target site for docking, and docking was carried out in standard precision (SP) mode with ibrutinib, prepared using the “Ligprep” functionality in Maestro. The docking pose obtained correctly positioned ibrutinib to make the adenine-mimicking hydrogen bonds to hinge residues Glu475 and Met477, accurately positioned the phenoxyphenyl in the hydrophobic back pocket, and oriented the linker-warhead in close proximity to Cys481 (panel A).¹² Superposition of the docked compound with the actual co-crystal structure of ibrutinib (PDB: 5P9J) reveals the striking accuracy of the docking poses (panel B).

¹² Because reversible docking does not form the covalent bond between the warhead and the Cys481 of BTK, the Cys481 was truncated to an alanine to avoid steric clash with the cysteine thiol. This is a standard approach when docking covalent ligands in reversible docking platforms.

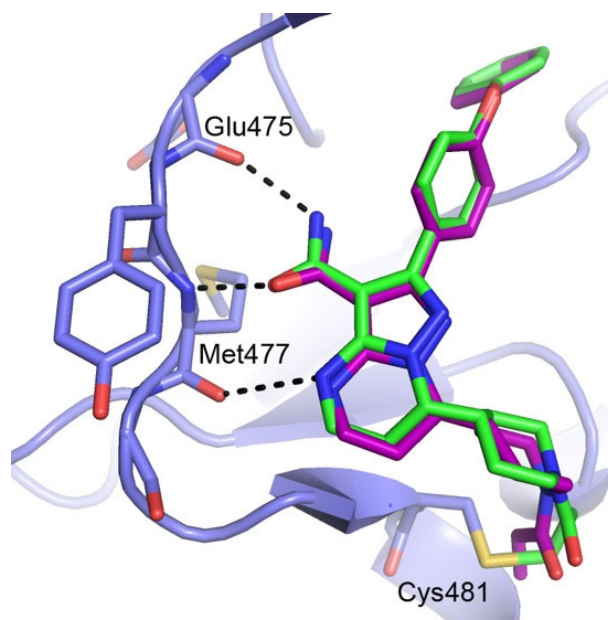


117. A POSA's ability to visualize docking of ibrutinib-like irreversible BTKIs in 2011 would not have been limited to ibrutinib itself or compounds with aromatic scaffolds. I performed the same process described above with zanubrutinib. The docking pose obtained correctly positioned zanubrutinib to make the adenine-mimicking hydrogen bonds to hinge residues Glu475 and Met477, accurately positioned the phenoxyphenyl in the hydrophobic back pocket, and oriented the linker-warhead in close proximity to Cys481 (panel C). Superposition of the docked compound with the actual co-crystal structure of zanubrutinib (PDB: 6J6M) demonstrates the accuracy and reliability of docking to predict the binding mode of ibrutinib-like BTKIs like zanubrutinib (panel D).



118. The functionality of the Maestro/Glide software that I used for docking was available in 2011. *See, e.g.*, EX2035; EX2036; EX2037; EX2041; EX2018, 179:15-182:3, 183:17-184:2 (Dr. Showalter admitting that Glide and Maestro/Schrödinger software was available in 2011); EX1052.001, .003, .022. While the software has been further developed since June 2011, the same ligand and protein preparation functionalities and standard precision (SP) and extra-precision (XP) docking modes were available then and were employed to obtain similarly precise docking of ligands in protein kinases when docked poses were compared with crystal structures of corresponding ligands. *See, e.g.*, EX2056; EX2057. Then, as now, a POSA would have understood that the availability of an appropriate structure for docking, ideally one with a similar ligand bound (as was available here with the Marcotte crystal structure), is the major determinant of the precision and accuracy of the predicted binding mode. Indeed, even manual docking of zanubrutinib based on superposition with B43 in the 3GEN structure of

Marcotte produces a pose closely similar to that in the crystal structure (PDB: 6J6M), as shown in the superposition below (crystal structure pose in green, manually docked pose in purple).



VIII. CLAIM CONSTRUCTION

119. I understand from counsel for Pharmacyclics that claim construction refers to determining the legal meaning of claim terms. I understand that this process begins with the words of the claims and that the words of a claim are generally given their ordinary and customary meaning. I have been informed that the ordinary and customary meaning of a claim term is the meaning that the term would have to a POSA at the time of the invention. I also understand that a patentee can define claim terms in the patent specification and that those definitions will control the meaning of those terms in the claims.

120. With respect to an “irreversible” BTKI, the specification expressly defines “irreversible Btk inhibitor” to mean:

an inhibitor of Btk that can form a covalent bond with an amino acid residue of Btk. In one embodiment, the irreversible inhibitor of Btk can form a covalent bond with a Cys residue of Btk; in particular embodiments, the irreversible inhibitor can form a covalent bond with a Cys 481 residue (or a homolog thereof) of Btk or a cysteine residue in the homologous corresponding position of another tyrosine kinase.

EX1001, 26:23-31.

121. I agree with Dr. Showalter’s opinion that the specification’s express definition of “irreversible Btk inhibitor” is consistent with a POSA’s understanding of this term. *See* EX1003, ¶¶127-128. In my analysis of the Challenged Claims, I have used this definition of “irreversible” BTK inhibitor.

122. With respect to an “optionally substituted fused heterocyclic ring system,” the specification expressly defines the terms appearing in “optionally substituted fused heterocyclic ring system.” I agree with Dr. Showalter’s opinion that the specification’s express definitions of the terms appearing in “optionally substituted fused heterocyclic ring system” are consistent with a POSA’s understanding of these terms. *See* EX1003, ¶¶129-133. In my analysis of the Challenged Claims, I have used these definitions to define “optionally substituted fused heterocyclic ring system.”

IX. PERSON OF ORDINARY SKILL IN THE ART

123. I understand that my opinions concerning patentability must be judged from the perspective of POSA, a hypothetical person who is aware of all pertinent prior art in the field and who is a person of ordinary creativity.

124. In determining the level of ordinary skill for my analysis of the '803 Patent, I was asked to consider, for example, the types of problems encountered in the field, the prior solutions to those problems, the sophistication of the technology, and the educational level of active workers in the field.

125. For the '803 Patent, a POSA in June 3, 2011 would have been a team, with at least one member having at least a medical degree with training in hematology and oncology, including several years of clinical experience in treating hematologic malignancies, and another member or members having at least a Ph.D. in chemistry, organic chemistry, or related field with training as a medicinal chemist and in the structure of kinases or structure-function relationship of kinase inhibitors. 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.

126. I understand that Dr. Showalter has proposed that a POSA “would have been part of a team that included at least (1) a member that had at least a Ph.D. in chemistry, organic chemistry, or related field with training as a medicinal

chemist ('chemist member'), and (2) a member that had at least a medical degree with training in hematology and oncology, including several years of clinical experience in treating hematologic malignancies ('clinical member')." EX1003, ¶136. Dr. Showalter's definition does not expressly account for the relevance of the wealth of structural information available about the kinase active site and the developed understanding of the structure-function relationship of kinase inhibitors. A proper definition would explicitly account for this relevant knowledge, *i.e.*, "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." My opinions set forth in this Declaration would not change under Dr. Showalter's definition.

127. I would have qualified as a member of the POSA team as of the claimed June 3, 2011 priority date of the '803 Patent, and I believe that I have a sufficient level of knowledge, experience, and education to provide an expert opinion in the field of the '803 Patent. In particular, I have developed and researched kinase inhibitors, including irreversible kinase inhibitors that interact with kinase active sites and homologous cysteines near the ATP binding site for most of my professional career. As part of my research, I have developed and expanded on structure-function relationships for kinase inhibitors.

128. Unless otherwise stated, my opinions in this Declaration are based on the perspective of the POSA described above as of June 3, 2011.

X. THE '803 PATENT SPECIFICATION DESCRIBES THE IRREVERSIBLE INHIBITORS OF THE CHALLENGED CLAIMS

129. Dr. Showalter opines that the Challenged Claims of the '803 Patent are not adequately supported by the priority non-provisional applications of U.S. Patent No. 11,672,803 including App. No. 13/153,317 “for at least two reasons.” *See* EX1003, ¶185; *see also* ¶¶186-231. First, Dr. Showalter opines that “[t]he specification does not describe the full scope of the Structural Limitations, including any of the three non-biaryl subgenera, the full scope of the biaryl subgenus, and BRUKINSA.” EX1003, ¶¶188-210. Second, Dr. Showalter opines that “[t]he specification does not describe any species other than IMBRUVICA that would covalently bind Cys481 or another amino acid residue of Btk.” EX1003, ¶¶211-220. I disagree with Dr. Showalter’s opinions.

130. In my opinion, the specification adequately describes the irreversible inhibitors of the Challenged Claims. The specification describes common structural features for irreversible BTKIs for use in the claimed methods. Additionally, the specification provides blaze marks to the specific genus of irreversible BTKIs for use in the claimed methods.

A. The Specification Describes Common Structural Features for Irreversible BTKIs for Use in the Claimed Methods

1. The Claimed Fixed Substituents Convey Irreversible BTK Inhibition Activity

a. The Linker-Warhead Is Responsible for Irreversible Inhibition of BTK

131. A POSA reading the '803 Patent would have understood that the linker-warhead structure recited in the claims covalently binds to the Cys481 residue in BTK. In doing so, the linker-warhead causes the compound to irreversibly inhibit BTK.

132. The specification teaches the importance of irreversible binding to Cys481 for selectivity to BTK. EX1001, 45:56-60 (“The Btk inhibitor compounds described herein are selective for Btk and kinases having a cysteine residue in an amino acid sequence position of the tyrosine kinase that is homologous to the amino acid sequence position of cysteine 481 in Btk.”). Moreover, the specification teaches that the linker-warhead forms the covalent bond to Cys481. *Id.*, 46:10-12 (“For example, some irreversible Btk-inhibitor compounds can form a covalent bond with Cys 481 of Btk (e.g., via a Michael reaction).”).

133. A POSA reading the '803 Patent would have therefore understood how the linker-warhead covalently binds to the Cys481 residue, irreversibly inhibiting BTK. *See supra* §§VI.D.1, VII.A.1; *see also* EX2018, 71:19-72:5. Based on such teachings from the '803 Patent, a POSA in 2011 would have understood

that Pan reported irreversible inhibitors of BTK exploited its known thiol-containing cysteine residue near the active site. Because only ten of the approximately 500 kinases have a cysteine at this position, a POSA in 2011 would have understood that targeting BTK's Cys481 for covalent binding would selectively and irreversibly inhibit BTK. *See supra* §VII.A.1; EX1060.001-002 (describing irreversible inhibitors of BTK including ibrutinib with different warheads and linkers to engage Cys481, wherein all “were highly potent inhibitors” with confirmed irreversibility via demonstrating activity of recombinant BTK pretreated with inhibitors not recoverable after multiple washes with inhibitor-free medium); EX2111, [208]-[209].

134. A POSA in 2011 would have been aware of additional art that was consistent with the '803 Patent's teaching that targeting BTK's Cys481 for covalent binding would selectively and irreversibly inhibit BTK. *See supra* §§VI.D.1, VII.A.1; EX2001, Fig. 2D (.0003) (Figure 2D of Marcotte depicting the crystal structure of BTK-KD/B43 (PDB: 3GEN) and showing the substituent oriented towards Cys481), .0007 (“Cys481 in the active site of BTK-KD could also be exploited to gain kinase selectivity in which a small molecule may be irreversibly bound to this cysteine via a covalent bond.”); EX1077.005-006, Box 1 (.007) (“[S]caffolds with moderate potency and selectivity can be converted to highly potent and selective inhibitors by the judicious introduction of an

electrophile that can target unique cysteine residues.”). A POSA reading the ’803 Patent would therefore know that ibrutinib forms a covalent bond with the Cys481 residue of BTK and thereby irreversibly inhibits BTK. *See supra* §§VI.D.1, VII.A.1; EX1001, 138:33-36 (reporting clinical results that ibrutinib occupies BTK in patients).

135. Based on the disclosures in the specification, combined with the knowledge in the art in 2011, a POSA would have recognized the importance of the linker-warhead to the function of the irreversible BTKI. By covalently binding to the Cys481 residue of BTK, the linker-warhead causes the compound to irreversibly inhibit BTK.

136. Later data confirmed what a POSA reading the ’803 Patent in 2011 would have understood about the importance of the linker-warhead. *See supra* §VII.A.1. First, the ibrutinib crystal structure provides post-priority confirmation of the linker-warhead covalently binding to BTK’s Cys481 in order to selectively and irreversibly inhibit BTK, as the ’803 Patent disclosed. *See supra* §VII.A.1; EX1076.005-006, Fig. 3a (.006). Second, later experiments, including Petitioner’s own experiments, confirmed the importance of the linker-warhead. For example, Guo reports that Petitioner experimented with removing the warhead from compounds that were similar to zanubrutinib (differing by linker). *See* EX1053.003-004. When removing the warhead, these zanubrutinib-like

compounds had 100s of fold difference in IC₅₀ with the warhead versus without the warhead. *See id.* (“*Note*: To exclude the possibility that the ***aforementioned compounds without warheads are potent on their own***, IC₅₀ values of 20 and 21 without warheads were evaluated on biochemical assay as 200 and 1000 nM, respectively.” (emphasis added)). Specifically, one of the zanubrutinib-like compounds (compound 20) had an IC₅₀ value of 0.62 nM with the warhead and 200 nM without the warhead. *See id.* Another zanubrutinib-like compound (compound 21) had an IC₅₀ value of 4.7 nM with the warhead and 1000 nM without the warhead. *See id.*

b. Orientation of Linker-Warhead by Rest of Molecule (Z' and Phenoxyphenyl) Is Permissive

137. A POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that the linker-warhead could approach Cys481 from different directions. Dr. Showalter overstates the precision required for Cys481 interaction with the warhead. *See, e.g.,* EX1003, ¶48 (“The chirality in the linker is also a critical component of the overall structure of the BTKIs, and there would have been no basis to expect that BRUKINSA’s warhead would reach the same location of Cys481 in Btk as IMBRUVICA.”); *see also id.*, ¶48 (“[T]he chirality in the linker must cooperate with the remaining structural features of the BTKI (e.g., the Z'-structure) such that the warhead can be aligned with the Cys481 residue of Btk in a proper angle and

distance for the Michael reaction to take place. There would have been no basis to believe that BRUKINSA's warhead would reach the same location of Cys481 in BTK as IMBRUVICA."). I disagree with Dr. Showalter's opinions.

138. A POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that a BTKI could form a covalent bond with BTK's Cys481 from warheads with different orientations. The specification discloses ibrutinib, its opposite enantiomer (with a different stereochemistry of the linker-warhead), and a racemic mixture of the two irreversibly inhibit BTK. *See* EX1001, 65:10-25 (ibrutinib), 79:50-65 (ibrutinib), 80:55-57 (compound 13, ibrutinib), 80:63-65 (ibrutinib), 77:5-25 (racemic mixture), 80:38-40 (compound 4, racemic mixture), 80:1-15 (ibrutinib enantiomer). With these disclosures, a POSA would have understood that the linker-warhead could approach Cys481 from different directions to form a covalent bond and irreversibly inhibit BTK.

139. A POSA reading the '803 Patent to identify ibrutinib-like BTKIs for use in the claimed method would have also known why the linker-warhead could approach Cys481 from different directions and covalently bind with Cys481. *See supra* §§VI.D.1, VII.A.2. As I have explained, a POSA reading the '803 Patent would have understood that the Marcotte structure and its deposited density maps show that BTK's Cys481 can adopt different orientations (*i.e.*, can rotate) and is

solvent-exposed (*i.e.*, has fewer steric hindrances). *See supra* §VII.A.2; EX2001, Fig. 2D (.0003) (Figure 2D of Marcotte depicting the crystal structure of BTK-KD/B43 (PDB: 3GEN) and showing that the Cys481 residue of BTK adopts two orientations and is relatively solvent-exposed). Because Cys481 can rotate and has fewer steric hindrances, a POSA would have understood that Cys481 could be targeted with different warhead trajectories. *See supra* §§VI.D.1, VII.A.2. As I have explained, a POSA in 2011, having the information demonstrating ibrutinib-like binding from Marcotte, would have understood that Pan reports potent irreversible BTKIs that used warheads with different orientations, warheads with different lengths, or different linkers all able to covalently bind BTK's Cys481. *See supra* §VII.A.2; EX1060, Tbl. 3 (.003).

140. Based on the disclosures in the specification, combined with the knowledge in the art in 2011, a POSA would have understood that the linker-warhead could approach Cys481 from different directions to form a covalent bond and irreversibly inhibit BTK.

141. Later data further confirms what a POSA in 2011 would have understood reading the '803 Patent: that the linker-warhead could approach Cys481 from different directions. In fact, the very data on which Dr. Showalter relies confirms such permissiveness. *See* EX1003, ¶73 (citing EX1053, Tbl. 6 (.005)). Data on zanubrutinib shows that variation in the positioning of the warhead

still allows for the warhead to covalently bind with Cys481. *See* EX1053, Tbl. 6 (.005). Guo discloses data with separated R and S isomers of zanubrutinib showing IC₅₀ values of 0.30 nM (S) vs. 11 nM (R). *See* EX1053, Tbl. 6 (.005). While Dr. Showalter emphasizes the difference between these two values, that difference is irrelevant—both are able to potently and irreversibly inhibit BTK by binding covalently to Cys481. *See* EX1053.003 (stating that “covalent bond formation with Cys481 was further confirmed using serine mutant assay and fast dilution experiment” (citing Supporting Information (EX2039) at p S6)). Indeed, I understand that when presented with Guo in his deposition, Dr. Showalter admitted that a POSA in 2011 would have viewed zanubrutinib and its R isomer as having “a high level of potency.” EX2018, 125:17-128:15.

c. The Phenoxyphenyl Moiety Directs Potency and Selectivity in BTK Binding

142. A POSA reading the '803 Patent to identify ibrutinib-like BTKIs for use in the claimed method would have understood that ibrutinib's phenoxyphenyl moiety is important for potency and selectivity in BTK binding. When reading the specification, a POSA would have recognized that the specification teaches the importance of the phenoxyphenyl moiety in a compound intended to inhibit BTK. All depicted structures of irreversible BTKI species in the specification include a phenoxyphenyl moiety attached to a heterocyclic scaffold, which a POSA would have understood to drive specific binding to BTK. EX1001, 65:10-80:35.

143. As I have explained, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that an ibrutinib-like BTKI must orient its hydrophobic phenoxyphenyl moiety to bind within BTK's "back pocket," furthering potency and selectivity in BTK binding. *See supra* §§VI.D.2, VII.A.3; *see also* EX2001.0004-0005 (confirming that the phenoxyphenyl of B43 binds within the hydrophobic back pocket); EX1052.002, Fig. 2 (.002) (describing the known "specificity pocket" adjacent to the hinge region that furthers inhibitor selectivity); EX1060.001-004 (reporting irreversible inhibitors that include a phenoxyphenyl moiety and have potent and selective inhibition of BTK). Indeed, like the specification taught, Dr. Showalter admitted that, in 2011, "a POSA would understand that the back pocket would contribute certainly to potency and possibly also to selectivity." EX2018, 104:15-105:4; *see also id.*, 71:7-18.

144. Based on the presence of the phenoxyphenyl moiety in all of the irreversible BTKI species disclosed in the specification, combined with the knowledge in the art in 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would recognize the importance of the phenoxyphenyl moiety to the irreversible BTKI compound and how the phenoxyphenyl moiety furthers potency and selectivity by binding within BTK's back pocket.

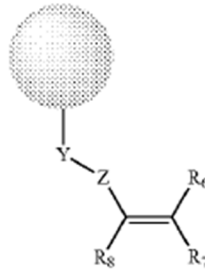
2. Claimed Z' Includes Common Structural Features That Bind Within BTK's Hinge Region

a. The Specification's Teaching Emphasizes Binding to the BTK Active Site, Which Requires Binding within the BTK Hinge Region

145. The claims limit the Z' of the ibrutinib-like irreversible BTKI to optionally substituted fused 5:6 heterocycles having 2-4 nitrogen heteroatoms with at least one nitrogen heteroatom in each ring. *See* EX1001, 151:64-152:2 (claim 1). Certain dependent claim further limit the number of nitrogen heteroatoms. *Id.*, 154:20-21 (claim 12, limiting to 3 nitrogen heteroatoms); *id.*, 156:20-22 (claim 20, same). The specification describes the structural features of these claimed Z'-scaffolds. Indeed, as Dr. Showalter acknowledges, “[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) that includes a fused heterocyclic ring system (*e.g.*, a fused heterobicyclic ring) and substitutions present on the ring system.” EX1003, ¶32. I agree that the structural features for Z' in the Challenged Claims are “typical.”

146. The specification emphasizes binding to the BTK active site. Formula E (included below) provides a structure, represented as an orb, that “binds to the *active site*” of BTK. EX1001, 61:65-62:17 (emphasis added).

Formula (E)



wherein:

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

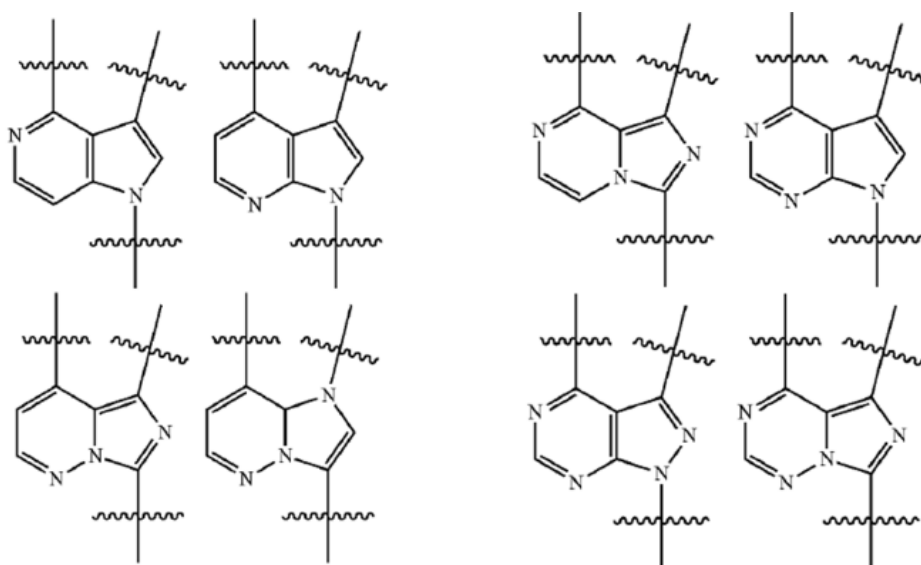
147. A POSA would have understood the specification's Formula E as referring to the understanding that diverse structures would bind within the active site. A POSA would have understood that this disclosure reflects the structure-function relationship for the hinge-binding region of the claimed ibrutinib-like irreversible BTKIs. As I have explained, in light of the specification's teachings, a POSA reading the '803 Patent in 2011 to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have had sophisticated knowledge of the various regions of BTK's active site and their roles, and the critical role of the hinge region of the active site for forming H-bonds with kinase inhibitors. *See supra* §§VI.D, VI.D.3, VII.A.4. As I have also explained, in 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that ATP-competitive kinase inhibitors make one to three H-bonds with specific amino acid residues of the kinase hinge region to effectively bind to the kinase. *See supra* §§VI.D.3, VII.A.4; *see also*

EX2028.0002-0004. Indeed, a POSA would have understood that Formula E discloses an element that makes the appropriate H-bonds with the BTK hinge region in order to effectively bind to BTK's active site while orienting the fixed substituents appropriately. Formula E teaches a POSA to select appropriate scaffolds, consistent with a POSA's sophisticated understanding of the BTK active site and hinge in 2011.

148. In 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood from the specification's disclosures and consistent prior art that the hinge-binding element of the ibrutinib-like irreversible BTKIs can exhibit structural diversity because a defining attribute of the hinge-binding element is its ability to have H-bond acceptors/donors arranged in a suitable geometry to form one to three H-bonds with specific amino acid residues of the hinge. *See supra* §§VI.D.3, VII.A.4. Consistent with the '803 Patent's disclosures, a POSA in 2011 would have known that diverse heterocyclic core scaffolds were capable of making these hinge interactions, including partially saturated scaffolds. *See* EX1077.004; EX2028.0003-0004; EX2023, Formula I (1:65-2:6), Formula II (2:29-37), Formula III (2:56-65), 53:1-103:38 (reporting 85 example structures with partially saturated 5:6 fused scaffolds and corresponding inhibition activity against two kinases); EX2026, claim 1, claim 10, [0023], [0076], [Abstract] (BTKIs with partially

saturated scaffolds); EX2027, Examples 16(1), 16(2), 16(3), 21, 21(1), 25(1), 32, 32(1) (BTKIs with scaffolds having additional substitutions).

149. As an example of structures for binding to the BTK active site, the specification teaches substituted 5:6 fused heterocyclic scaffolds (both unsaturated and partially saturated):



EX1001, 62:44-63:20. These examples reinforce the suitability of the “typical” 5:6 heterocyclic ring structure as a component of the hinge-binding element, as incorporated into the Challenged Claims in the requirements for Z’. *See* EX1003, ¶32. Moreover, the three substitutions of these examples reinforce the requirements of the Challenged Claims. Formula E teaches that one of these substitutions will be the linker-warhead. A second substitution is the phenoxyphenyl, as emphasized and taught by the specification and reinforced by a POSA’s understanding in 2011 of the specification’s phenoxyphenyl group binding within BTK’s back-pocket.

The third substitution on the specification's example scaffolds provides an opportunity for H-bond donor/acceptor structural elements, consistent with a POSA's understanding in 2011 of the requirements for binding to the active site as necessitating one to three H-bonds with specific amino acids of the kinase hinge.

b. The Specification's Z' Must Be Viewed in Light of POSA's Mature Understanding of Kinase Hinge Binding in 2011

150. The Challenged Claims require an irreversible inhibitor of BTK that includes a Z'-scaffold that binds to the BTK hinge region, and specific, required substituents on Z': the phenoxyphenyl group binding to the hydrophobic back pocket and the linker-warhead covalently binding to Cys481. A POSA reading the specification in 2011 would have understood that the Z'-scaffold needs to allow for the Challenged Claims' specific fixed substituents to orient properly to bind BTK.

151. First, as I have explained, in 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that Cys481 can be targeted by different linker-warhead trajectories because Cys481 can rotate and is solvent-exposed. *See supra* §§VI.D.1, VII.A.2, X.A.1.b. The need for the linker-warhead to be oriented generally towards Cys481 would limit the scope of acceptable Z'-scaffolds.

152. Second, as I have also explained, in 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that the phenoxyphenyl group would need to be oriented to allow for binding within BTK's hydrophobic back pocket, which would limit the scope of acceptable Z'-scaffolds. *See supra* §§VI.D.2, VII.A.3, X.A.1.c. The relationship between the phenoxyphenyl and atoms involved in H-bonding to the hinge was illustrated with the crystal structure of Marcotte. *See* EX2001 (PDB: 3GEN); *supra* §VII.B.2. Moreover, as discussed above, the specification, in combination with the knowledge in the art in 2011, directs the inclusion of a phenoxyphenyl moiety appended to the hinge-binding element to bind within BTK's back-pocket (specificity pocket) because *every example species* includes the phenoxyphenyl moiety. *See supra* §X.A.1.c. Accordingly, I specifically disagree with Dr. Showalter's assessment that the specification and Formula E only teach "*potentially* including a hydrophobic moiety [phenoxyphenyl]." EX1003, ¶208 (emphasis added).

153. As I have explained, in 2011, a POSA reading the '803 Patent to identify ibrutinib-like BTKIs for use in the claimed method would have used virtual docking to aid in identifying irreversible ibrutinib-like BTKIs. *See supra* §VII.B; *see also* EX2018, 52:12-53:4, 117:10-21, 171:18-173:16, 177:10-179:9. Therefore, a POSA reading the '803 Patent would have been able to visualize the

Z'-scaffolds that satisfy the need for H-bonds to the hinge and the ability for the phenoxyphenyl to occupy the hydrophobic back pocket and for the linker-warhead to covalently bind to Cys481.

3. Dr. Showalter's Opinions are Unsupported

a. Dr. Showalter's Opinion that Hinge-Binding Was Unpredictable Is Contradicted by the Knowledge in the Art in 2011

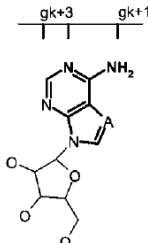
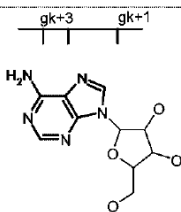
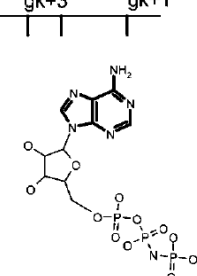
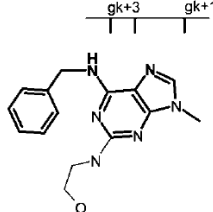
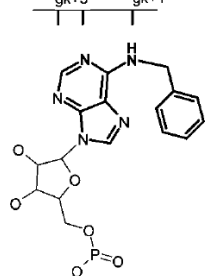
154. Dr. Showalter opines that the structure-activity relationship for the Z'-scaffolds binding to BTK was unpredictable in June 2011. *E.g.*, EX1003, ¶¶59-60, 65-66, 70, 76, 240, 242, 254-256, 279. In particular, Dr. Showalter opines that “while the Z'-structure is expected to engage the ATP-binding site of Btk's kinase domain, its effects on the Btk binding interactions are highly unpredictable.” EX1003, ¶75. Dr. Showalter further opines that “as of June 2010/2011, there was a 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. In support for these opinions, Dr. Showalter primarily refers to Ghose (EX1052), Garuti (EX1049), U.S. Patent Application Publication No. 2020/0140432 (“'432 Publication”) (EX1036); Pan (EX1060), Honigberg (EX1055), Brullo (EX1044), and Zhang 2021 (EX1076). *E.g.*, EX1003, ¶¶59-60, 65-66, 70, 76, 240, 242, 254-256, 279. I disagree with Dr. Showalter's opinions.

Initially, Dr. Showalter fails to cite Marcotte, which provides an important part of the foundation for the significant structure-function relationship for ibrutinib-like irreversible BTKIs for use in the claimed method. Moreover, Dr. Showalter misconstrues and ignores the teachings of the references on which he relies. These references actually **support** that a POSA reading the '803 Patent in 2011 would have understood the structure-activity relationship for ibrutinib-like irreversible BTKIs and the structure-function relationship for binding of such inhibitors to the highly conserved kinase hinge.

155. **First**, Dr. Showalter opines that Ghose shows that “changing the substitution pattern of the Z’-structure of a kinase inhibitor can unpredictably affect how the Z’-structure of the kinase inhibitor is oriented in the kinase domain, which further determines the bioactive orientation of the kinase inhibitor.” EX1003, ¶65 (citing EX1052.002-010). However, a POSA in 2011 reading the '803 Patent to identify additional ibrutinib-like irreversible BTKIs would have understood that Ghose teaches the exact opposite. In a section titled “***Empirical Rules to Predict Hinge Binding Orientation***,” explaining that it is “***straightforward***” to identify the moieties of a kinase inhibitor most likely to be involved in hinge binding. EX1052.019 (emphases added). Ghose further explains that hinge binding could be “categorized in terms of the ligand core structure and ***a few simple empirical rules***.” EX1052.020 (emphasis added). Ghose also teaches that because “[m]ost

parts of the ATP binding site show limited movement,” “through an analysis of the binding modes of different types of kinase ligands, *one can anticipate the binding mode of a related ligand* with ‘kinase inhibitor features.’” EX1052.002 (emphasis added). Ghose states that “[s]uch an analysis is extremely useful in deciding, for instance, where to place a hydrogen acceptor or donor atom, install a solubilizing group, or include a hydrophobic modification.” EX1052.002; *see also* EX2018, 122:15-125:8. Therefore, applying Ghose to the teaching of the ’803 Patent, Ghose expressly informs a POSA of how to *predict* hinge binding of additional Z'-scaffolds—teaching a POSA exactly what Dr. Showalter claims is unpredictable.

156. Dr. Showalter also relies on Ghose’s Table 2, opining that “subtle changes in the substitution pattern of the Z’-structure” can “present distinct orientations” in “how the Z’-structure of the kinase inhibitor is oriented in the kinase domain.” EX1003, ¶65 (citing EX1052, Tbl. 2 (.007-010)). However, Dr. Showalter crops Ghose’s Table 2 and does not provide the full context. As shown below in some of the uncropped entries from Ghose’s Table 2, the “distinct orientations” are due to structural differences among different specific kinases (with specific protein structures), not changes in the substitution pattern of the Z’-scaffold.

Scaffold	Most Common Binding Mode Illustrated in 2D ²	Frequency in PDB ³	Unique Kinases Entries	Kinases (PDB ID)
1		89	40	ABL(2g2f, 2g2i), ABL1(2g1t), ACK(1u54), AKT2(1o6k, 1o6l), CDK2(1b38, 1b39, 1fin, 1fq1, 1gy3, 1hek, 1jst, 1qmz, 2ceh, 2ejm), CDK7(1ua2), CHK2(2cn5), CSNK1(1csn), CSNK1G2(2c47), CSNK2A(1daw, 1ds5, 1lp4), CSNK2A1(1pjk, 1ymi), DAPK1(1igl, 1jkk, 1jkl), EPHA2(1mqb), EPHB2(1jpa), FAK1(1mp8), GCN2(1zy5, 1zyd), GSK3B(1j1b, 1j1c, 1o9u, 1pyx), HCK(1ad5), IGF1R(1jqh, 1k3a), INSR(1gag, 1i44, 1ir3, 1rqg), KIT(1pkg), LCK(1qpc), MAP2K1(1s9j), MAP2K2(1s9i), MAPK1(1goi), MAPK10(1jnk), MAPK12(1cm8), MAPKAPK2(1ny3), PDPK1(1h1w, 2biy), PHKB(1phk, 1ql6), PIM1(1xrl, 1yi4, 1yxt), PKNB(1mru, 1o6y), PRKACA(1atp, 1bkx, 1cdk, 1fmo, 1jbp, 1l3r, 1q24, 1rdq, 1u7e), PRKR(2a19), RIO1(1zp9, 1ztf, 1zth), RIO2(1tqm, 1tqp, 1zao, 1zar), SKY1(1q8y, 1q97, 1q99), SPRK1(1wbp), STK6(1mq4, 1muo, 1ol5, 1ol6, 1ol7), TAO2(1u5r)
1a		1	1	PIM1(1yxu)
1b		1	1	PIM(2bzk)
5		5	3	CDK2(1g5s, 1w0x, 2a4l), CDK5(1unl), MAPK1(4erk)
5a		1	1	SRCK(1ksw)

EX1052, Tbl. 2 (.007-008) (scaffolds 1, 1a, 1b; 5, 5a) (excerpted); *see also* EX1052.003, .005. In fact, Ghose teaches that “[i]t is reasonable to encounter different binding modes” among different kinases due to specific protein

structures. EX1052.003. As an example, when discussing PIM1 kinase (PDB: 1yxu), Ghose explains that “[i]t is reasonable to encounter different binding modes for PIM1 bound ligands because the only hydrogen bond donor residue (gk+3, Figure 2) is missing with a proline in this position.” EX1052.003; *see also* EX2018, 117:22-121:9. And as another example, when discussing the different binding modes for scaffolds 5 and 5a, Ghose explains that these different binding modes are “likely due to the gatekeeper being replaced by Gly” in SRC kinase. EX1052.005.

157. Additionally, even where substitution patterns of the Z'-scaffold do play a role in the differences in hinge binding, Ghose teaches that binding to the hinge is nevertheless predictable. As an example, Ghose explains that within fifteen related hinge-binding scaffolds, “[a] large substituent in the 8-position flipped the ring.” EX1052.003 (referring to Table 2, 2a). However, contrary to Dr. Showalter's opinion, Ghose does not contend that this would be unpredictable. Rather, Ghose teaches that “through an analysis of the binding modes of different types of kinase ligands,” a POSA would have been able to “anticipate the binding mode of a related ligand with ‘kinase inhibitor features.’” EX1052.002. Ghose and its tables show how informed a POSA would have been in 2011 of the significant structural information concerning how numerous scaffolds orient and bind within the hinge region of numerous kinases.

158. **Second**, Dr. Showalter opines that Garuti supports that “there was a 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 (citing EX1049.001); *see also* EX1003, ¶¶60, 254. However, consistent with the teachings of the ’803 Patent, Garuti teaches the significant understanding in 2011 of the structure-function relationship for targeting BTK’s Cys481. Garuti explains how to select an appropriate structure to allow for covalent bonding with Cys481 **and** teaches the importance of H-bonding for selecting a scaffold to bind with the hinge region. Specifically, Garuti teaches that “important parameters” include “the corrected orientation of the Michael acceptor toward the cysteine and a short distance” to the cysteine side chain. EX1049.001. Garuti further explains that hinge-binding interactions place the warhead in the correct position to bind with the cysteine residue of the kinase. *See id.* Garuti teaches that, with regards to hinge binding, various scaffolds, including heterocyclic scaffolds, have been used for inhibitors and that these scaffolds “form hydrogen bonding with the hinge region.” *Id.*

159. **Third**, Dr. Showalter opines that the **post-priority** ’432 Publication supports that “substitutions on the Z’-structure have an unpredictable effect on Btk inhibition, indicating that they likewise have an unpredictable effect on irreversible

binding.” EX1003, ¶279 (citing EX1036); *see also* EX1003, ¶76 (citing EX1036). In rendering his opinion, Dr. Showalter points to Z'-scaffolds that he contends fall within the genus of the claims, with varying IC₅₀ values. EX1003, ¶76 (citing EX1036). However, the '432 Publication does not support Dr. Showalter's opinions. The '432 Publication shows that structures falling within the genus of the Challenged Claims are BTKIs, with potent IC₅₀ ranging from 1-30 nM. *See* EX1036.011-083 (example structures), .084-085 (IC₅₀ values). Accordingly, the '432 Publication confirms that structures with common structural features of the genus impart the claimed function of BTK inhibition. Dr. Showalter appears to (illogically) equate these modest differences in potency with “unpredictability.” Neither the '432 Publication or Dr. Showalter mentions approaches that were or might have been employed to predict these differences, much less their failure to do so. And in fact, I understand that when asked about these structures from the '432 Publication at his deposition, Dr. Showalter admitted that the structures would have been viewed by a POSA in 2011 as “potent” BTK inhibitors. *See* EX2018, 130:7-132:8.

160. ***Fourth***, Dr. Showalter opines that the Pan and Honigberg references, which include ibrutinib inventors as authors, support a “limited understanding” of the structure-function relationship, including the covalent bonding between the warhead and Cys481 and the H-bonding between the scaffold and hinge region

residues. EX1003, ¶240 (citing EX1060.001-002; EX1055.004). However, neither Pan nor Honigberg shows that there was a “limited understanding” of the structure-function relationship. As I have explained, Pan reports that Cys481 in BTK is “a nucleophilic site, which could potentially form a covalent complex between Btk and an electrophilic inhibitor.” EX1060.001; *see also supra* §VII.A.1. Pan also “confirm[s] the irreversibility” of the tested BTKIs using two methods: “1) after recombinant Btk was pretreated with compounds, its activity was not recovered by multiple washings with inhibitor-free medium; and 2) a major peak was observed by mass spectrometry corresponding to the molecular weight of a 1:1 covalent complex between compound 4 and Btk.” EX1060.001-002; *see also supra* §VII.A.1. A POSA, having the ibrutinib-like binding mode from Marcotte, would understand that the irreversible inhibitors in Pan covalently bind BTK’s Cys481.

161. As for Honigberg, there is nothing in Honigberg, much less at Dr. Showalter’s cited page (EX1055.004), reporting anything about the “limited understanding” of the structure-function relationship of BTK inhibition with ibrutinib-like structures. Rather, Honigberg reports preclinical data showing ibrutinib’s BTK inhibitor activity, as well as its selectivity for BTK in the context of a complex cellular proteome. EX1055.004.

162. ***Fifth***, Dr. Showalter opines that two ***post-priority*** references—Brullo and Zhang 2021—report the crystallography data for BTK-ibrutinib (PDB: 5P9J)

and BTK-zanubrutinib (PDB: 6J6M), which allegedly show that “Btk inhibition involves complicated interactions that are highly unpredictable.” EX1003, ¶240 (citing EX1044 and EX1076); *see also* EX1003, ¶¶59, 70. I disagree. Neither Brullo nor Zhang 2021 describe the interactions as “highly unpredictable.” Brullo and Zhang 2021 simply summarize the crystal structure. In my opinion, nothing about the crystal structures nor their summaries of this data suggests unpredictability or surprising results. In fact, as Dr. Showalter conceded in his deposition, Brullo states 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 which include the cation- π contact between the phenoxyphenyl ring and Lys430 side chain and the hydrogen bonds with Met477 and Glu475 backbones.” EX1044.003 (emphasis added); EX2018, 115:12-116:15 (Dr. Showalter admitting that ibrutinib and zanubrutinib have “similar[]” binding patterns). (Notably, the “hydrogen bonds with Met477 and Glu475 backbones” are the prototypical one to three H-bonds with the GK+1 (Glu475) and GK+3 (Met477) kinase hinge residues that mimic the interactions of the kinase with the adenine of ATP and which I have discussed at length. *See supra* §§VI.D.3, VII.A.4-VII.A.5, X.A.2.a.). And indeed, despite admitting that Marcotte would be “helpful” to a POSA, EX2018, 43:20-44:9, in his declaration, Dr. Showalter

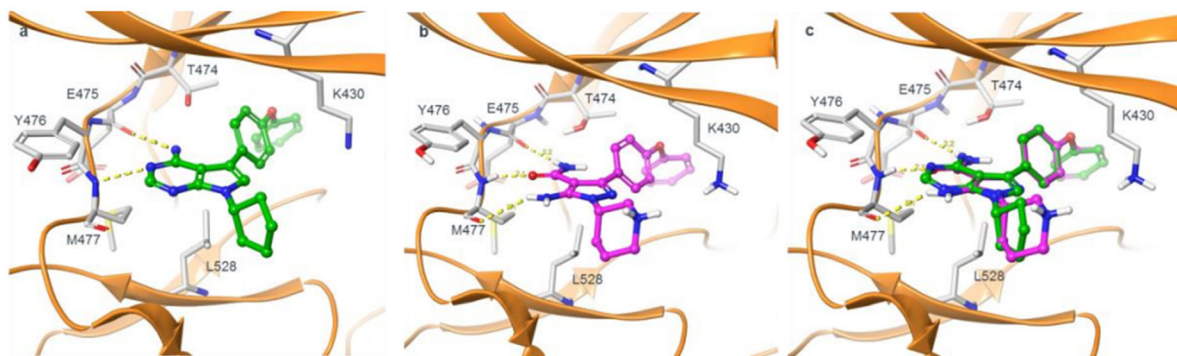
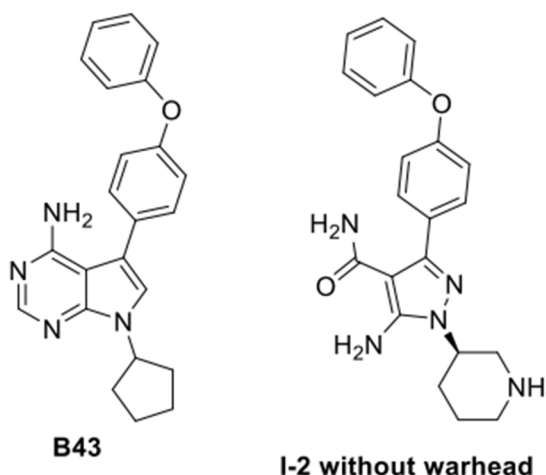
ignores the crystal structure, which similarly shows significant overlap in the binding with ibrutinib. EX2001 (PDB: 3GEN); *see supra* §VII.B.2.

163. Additionally, with respect to Brullo, Dr. Showalter interprets Brullo's ligplot diagrams to suggest that the interactions between ibrutinib and zanubrutinib are different, but that interpretation conflicts with Brullo's *own interpretations* of the "similar bioactive conformations" within the BTK active site and that the two complexes are "stabilized by similar interactions." EX1003, ¶63; EX1044.003. Moreover, the "ligplot" diagrams reproduced by Dr. Showalter appear to be "ligand interaction diagrams" prepared using the program Maestro (Schrodinger). Like "ligplot" diagrams prepared by the programs Ligplot and Ligplot+, these are 2D representations of three-dimensional interactions. Unlike Ligplot+, which I have used to compare the structure-function relationships of ibrutinib and zanubrutinib above (¶96), to my knowledge, Maestro does not offer the possibility of directly comparing binding of two or more ligands in a similar manner. Thus, the consistency in positions of the residues is not maintained in panels C and D of Figure 2 of Brullo et al. That said, careful inspection of these ligand interaction diagrams reveals that they provide the same information and identify the same interacting residues as in the Ligplot+ diagram above (with minor differences owing to the 4.0Å default cutoff in Maestro versus 3.9Å in Ligplot+). Thus, considering these diagrams, the Ligplot+ diagrams that I generated above, and the

overlaid BTK-ibrutinib and BTK-zanubrutinib crystal structures (*see supra* §VII.A.5), I agree with Brullo that “ibrutinib and zanubrutinib share similar bioactive conformations within the wild-type Btk binding site” and that “beside the covalent bond with Cys481, the two complexes are mainly stabilized by similar interactions which include the cation- π contact between the phenoxyphenyl ring and Lys430 side chain and the hydrogen bonds with Met477 and Glu475 backbones.” EX1044.003. Finally, Dr. Showalter suggests that different scientific groups disagree, based on the same crystallography data, as to whether zanubrutinib forms two versus three hydrogen bonds with the hinge, and goes on to relate this to the “complexity and unpredictability of the interactions involved.” EX1003, ¶63. The “disagreement” Dr. Showalter suggests arises not from actual differences in scientific opinion, but likely from differences in defaults used to define hydrogen bonds in the software used to analyze and illustrate the interactions (where one group used a longish distance between heavy atoms of about 3.3Å).

164. I further disagree that this has anything to do with complexity or predictability – the hinge binding interactions of zanubrutinib as seen in the crystal structure match those expected and predicted by docking the structure (without the warhead) into the structure of Marcotte using modeling capabilities available in 2011. *See supra* §VII.B.2. Similar to what a POSA would have done in 2011,

Petitioner itself used the Marcotte 3GEN crystal structure to predict how a zanubrutinib analog would bind to BTK. *See* EX2039, Fig. 1 (.0003-0004); EX2018, 128:16-130:6. As shown below, Petitioner's modeling shows precise alignment between these structural features of Marcotte and zanubrutinib, EX2039, Fig. 1 (.0003-0004), which were later confirmed in the crystal structure of zanubrutinib bound to BTK. *Compare* EX1044, Fig. 2B (.004).



EX2039, Fig. 1 (.0003-0004).

165. *Sixth*, Dr. Showalter *cites no support* for his opinion that “a POSA would not have been able to predict how other Z’-structures, 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. In making this unsupported statement, Dr. Showalter also does not address how his own cited reference (Ghose) reports diverse fused heterocyclic ring systems that productively bind within the hinge. For example, Ghose’s Table 3 reports hinge-binding scaffolds that include partially saturated and non-aromatic heterocycles that productively bind within the hinge. EX1052.003, Tbl. 3 (.012-013) (scaffolds 30, 31, 33, 37, 39), .017. I understand that when Dr. Showalter later examined Ghose’s Table 3 at his deposition, Dr. Showalter admitted that Ghose’s Table 3 reports many hinge-binding scaffolds, including scaffolds with partially non-aromatic heterocycles that productively bind within the hinge. EX2018, 75:10-78:7. Moreover, as noted above, Petitioner, using structural data and tools that were widely available to a POSA in June 2011, accurately predicted the binding mode of a compound having zanubrutinib’s hinge-binding elements, phenoxyphenyl, and linker. *See* EX2039, Fig. 1 (.0003-0004); *see also* EX2018, 128:16-130:6. Thus, I strongly disagree that the binding mode of zanubrutinib was unpredictable to a POSA in 2011.

b. Dr. Showalter Presents Flawed Analyses Regarding the Specification's Description of the Irreversible Inhibitors of the Challenged Claims

(1) Contrary to Dr. Showalter's Assertions, Zanubrutinib Is an Adenine Mimic Like Ibrutinib

166. Dr. Showalter opines that the claims are not sufficiently supported by the specification because “[t]he disclosed structures fail to describe any BTKIs that are not adenine-mimetic.” EX1003, ¶¶190, 193. He additionally opines that zanubrutinib does not mimic adenine, and that zanubrutinib is not sufficiently supported by the specification. EX1003, ¶¶50-52, 194-207.

167. In my opinion, a POSA would use “adenine mimic” to refer to hinge-binding scaffolds that mimic the interactions of the adenine portion of ATP, not limited to structures that are isosteric (or approximately isosteric) with adenine, as Dr. Showalter narrowly applies. Nevertheless, Dr. Showalter’s focus on “adenine mimics” is artificial. As I have explained, a POSA’s focus in understanding the structure of Z’ of the specification would be the H-bonds that the Z’ would form with the kinase hinge. *See supra* §§VI.D.3, VII.A.4, X.A.2. In this regard, contrary to Dr. Showalter’s opinions, ibrutinib and zanubrutinib bind to BTK the same way from a structural perspective: largely overlapping placement in three-dimensional space and both making the key H-bond interactions with BTK residues that adenine makes. *See supra* §VII.A.5; *see also supra* §VII.B.2. In fact, zanubrutinib makes

H-bonds with the hinge of BTK that correspond to those made by ibrutinib and adenine. *See supra* §VII.A.5; *see also supra* §VII.B.2. Zanubrutinib is recognized to be an adenine analogue, including by Petitioner itself. *See supra* §VII.A.5. In a 2023 publication, Petitioner admitted that the “***five approved BTK inhibitors all have similar hinge binding to ATP***. Therefore, we wanted to differentiate from the five approved BTK inhibitors by aiming for very high selectivity to minimize kinase off-target effects while maintaining the similar hinge binding to ATP, which is very challenging.” EX2020.0002 (emphasis added); *see also* EX1076.005 (“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.”), Tbl. 1 (.011) (including zanubrutinib in review); *supra* §VII.A.5; EX2018, 82:10-84:4, 84:13-85:21, 93:7-20, 115:12-116:15. Accordingly, Dr. Showalter’s opinion that zanubrutinib’s Z’-scaffold “does not attempt to mimic adenine” is incorrect. EX1003, ¶52.

168. I disagree with Dr. Showalter that differences in aromaticity of the 5:6 rings of zanubrutinib on the one hand and ibrutinib and adenine on the other are relevant to how a POSA in 2011 would have understood zanubrutinib to be an adenine mimic. EX1003, ¶¶51-52. Again, the central focus for a POSA reading the ’803 Patent to identify ibrutinib-like BTKIs for use in the claimed method is the ability of a Z’-scaffold to form appropriate H-bonds with the BTK hinge and then

orient the phenoxyphenyl and linker-warhead substituents correctly. EX1077.003; EX1052.020; *supra* §X.A.1-X.A.2; *see also supra* §§VI.D, VII.A.1-VII.A.4. The non-aromaticity of the 6-membered ring of zanubrutinib is irrelevant to its recapitulation of the H-bonds made by adenine with the kinase hinge—it is the amide group of zanubrutinib that makes the adenine-mimicking H-bonds, and this is not affected by the aromaticity of the six-membered ring. Furthermore, fused heterocyclic hinge-binding scaffolds where one of the rings is non-aromatic had been reported as of 2011. *See* EX2028, Fig. 5 (.0004) (disclosing a “highly potent, novel inhibitor[]” with a fused heterocyclic hinge-binding scaffold where one of the rings (7-membered ring) is **non-aromatic**); EX2023, 1:65-2:6, 53:1-103:38 (describing examples of 5:6 heterocyclic scaffolds where 6-membered ring is **non-aromatic**); EX2026, claims 1, 10 (claiming formulas (I) and (Ia) which contain a fused tri-heterocyclic hinge-binding scaffold where one of the rings (6-membered ring) is **non-aromatic**); EX1052.003, Tbl. 3 (.012-013) (scaffolds 30, 31, 33, 37, 39 are partially **non-aromatic**), .017; *see also supra* §VII.A.4.

169. While I agree with Dr. Showalter that ibrutinib and zanubrutinib have different H-bond donors/acceptors on their Z'-scaffold, I disagree that differences in which atoms of the irreversible BTKI participate in H-bonds with the kinase hinge is determinative of the ability to bind the hinge. EX1003, ¶¶61-62. A POSA reading the '803 Patent to identify ibrutinib-like BTKIs for use in the claimed

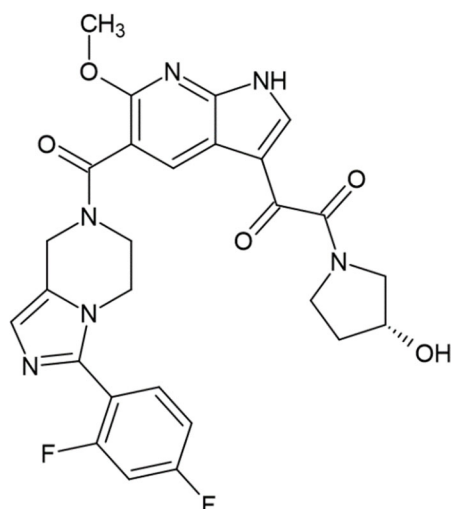
method would have been able to identify potential H-bond acceptors/donors in Z' based on chemical structure and consider the optimal geometry of these acceptors/donors based on the available structural information for BTK. *See supra* §§X.A.2, VI.D.3, VII.A.4, VII.B.2; EX2001 (PDB: 3GEN) (published detailed crystal structure of a reversible inhibitor with ibrutinib-like binding bound to the ATP active site). A POSA would have been aware that the commonality between hinge-binding elements in large collections of kinase inhibitors is not precise recapitulation of atomic structure, but whether there are “hydrogen donor–acceptor–donor atoms at certain distances from each other in the molecule as well as donor–acceptor and acceptor–donor pairs.” EX2028.0003. And as illustrated above (¶88), the diversity of known hinge-binding elements in BTKIs further confirms what a POSA in 2011 would have understood from the '803 Patent about the fungibility of hinge-binding elements. Moreover, a POSA in 2011 would have known that the claimed structures of Z' would be directed into productive orientation by virtue of the fixed elements of the claimed structures: the phenoxyphenyl occupying the hydrophobic back pocket and the linker-warhead covalently binding to Cys481. *See supra* §X.A.2.b; *see also supra* §VII.B.2.

(2) Dr. Showalter's Analysis of Genus Diversity Allegedly Not Represented by the Specification

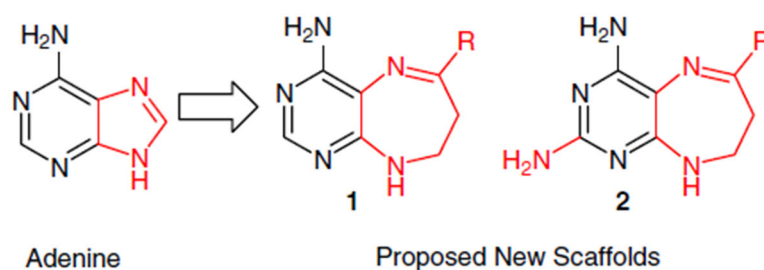
**Focuses on Irrelevant Differences Between
Ibrutinib and Zanubrutinib**

170. Dr. Showalter points to various differences in structure among species meeting the structural requirements of the compounds for use in the claimed methods as evidence of the diversity and breadth of the compounds within the genus. EX1003, Section VIII. A POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that the central focus for identifying an appropriate Z'-scaffold is the ability of the structure to form appropriate H-bonds with the kinase hinge and then orient the phenoxyphenyl and linker-warhead substituents correctly. *See supra* §X.A.1-X.A.2; EX1077.003; EX1052.020; *see also supra* §§VI.D, VII.A.1-VII.A.4, VII.B.2. Curiously, Dr. Showalter understands and even explicitly states that it is the overall structure of a BTKI that is important for its function in binding and inhibiting BTK including proper positioning of the linker-warhead groups for covalent bond formation with Cys481, EX1003, ¶39, but he proceeds to ignore this fact in much of his analysis. He highlights differences that have no direct connection to H-bonding with the kinase hinge or orientation of the fixed substituents and are therefore not determinative as to whether a Z'-scaffold of the '803 Patent would predictably bind to the hinge and properly position the phenoxyphenyl and linker-warhead substituents.

171. **First**, I disagree with Dr. Showalter that differences in the saturation state of ibrutinib and zanubrutinib are relevant to whether a Z'-scaffold would predictably bind to the hinge. EX1003, ¶¶40-41. Again, the central focus for a POSA reading the '803 Patent to identify ibrutinib-like BTKIs for use in the claimed method is the ability of the Z'-scaffold to form appropriate H-bonds with the kinase hinge and then orient the phenoxyphenyl and linker-warhead substituents correctly. *See supra* §§X.A.1-X.A.2; EX1077.003; EX1052.020; *see also supra* §§VI.D, VII.A.1-VII.A.4, VII.B.2. Consistent with what a POSA would have understood from the '803 Patent, a POSA in 2011 would have known from the art of partially saturated hinge-binding elements that were capable of fitting into the hinge region of BTK and other kinases. *See* EX2055 (PDB: 2QD9); EX2038, Fig. 1 (.0001); EX2053 (PDB: 1AGW); EX2026, claims 1, 10; EX1052.003, Tbl. 3 (.012-013) (scaffolds 30, 31, 33, 37, 39); EX2023, 1:65-2:6. For example, the *pre-priority* p38alpha MAP kinase inhibitor discloses a *partially saturated* hinge-binding element:

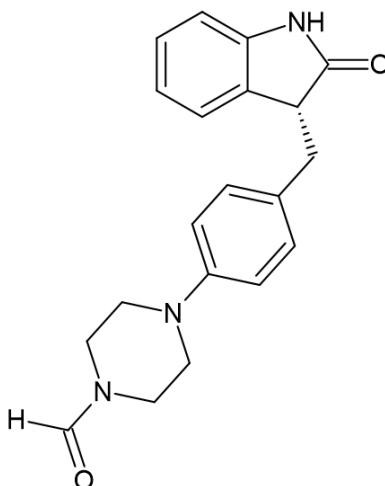


EX2055 (PDB: 2QD9).¹³ As another example, Gracias—a *pre-priority* reference—reports the design of new scaffolds for tyrosine kinase inhibitors and discloses a *partially saturated* hinge-binding element:



EX2038, Fig. 1 (.0001). As another example, the *pre-priority* FGFR1 inhibitor discloses a *partially saturated* hinge-binding element:

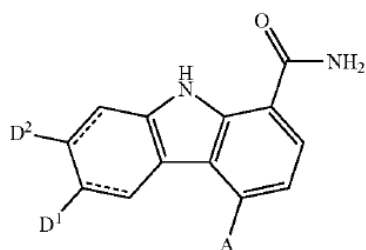
¹³ Compound structures were drawn by inserting the chemical name for the ligand into ChemDraw.



EX2053 (PDB: 1AGW). And as another example, the pre-priority BTKIs claimed in U.S. Patent Application Publication No. 2010/0160303 contain a *partially saturated* hinge-binding element:

What is claimed is:

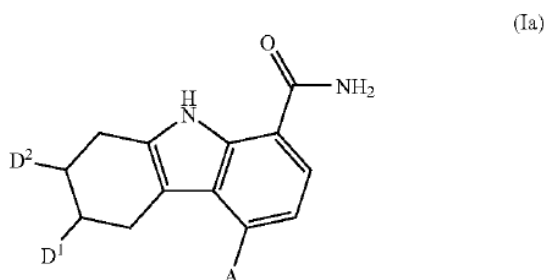
1. A compound according to formula (I):



(I)

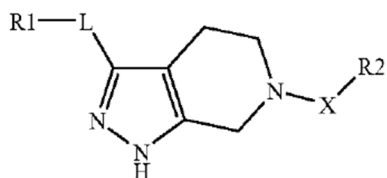
or a salt thereof, wherein
the dashed lines are either single or double bonds;

10. The compound of claim 9, wherein a compound of formula (I) is (Ia) or (Ib)



EX2026, claim 1 (formula (I)), claim 10 (formula (Ia)).

172. The '820 Patent further describes a partially saturated hinge-binding 5:6 fused heterocyclic scaffold with a partially saturated 6-membered ring:

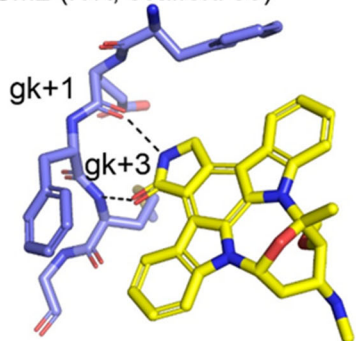


EX2023, 1:65-2:6.

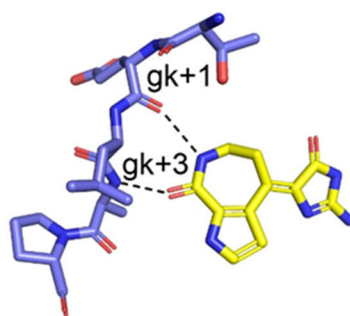
173. Further, as Dr. Showalter admitted in his deposition, Dr. Showalter's cited reference Ghose expressly identifies at least five non-aromatic hinge-binding elements, including a subset of those mentioned above, and provides Protein Data Bank accession codes for representative examples. EX1052.003, Tbl. 3 (.012-013) (scaffolds 30, 31, 33, 37, 39); EX2018, 75:10-78:7. A subset of these is illustrated in the figure below. Notably, these non-aromatic scaffolds include that of staurosporine, a widely known natural product that inhibits many kinases. Additionally, these examples include both planar and non-planar hinge-binding

elements, including a “matched pair” of compounds bound to p38alpha with one nitrogen (non-planar) versus two nitrogens (planar) in the non-aromatic ring that H-bonds with the hinge (1OVE versus 1M7Q). Note that despite their differences in heteroatoms and planarity, these compounds nevertheless bind to p38alpha in a closely similar manner.

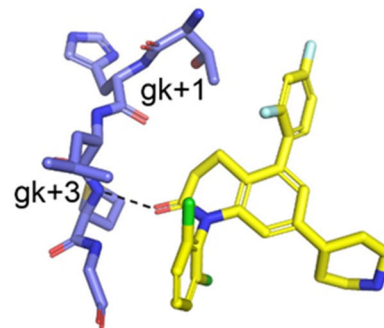
1SM2 (ITK, scaffold 30)



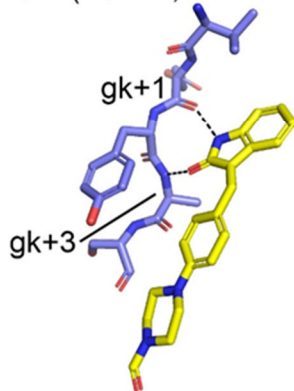
1U4D (ACK, scaffold 37)



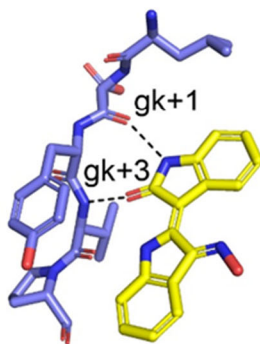
1OVE (P38α, scaffold 33)



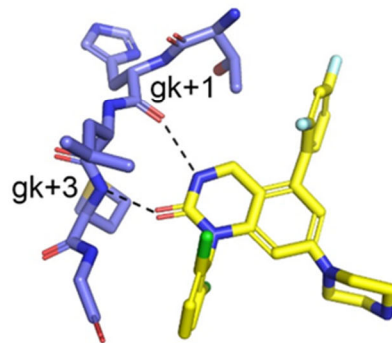
1AGW (FGFR1, scaffold 31)



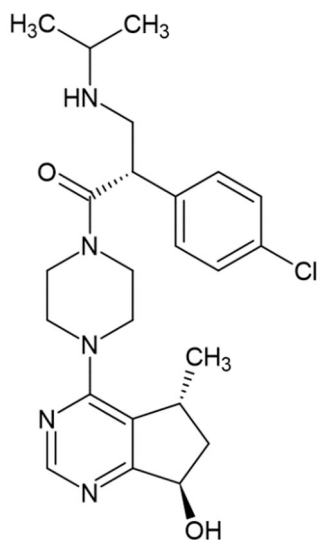
1Q41 (GSK3β, scaffold 39)



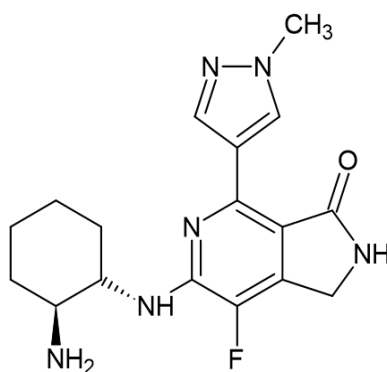
1M7Q (P38α, scaffold 33)



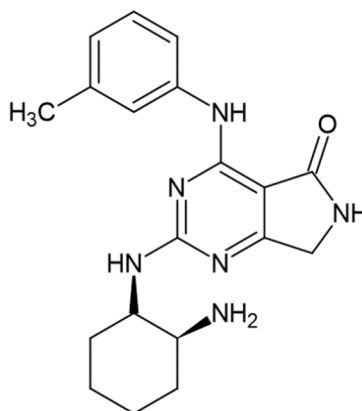
174. Moreover, other later kinase inhibitor hinge binding scaffolds further confirm what a POSA would have understood in 2011 from the '803 Patent and prior art: that partially saturated structures allow for productive H-bonds to the hinge. Some examples are shown below:



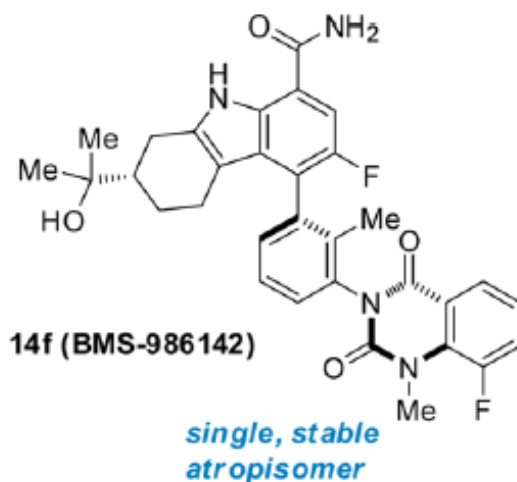
EX2049 (PDB: 4EKL).



EX2046 (PDB: 5TR6).



EX2046 (PDB: 5TT7).



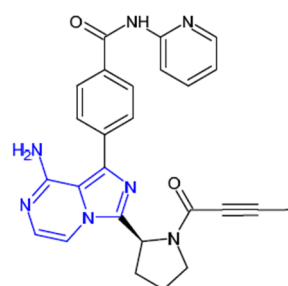
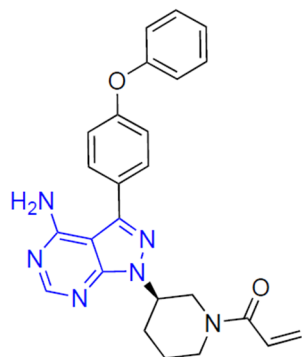
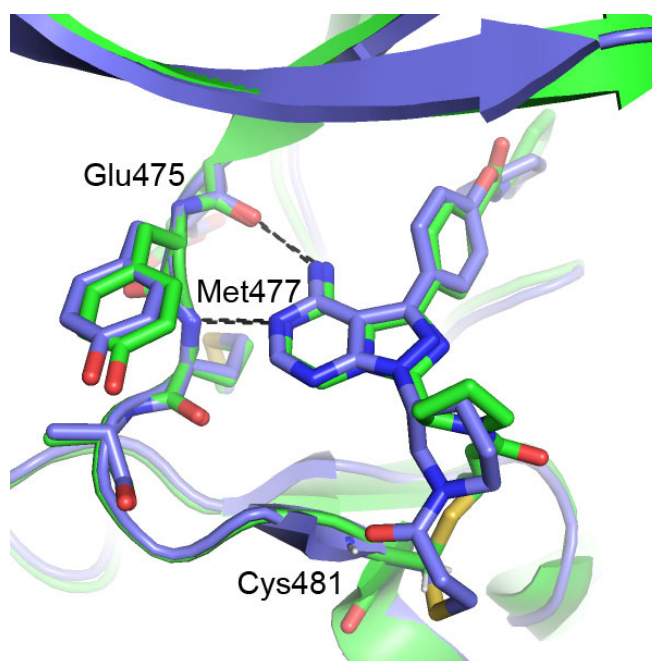
EX2061, Fig. 3 (.0003) (excerpted) (PDB: 5T18).

175. Additionally, in alleging the importance of aromaticity (or saturation state) of hinge-binding components, Dr. Showalter repeatedly emphasizes their planarity. EX1003, ¶¶41, 50-52. But these partially saturated structures are not fully planar, including formula (Ia) of claim 10 of US 2010/0160303, as well as compound 4EKL in which the hydroxyl substituent of the saturated five-membered ring is a hydrogen bond donor to the kinase hinge. EX2026, claim 10 (formula (Ia)); EX2049 (PDB: 4EKL). The '820 Patent further discloses 85 example kinase inhibitor compounds having a 5:6 heterocyclic scaffold where the 6-membered ring is saturated, and thus not planar, similar to that in zanubrutinib. EX2023, 53:1-103:38.

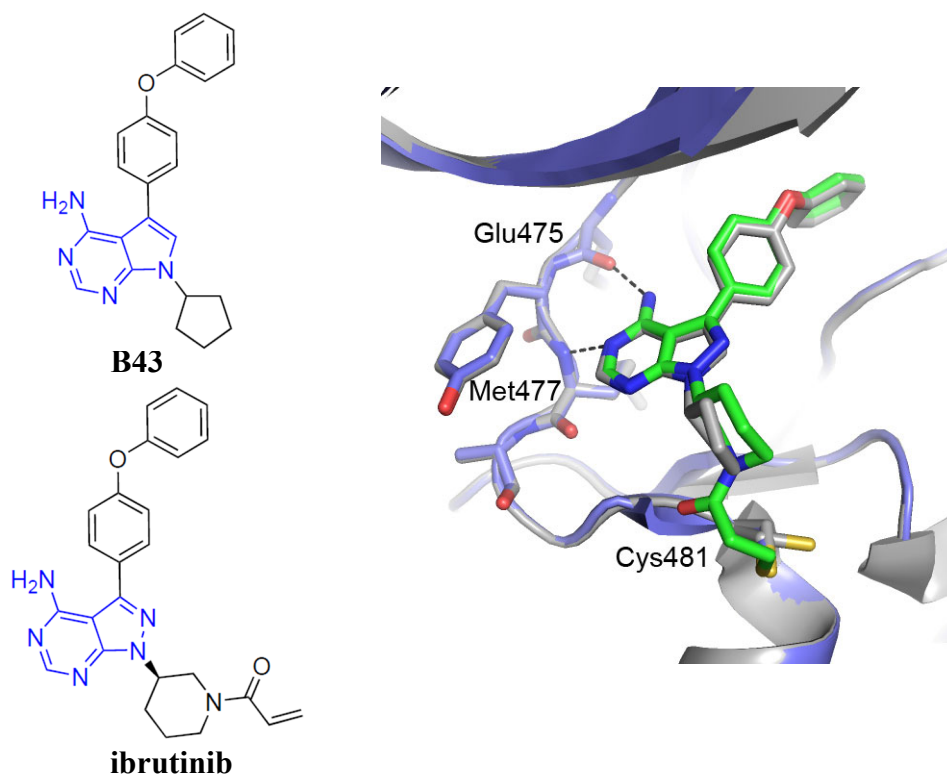
176. **Second**, I disagree with Dr. Showalter that the differences in heteroatom patterns of the heterocyclic ring systems of ibrutinib and zanubrutinib are determinative as to whether the Z'-scaffold of the '803 Patent would

predictably bind to the hinge. EX1003, ¶42. As I have explained, a POSA in 2011 would have understood that the relevance of these heteroatom substitution patterns of the Z'-scaffold is limited to its impact on the ability of the structure to provide suitable H-bond donor/acceptors for binding to the BTK hinge region and to allow substitution for proper placement of the phenoxyphenyl and linker-warhead groups. *See supra* §X.A.1-X.A.2, *see also supra* §§VI.D, VII.A.1-VII.A.4, VII.B.2. Indeed, the specification teaches heterocyclic scaffolds with different heteroatom substitution patterns. EX1001, 62:44-63:20.

177. Further, another irreversible BTK inhibitor, acalabrutinib, has a different heteroatom substitution pattern of its heterocyclic ring system as compared to ibrutinib, but the heteroatom and ring substituents that hydrogen bond to the hinge are the same as in ibrutinib and it binds identically to the BTK hinge region as compared to ibrutinib. An overlay of BTK-acalabrutinib (PDB: 8FD9) and BTK-ibrutinib (PDB: 5P9J) is shown below. Acalabrutinib is shown with carbon atoms colored green, and ibrutinib is shown with carbon atoms colored blue.

**acalabrutinib****ibrutinib**

As another example, Marcotte has a different heteroatom substitution pattern of its heterocyclic ring system as compared to ibrutinib, but binds identically to the BTK hinge region as compared to ibrutinib. *See* EX2001.0005. An overlay of the B43 from Marcotte bound in the BTK active site (PDB: 3GEN) and BTK-ibrutinib (PDB: 5P9J) is shown below. B43 from Marcotte is shown with carbon atoms colored gray, and ibrutinib is shown with carbon atoms colored green.



178. **Third**, the distinction in the placement of the phenoxyphenyl and linker-warhead substituents on the heterocyclic ring systems of ibrutinib and zanubrutinib is not in itself determinative of binding to BTK. EX1003, ¶¶46-47. A POSA reading the '803 Patent to identify ibrutinib-like BTKIs for use in the claimed method would understand the relevant comparison is not based on the numbering of the specific heterocyclic ring systems of the two compounds, but rather the orientation in space of the phenoxyphenyl and linker-warhead *relative to the compounds' H-bond acceptors/donors*, which is preserved across the two compounds. See *supra* §X.A.1-X.A.2; see also *supra* §§VI.D, VII.A. Indeed, as I have explained, ibrutinib and zanubrutinib bind to BTK the same way from a

structural perspective: largely overlapping placement in three-dimensional space and both making the key H-bond interactions with BTK residues that adenine makes. *See supra* §VII.A.5. As I have explained, a POSA in 2011 reading the '803 Patent would have used virtual docking to identify the **relevant** geometry and orientation of the phenoxyphenyl and linker-warhead substituents to bind to BTK's back pocket and covalently bind to Cys481, respectively. *See supra* §§VII.B.2, X.A.2.b.

179. **Fourth**, I disagree with Dr. Showalter that the difference in how the linkers of ibrutinib and zanubrutinib connect the Z'-scaffolds and the warheads is relevant and would mean that "[t]here would have been no basis to believe that BRUKINSA's warhead would reach the same location of Cys481 in BTK as IMBRUVICA." EX1003, ¶48; *see also* EX1003, ¶47. The relevant comparison is not based on the linker chirality of the two compounds. Again, a POSA reading the '803 Patent to identify ibrutinib-like BTKIs for use in the claimed method would understand the relevant comparison is instead the orientation in space of the phenoxyphenyl and linker-warhead **relative to the compounds' H-bond acceptors/donors**. *See supra* §X.A.1-X.A.2; *see also supra* §§VI.D, VII.A.1-VII.A.4. Additionally, a POSA in 2011 would have recognized from the '803 Patent and consistent teachings from the art that the Cys481 is not fixed, and would have therefore understood that there would be no requirement for zanubrutinib's

warhead to follow the same trajectory as ibrutinib. *See supra* §§VI.D.1, VII.A.2, X.A.1.b. And as I have explained, a POSA in 2011 reading the '803 Patent would have used virtual docking based on Marcotte to identify the **relevant** geometry and orientation of the phenoxyphenyl and linker-warhead substituents to bind to BTK's back pocket and covalently bind to Cys481, respectively. *See supra* §§VII.B.2, X.A.2.b. Contrary to Dr. Showalter's assertion, a POSA in 2011 would have been able to readily dock and confirm that despite differences in their linker-warhead attachments and chirality, ibrutinib and zanubrutinib can both orient their acrylamide warhead to react with Cys481, thereby preserving this aspect of the structure-function relationship as taught by the '803 Patent's specification. *See supra* §VII.B.2.

(3) Dr. Showalter Inflates the Breadth of Potential Z'-Scaffolds

180. I agree with Dr. Showalter that “a POSA would not check their common sense at the door” in considering the Z' component. EX1003, ¶176. However, I do not agree that Dr. Showalter has always taken such common sense into account in his analysis. Dr. Showalter opines that “the Structural Limitations are directed to billions of species, and the Challenged Claims as a whole are directed to potentially billions of species.” EX1003, ¶178; *see also* EX1003, Section VIII. I disagree. Notably, Dr. Showalter's opinions on breadth focus on the breadth of the potential **Z'-scaffolds in isolation**. *See* EX1003, Section VIII. In

doing so, Dr. Showalter inflates the breadth of the potential ibrutinib-like irreversible BTKIs in the claims.

181. By focusing on the potential Z'-scaffolds in isolation, Dr. Showalter *ignores* the required substituents on Z', namely, the linker-warhead and the phenoxyphenyl group. *See* EX1003, Section VIII. As I have explained, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that the linker-warhead needed to be oriented generally towards Cys481 in order to covalently bind and that the phenoxyphenyl group needed to be oriented to bind within BTK's hydrophobic back pocket to be used in the claimed methods. *See supra* §X.A.1-X.A.2. In 2011, a POSA would have further understood that these required substituents on Z'—and their orientations and the potential steric hindrance that results from adding the substituents—would *limit* the scope of acceptable Z'-scaffolds. *See supra* §X.A.2.b. And as I have also explained, in 2011, a POSA reading the '803 Patent would have known to use virtual docking with the Marcotte structure to predict which Z'-scaffolds would satisfy the need for H-bonds to the hinge *and* the ability for the phenoxyphenyl to occupy the hydrophobic back pocket and for the linker-warhead to covalently bind to Cys481. *See supra* §X.A.2.b; *see also supra* §VII.B.2. Dr. Showalter does not account for these required substituents, and therefore, does not fully visualize the scope of the compounds as a POSA would

have in 2011. Specifically, Dr. Showalter does not account for whether the Z'-scaffolds that he identified would actually satisfy the need for H-bonds to the hinge *and* the ability for the phenoxyphenyl to occupy the hydrophobic back pocket and for the linker-warhead to covalently bind to Cys481. *See* EX1003, Section VIII; *see also* EX2018, 151:11-152:16, 163:8-17. A POSA in 2011 would have known of the structural information of Marcotte (PDB: 3GEN) to use in virtual docking and modeling of the ibrutinib-like irreversible BTKIs of the claims. *See supra* §VII.B.2. And as I have explained, in 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have known to use virtual docking in the Marcotte 3GEN structure to predict which Z'-scaffolds would satisfy the need for H-bonds to the hinge and the ability for the phenoxyphenyl to occupy the hydrophobic back pocket and for the linker-warhead to covalently bind to Cys481, as taught by the '803 Patent. *See supra* §X.A.2.b; *see also supra* §VII.B.2. Accordingly, by viewing Z' in isolation, Dr. Showalter inflates the breadth of the potential ibrutinib-like irreversible BTKIs.

182. Additionally, Dr. Showalter opines that each “fused heterocyclic ring system[]” “allow[s] for a vast number of structural species due to the diversity of the optional substitutions present on the ring system.” EX1003, ¶159. To arrive at his large figure of potential Z'-scaffolds, Dr. Showalter opines that multiple substituents can be added to the ring system—even opining that “the number of

substitutions permitted by ‘optionally substituted’ *can be potentially infinite.*” EX1003, ¶162 (emphasis added). However, Dr. Showalter’s opinion defies rational drug design and common sense. A POSA reading the ’803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that the Z’ of the compound would *not* have been substituted to the degree that Dr. Showalter suggests—and certainly not “infinite[ly]” substituted. Adding too many substituents to the ring system would be nonsensical because this would lead to a potential steric clash and an inappropriately-sized small molecule for oral administration (*i.e.*, Lipinski’s rule of five would be violated). EX2018, 50:10-51:12 (Dr. Showalter admitting that a POSA would have known and found the Lipinski rules “helpful” in guiding the selection of properties for orally bioavailable compounds in 2011); *see also id.*, 146:13-15. Indeed, even adding *one* substituent to each of the seven Rs on a Z’-scaffold—let alone “infinite” substitutions—would violate Lipinski’s rule of five. *See* EX2012, ¶46; *see also id.*, ¶¶41-45. A POSA in 2011 might have considered additional substitutions to alter selectivity, potency, PK properties, etc., but would have considered them in light of the predicted binding mode and would have assessed whether they were likely to be tolerated with the aid of docking to the Marcotte structure. Because Dr. Showalter’s irrational and nonsensical substitutions opinion underlies his Z’

calculations, Dr. Showalter incorrectly inflates the breadth of compounds within the claims.

(4) Dr. Showalter's Belated Post-Priority References Support Predictability

183. I understand that after Dr. Showalter submitted his declaration in support of Petitioner's Petition, Dr. Showalter belatedly pointed to two post-priority references in his deposition that he claims meet the structural limitations of the Challenged Claims and are "inactive": U.S. Patent No. 10,358,446 ("446 Patent") and an ACS Medicinal Chemistry Letter ("Zhang 2020"). *See* EX2018, 12:11-15:12; EX2024; EX2063. I have reviewed these references and have identified three compounds in the '446 Patent and two compounds in Zhang 2020 that meet the structural limitations of the Challenged Claims. These compounds do not change my opinions and instead support the sophisticated structure-function relationship for ibrutinib-like BTKIs as of 2011, as taught by the '803 Patent.

184. I identified three compounds from the '446 Patent that meet the structural limitations of the Challenged Claims: compound 20, compound 30, and compound 122. EX2024.0027, .0031, .0061. The '446 Patent reports BTK inhibition of these compounds as IC_{50} ranges: compound 20 (10-100 nM), compound 30 (>10000 nM), and compound 122 (1000-10000 nM). *Id.*, .0118-0119. With an IC_{50} value in the 10-100 nM range, compound 20 is a potent inhibitor of BTK, confirming the common structural features of the Challenged Claims

result in BTK inhibition. As for compounds 30 and 122, docking into the Marcotte structure reveals these compounds as poor candidates for irreversibly inhibiting BTK as required by the claims. As I have explained, in 2011, a POSA reading the '803 Patent to identify ibrutinib-like BTKIs for use in the claimed method would have known to use virtual docking to predict which Z'-scaffolds for ibrutinib-like BTKIs would satisfy the need for H-bonds to the hinge and the ability for the phenoxyphenyl to occupy the hydrophobic back pocket and for the linker-warhead to covalently bind to Cys481. *See supra* §§X.A.2.b, VII.B.2. Docking with Maestro/Glide for Compound 30 did not yield a binding pose with the phenoxyphenyl and linker-warhead properly positioned in the BTK active site. For compound 122, one pose was obtained in which the phenoxyphenyl group was properly positioned and the linker-warhead was oriented toward Cys481, but the heterocyclic scaffold was not positioned to make even one H-bond to the hinge, resulting in a docking score that was markedly worse for Compound 122 as compared to Compound 20 (-6.3 for Compound 122 as compared to -8.2 for Compound 20).¹⁴ The best docking pose for Compound 30—which revealed the scaffold would not make any H-bonds to the BTK hinge residues—was even

¹⁴ A larger negative score indicates a more favorable docking. As a point of reference, ibrutinib docks with a score of -8.8 in this exercise.

worse, with a score of -5.5. Therefore, a POSA would have recognized that Compounds 30 and 122 were unlikely to productively bind to BTK to irreversibly inhibit it. Thus, the reported IC_{50} values for these compounds in the '466 Patent are not surprising. Based on the docking results, a POSA would have deprioritized these compounds for synthesis and further consideration—appropriately, as it turned out. As such, the compounds and associated activities disclosed in this reference actually support the sophisticated structure-function relationship for ibrutinib-like BTKIs in 2011, as taught by the '803 Patent.

185. Zhang 2020 discloses two compounds that meet the structural limitations of the Challenged Claims and reports BTK inhibition of these compounds with IC_{50} values: compound 7 (>1000 nM) and compound 8 (2.1 nM). EX2063, Fig. 3 (.0002). Docking these compounds into the Marcotte structure using Maestro/Glide indicates that both can be accommodated in the BTK active site, with the phenoxyphenyl positioned in the back pocket of BTK and the linker-warhead approaching Cys481. However, the docking score was markedly better for Compound 8 as compared with Compound 7 (-9.3 for compound 8 as compared with -6.5 for Compound 7). Accordingly, a POSA would have prioritized Compound 8 over Compound 7 for synthesis and further testing. Zhang 2020 describes Compound 7 as having “weaker potency” and its activity would have been readily identified in a straightforward IC_{50} kinase assay. EX2063.0002. As

Dr. Showalter acknowledges, in the 2011 time frame, an IC₅₀ even around 1000 nM may have been considered “active.” EX2018, 37:22-39:3. Compound 8 with its IC₅₀ of 2.1 nM further confirms that compounds having the structural features of the claims are potent inhibitors of BTK. EX2063, Fig. 3 (.0002).

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

186. Dr. Showalter premises his opinions of alleged insufficient blaze marks on the lack of blaze marks to the Z'-scaffolds that satisfy the claims. EX1003, ¶¶188-209, 213-219, 227, 230. Dr. Showalter opines that Formula E in the specification “does not provide any blaze marks to the Structural Limitations.” EX1003, ¶208; *see also id.* ¶208 (“[T]here are no blaze marks in the specification that would guide a POSA from the broad, generic skeleton of Formula (E) to the Structural Limitations.”). I disagree. The specification provides blaze marks to the claimed genus of irreversible BTKIs for use in the claimed methods. While the fixed structural features (phenoxyphenyl and linker-warhead) are based on the specification’s preferred embodiment (ibrutinib), the specification also identifies variability for the heterocyclic hinge-binding scaffold where the phenoxyphenyl back-pocket binder and linker-warhead attach in order to bind—and irreversibly inhibit—BTK.

187. With respect to the fixed structural features, the specification provides blaze marks to the fixed phenoxyphenyl of the claims because all depicted

structures of irreversible BTKI species in the specification include a phenoxyphenyl moiety which binds within BTK's hydrophobic back pocket and drives specific binding to BTK. EX1001, 65:10-80:35; *see also supra* §§VI.D.2; X.A.1.c. These disclosures identify the patent's preference for the phenoxyphenyl moiety for binding BTK. Additionally, there is an explicit preference for ibrutinib in the specification. Ibrutinib is identified as a preferred compound in the specification and, as I understand, was the only compound used clinically to treat CLL/SLL in the '803 Patent examples. *See* EX1001, 80:63-65, 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), 147:42-148:56 (Example 15); *see also supra* §VI.D.1-VI.D.2. Because ibrutinib has the claimed phenoxyphenyl moiety, the specification further provides blaze marks to the phenoxyphenyl moiety in this manner.

188. Moreover, the specification provides blaze marks to the specific linker-warhead of the claims and the combination of the linker-warhead and phenoxyphenyl. First, the specification provides blaze marks to the fixed linker-warhead of the claims because the linker and the warhead structures appear among a narrow selection of options for these components. *See, e.g.*, EX1001, 52:45-53:19 (disclosing claimed linker structure in four out of eight embodiments), 54:55-55:10

(disclosing claimed warhead structure in one out of five embodiments); *see also supra* §VI.D.1.

189. Second, because ibrutinib is identified as a preferred compound in the specification and because ibrutinib has the claimed linker-warhead, the specification further provides blaze marks to the claimed linker-warhead in combination with the phenoxyphenyl moiety.

190. Third, the specification's examples also provide blaze marks to the claimed linker-warhead in combination with the phenoxyphenyl moiety. I understand that the compound used in the examples is ibrutinib. The examples therefore show that the specific combination of ibrutinib's phenoxyphenyl moiety and linker-warhead effectively inhibits BTK and treats CLL/SLL patients—further providing blaze marks to the combination of the claimed linker-warhead and phenoxyphenyl moiety for use in the claimed method. *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), 147:42-148:56 (Example 15).

191. With respect to Z', the specification's Formula E discloses that the linker-warhead can be attached to a variable scaffold that binds to the BTK active site, and the specification discloses specific hinge-binding scaffold examples. *See* EX1001, 61:65-63:20; *see also supra* §§VI.D.3, X.A.2.a. *All* of the specific hinge-binding scaffold examples are substituted 5:6 fused heterocycles (including

partially saturated and aromatic 5:6 fused heterocycles), thereby directing a POSA to the claimed structural features for Z'. *See* EX1001, 62:44-63:20. However, although the specification teaches clear preferences for the fixed components of the BTKI (phenoxyphenyl moiety and the linker-warhead), the specification leaves flexibility and variability for the Z'-scaffold with specific structural constraints (5:6 fused ring requiring certain heteroatoms) and an understood structure-function relationship in 2011.

192. The specification's disclosure of a diversity of hinge-binding scaffolds comports with the understanding of a POSA reading the '803 Patent to identify ibrutinib-like BTKIs for use in the claimed method about the permissiveness and variability of hinge-binding scaffolds used to bind within BTK's active site. As I have explained, in June 2011, based on the '803 Patent and art, a POSA would have known that hinge-binding elements can exhibit structural diversity because a defining attribute of a hinge-binding element is its ability to have H-bond acceptors/donors arranged in a suitable geometry to form one to three H-bonds with specific amino acid residues of the hinge. *See supra* §§X.A.2.a, VII.A.4; *see also supra* §VI.D.3. As I have further explained, a POSA reading the '803 Patent would have been aware of diverse heterocyclic scaffolds for binding to the hinge region. *See* EX1077.003-004; EX2028.0003-0004; EX1052.003-018; EX1073, Tbl. 2 (.009) (BTK inhibitors); EX2026, claim 1, claim 10, [0023],

[0076], [Abstract] (BTK inhibitors); *see also supra* §§X.A.2.a, VII.A.4. Indeed, in June 2011, a POSA would have known of the well-understood correlation between the heterocyclic scaffold structure and the hinge-binding function. *See supra* §§X.A.2.a, VII.A.4, VI.D.3. Therefore, in the context of a POSA's knowledge in 2011 of this correlation and the wide variety of hinge-binding heterocyclic scaffolds to use, the specification provides blaze marks to the Z'-scaffold of the claims: a variable hinge-binding structure with specific structural constraints (5:6 fused ring requiring certain heteroatoms).

193. Furthermore, in June 2011, a POSA reading the '803 Patent would have known the structure of BTK and its interactions with the ibrutinib scaffold from the Marcotte structure. *See* EX2001, Fig. 2 (.0003); §VII.A-VII.B; *see also* EX1052.019-020 (explaining that hinge binding could be “categorized in terms of the ligand core structure and a few simple empirical rules” and explaining that it was “straightforward to identify the moieties most likely to be involved in hinge binding”). In fact, both Pan and Marcotte disclose inhibitors with fixed structural features (phenoxyphenyl moiety in Marcotte, and phenoxyphenyl moiety and linker-warhead in Pan) with an appropriate hinge-binding scaffold. EX1060.001-002; EX2001, Fig. 2 (.0003); *see also supra* §VII.B.2. A POSA would have read the specification's disclosures, and in light of the consistent extensive structural knowledge known in June 2011, would have understood that the specification

identifies the flexibility in choice/selection of a hinge-binding heterocyclic scaffold where the fixed phenoxyphenyl moiety and linker-warhead attach to bind BTK. In light of the relevant specification disclosures and the consistent sophisticated knowledge in June 2011 of the relationship between the heterocyclic scaffold structure and its hinge-binding function, the specification provides sufficient blaze marks to the specific genus of irreversible BTKIs for use in the claimed methods.

C. No Separate Analysis of Dependent Claims

194. Dr. Showalter does not provide a separate analysis regarding the written description of the limitations recited in the dependent claims, but rather relies solely on his analysis for independent claims 1 and 8. *See* EX2018, 185:17-186:5. Therefore, the dependent claims are fully described for all the same reasons as independent claims 1 and 8.

XI. THE '803 PATENT ENABLES THE IRREVERSIBLE INHIBITORS OF THE CHALLENGED CLAIMS

195. Dr. Showalter opines that the priority non-provisional applications of U.S. Patent No. 11,672,803 including App. No. 13/153,317 (filed June 3, 2011) “fail to teach a POSA how to make and use the full scope of the Challenged Claims without undue experimentation as required under § 112.” EX1003, ¶232. Specifically, Dr. Showalter opines that the specification does not provide any teachings or disclosure that would allow a POSA, without undue experimentation,

to determine which compounds that meet the express structural requirements for use in the claimed methods would be irreversible BTKIs that covalently bind BTK. *Id.*; *see also* EX1003, ¶¶232-271. For the reasons set forth below, I disagree with Dr. Showalter's opinions.

196. As I have discussed previously in §V.B, counsel for Pharmacyclics has informed me of the “*Wands* factors” that may be considered in determining whether practicing the claimed invention would require undue experimentation. The *Wands* factors include the amount of direction or guidance disclosed in the patent (*Wands* Factor 2), the presence or absence of working examples in the patent (*Wands* Factor 3), the nature of the invention (*Wands* Factor 4), the quantity of experimentation necessary (*Wands* Factor 1), the breadth of the claims (*Wands* Factor 8), the state of the prior art (*Wands* Factor 5), the relative skill of those in the art (*Wands* Factor 6), and the predictability of the art (*Wands* Factor 7).

197. In my opinion, as I further explain below, the *Wands* factors demonstrate that the Challenged Claims are enabled.

A. The Specification Provides Guidance and Working Examples for the Irreversible Inhibitors of the Challenged Claims (*Wands* Factors 2-4)

198. I disagree with Dr. Showalter that the “specification provides no working examples and limited guidance regarding covalently binding Cys481 or another residue of Btk.” EX1003, ¶247; *see also* EX1003, ¶¶248-251, 259-270.

Instead, the specification repeatedly emphasizes that the irreversible BTKIs to be used in the inventive methods form covalent bonds with Cys481. EX1001, 26:27-29 (“[I]n particular embodiments, the irreversible inhibitor can form a covalent bond with a Cys 481 residue”); *see also id.*, 3:18-20 (“In some embodiments, the Btk inhibitor forms a covalent bond with a cysteine sidechain of a Bruton’s tyrosine kinase.”); *id.*, 4:25-27 (same); *id.*, 46:42-45 (same); *id.*, 46:10-12 (“[S]ome irreversible Btk-inhibitor compounds can form a covalent bond with Cys 481 of Btk (e.g., via a Michael reaction)”). The specification further teaches that the formation of such a covalent bond with Cys481 imparts selectivity for such inhibitors. *Id.*, 45:56-64 (“Btk inhibitor compounds described herein are selective for Btk and kinases having a cysteine residue in an amino acid sequence position of the tyrosine kinase that is homologous to the amino acid sequence position of cysteine 481 in Btk.”).

199. I also disagree with Dr. Showalter’s opinion that “the specification never describes any specific structural features that would result in covalently binding Cys481.” EX1003, ¶248. The specification guides a POSA to what structures and structural features allow for irreversible BTK inhibition. Specifically, the specification guides a POSA to ibrutinib via the examples using ibrutinib to treat CLL/SLL patients. *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), 147:42-148:56 (Example 15); *see also supra* §VI.D.1. I understand that the clinical examples use ibrutinib, as Petitioner acknowledges. *See* Pet. 35-36. Moreover, as I have explained, the specification further guides a POSA to specific structural features of ibrutinib (claimed fixed phenoxyphenyl and claimed fixed linker-warhead) that are critical to irreversible BTK inhibition via the specification's emphasis of both of these features. *See supra* §§VI.D.1-VI.D.2, X.A.1.a-X.A.1.c, X.B. As I have also explained, the specification's emphasis of both of these fixed substituents to convey irreversible BTK inhibition activity aligns with what a POSA reading the '803 Patent to identify ibrutinib-like BTKIs for use in the claimed method would have recognized about their functional importance in light of the sophisticated structure-function relationship for ibrutinib-like BTKIs revealed in Marcotte. *See supra* §§VII.A.1-VII.A.3, VII.B.2, X.A.1.a-X.A.1.c. Additionally, although Dr. Showalter contends that "testing would be required to determine that any one candidate in fact covalently binds Btk," EX1003, ¶249, as I explain below, any such testing and experimentation to confirm irreversible inhibition of BTK would be routine. *See infra* §XI.B.

200. Dr. Showalter further claims that "[t]he specification also does not explain the role of the Z'-structure in the formation of the covalent bond between the Btk inhibitor and the Cys481 or any other residue of the Btk" and "does not

explain how any structural change in the Z'-structure can impact the activity of the Btk inhibitor in terms of the aforementioned functions [of covalently binding BTK or its Cys481 residue].” EX1003, ¶¶250-251. In doing so, Dr. Showalter fails to address the specification’s teaching of the Z'-scaffold as the hinge-binding element of the irreversible BTKIs for use in the claimed methods. *See supra* §§VI.D.3, X.A.2.a. He thus also fails to address the sophisticated understanding in June 2011 of a POSA from reading the '803 Patent and consistent art, particularly Marcotte, regarding the “active site” of protein kinases (and specifically the BTK active site) and the role of hinge binding of kinase inhibitors (and specifically BTKIs). *See supra* §§VI.D, VI.D.3, VII.A.4, VII.B.2, X.A.2.a-X.A.2.b.

201. As I have explained, a POSA reading the '803 Patent would have understood that the role of an “active site” binding structure—here, the Z'-scaffold—is to form appropriate hydrogen bonds with specific amino acid residues of the BTK hinge region (gate-keeper+1 (GK+1) and gate-keeper+3 (GK+3)), while orienting the phenoxyphenyl into the BTK hydrophobic back pocket and directing the linker-warhead towards Cys481. *See supra* §§VI.D, VII.A.1-VII.A.4, X.A.2.a-X.A.2.b. Furthermore, as I have discussed, in June 2011, a POSA would have been aware of the extensively studied conserved kinase hinge region and the detailed crystal structure information regarding the formation of hydrogen bonds between many different hinge-binding scaffolds and the kinase hinge. *See supra*

§§VI.D, VII.A-VII.B. With this proper context, (and in particular the specification's disclosures as to Z' (*see supra* §§VI.D.3, X.A.2)), it is my opinion that the specification provides significance guidance on and teaches the full scope of the claimed Z'-scaffolds. And more broadly, with this proper context (and in particular the specification's disclosures as to the specific structural features of the claimed ibrutinib-like irreversible BTKIs (*see supra* §§VI.D, X.A.1-X.A.2)), it is my opinion that the specification teaches the full scope of the irreversible inhibitors of the claims.

202. Accordingly, *Wands* factors 2-4 support that a POSA would have been able to make and use the ibrutinib-like irreversible BTKIs necessary for the claimed treatment method.

B. Routine Experimentation to Confirm Irreversible Inhibition of BTK (*Wands* Factor 1)

203. Dr. Showalter opines that “the quantity of experimentation would have been extensive.” EX1003, ¶¶235; *see also id.*, ¶¶236-246, 259-270. In particular, Dr. Showalter acknowledged that his undue experimentation opinion depends on how long it would take to make the full scope of compounds that fall within the claims. EX2018, 171:3-17. I do not agree that a POSA would engage in undue experimentation. In my opinion, only routine experimentation would have been needed to confirm compounds of the Challenged Claims irreversibly inhibit BTK.

204. I disagree with Dr. Showalter that a POSA in 2011 would have to start by synthesizing and physically screening candidate irreversible inhibitors of BTK. *See* EX1003, ¶¶236-242. Instead, as I have explained, a POSA reading the '803 Patent would have leveraged the teachings of the '803 Patent, the existing significant structural information about BTK bound to a ligand with ibrutinib-like binding (*see* EX2001), and virtual docking and modeling tools which were available and routinely used in June 2011. *See supra* §§VII.B, X.A.2.b; *see also supra* §§VI.D, VII.A. Dr. Showalter fails to account for this routine and common use of such docking and modeling just as he ignores both a POSA's sophisticated understanding of kinase hinge interactions and the specific structural information available for BTK from Marcotte in June 2011.

205. As I have described in §VII.B.2, in June 2011, a POSA would have available the detailed Marcotte crystal structure of BTK bound to B43 that shares the phenoxyphenyl and a similar Z'-scaffold with ibrutinib. *See* EX2001.0003-0005 (PDB: 3GEN).

206. Furthermore, in June 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have used modeling tools to identify appropriate substitutions or "scaffold swap" for the hinge-binding element for Formula E. *See supra* §§VII.B.1, X.A.2.b; EX2028.0004; *see also* EX1052.019-020, Fig. 7 (.020). Indeed, a POSA in 2011

would have been aware of examples of successful scaffold swaps. *See* EX2028.0004-0005; EX2038, Fig. 1 (.0001).

207. As I have explained, in my opinion, consistent with the teachings set forth in the '803 Patent, the structural information of Marcotte (PDB: 3GEN) would have provided a POSA with data for use in virtual docking and modeling of the irreversible BTKIs of the claims. *See supra* §VII.B.2. Marcotte provides information on key interactions between different parts of the BTK active site and BTKIs with ibrutinib-like binding. For example, Marcotte shows how the phenoxyphenyl enters the BTK hydrophobic “back pocket” and also participates in a pi-stacking interaction with the phenylalanine in the kinase DFG-motif. *See* EX2001.0005. Marcotte also details the H-bond interactions of heterobicyclic scaffold of B43 with the BTK hinge region. *See id.* Finally, Marcotte shows how the cyclopentyl ring of B43 occupies the space generally occupied by ATP ribose, in close proximity to Cys481. *See id.*

208. Moreover, the claim requirement that the compound be an irreversible BTKI imposes additional structural limitations. These considerations would limit the size and number of substitutions that a POSA would consider to include with the structure for Z'. Specifically, a POSA in 2011 would have modeled and visualized the full ibrutinib-like compound with its Z' and required phenoxyphenyl and linker-warhead substituents docked into Marcotte's structure of BTK. *See*

supra §X.A.2.b; *see also supra* §VII.B.2. A POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that the phenoxyphenyl would need to be oriented to extend into the BTK back pocket, and that additional substitutions of Z' would need to avoid a steric clash with the BTK structure. *See supra* §X.A.2.b; *see also supra* §X.A.3.b(3). Accordingly, virtual docking would have allowed a POSA in 2011 to visualize Z'-scaffolds that would bind the hinge region of the BTK active site while positioning the phenoxyphenyl to occupy the back-pocket and orient the linker-warhead towards BTK's Cys481 to covalently bind and irreversibly inhibit BTK. *See supra* §X.A.2.b; *see also supra* §VII.B.2.

209. Employing these virtual docking tools, applying the teachings of the '803 Patent as well as the specific structural information available for BTK (*i.e.*, EX2001.0003-0005 (PDB: 3GEN)), and applying the sophisticated understanding in 2011 of the structure-function relationship for the components of irreversible BTKIs of the claims, a POSA would have routinely identified and excluded structures that were plainly not operable—*i.e.*, structures that would not be accommodated within the known structural conformation of BTK bound to a BTK inhibitor with ibrutinib-like binding. Visualizing the docking of a candidate BTKI could be accomplished in a matter of minutes.

210. In my opinion, with the guidance from the specification regarding the ability of ibrutinib to treat CLL/SLL patients and the use of virtual docking to assess additional potential irreversible BTKIs suitable for use in the claimed methods, a POSA in 2011 would have needed only routine experimentation to confirm the ability of selected compounds to irreversibly inhibit BTK. Using widely available and routinely employed software for reversible ligand docking in 2011, a POSA would first dock structures of potential interest into BTK, using the structural information detailing the ibrutinib-like binding mode to BTK in Marcotte. *See generally* EX2001. A POSA in 2011 would understand that the accuracy of docking is improved when structures with similar ligands are available and would recognize the correspondence in overall structure of compounds of the '803 Patent with that of compound B43 in the Marcotte structure, in particular the phenoxyphenyl substituent. Based on the teachings of the '803 Patent, visual examination of obtained docking poses, their correspondence to the binding mode of B43 in the Marcotte crystal structure, comparison with the docking pose obtained with ibrutinib, lack of steric clashes, and evaluation of numerical docking scores produced by the chosen docking software, a POSA in 2011 would have prioritized compounds for synthesis and biochemical testing. A compound predicted to be an irreversible inhibitor based on this approach in 2011 would have a high probability of irreversibly inhibiting BTK in confirmatory biochemical

testing. Indeed, Petitioner did precisely this modeling for a zanubrutinib analog and accurately predicted, based on the Marcotte crystal structure, how a zanubrutinib analog would bind within BTK's active site. *See* EX2039, Fig. 1 (.0003-0004); EX2018, 128:16-130:6; *see also supra* §X.A.3.a.

211. In the preceding paragraph, I specified software for *reversible* ligand docking to make a distinction with software tools for *covalent* ligand docking. In June 2011, a POSA reading the '803 Patent would have understood that tools for reversible ligand docking were widely available and near-universally employed by pharmaceutical discovery teams. While covalent docking was less developed during this time period (*see generally* EX2034; EX2045), a POSA in 2011 would have had access to at least one freely available docking program with covalent docking capability (AutoDock4) (*see* EX2054), which further enhanced the predictive power of computational docking.

212. Additionally, Dr. Showalter improperly inflates the scope of experimentation that is required to confirm that the compounds visualized by virtual docking irreversibly inhibit BTK. *See* EX1003, ¶¶243-245. The tests to confirm irreversible BTK inhibition are taught by the specification and the art and are themselves routine and capable of being performed at high throughput. The specification teaches assays (*e.g.*, IC₅₀ testing) that can identify inhibitors of BTK, and that performing these assays with repeat washing with inhibitor-free medium

can confirm that inhibitor is in fact an *irreversible* BTK inhibitor. EX1001, 45:55-46:12. This method was also used in Pan to confirm the irreversibility of ibrutinib and related compounds. *See* EX1060.002. The specification teaches that such assays are amenable to being automated as “high throughput assays” and concludes that “automated systems thereby allow the identification and characterization of *a large number of irreversible Btk compounds without undue effort.*” EX1001, 46:22-35 (emphasis added). Indeed, it is routine to measure IC₅₀ values to assess inhibition activity. Moreover, the specification and art as of 2011 further teach the use of mass spectrometry to confirm the formation of a covalent complex between BTK and a candidate BTKI. *See* EX1001, 46:6-12; EX1060.002.

213. In addition, Petitioner’s cited reference, Honigberg, provides a detailed approach to testing the selectivity of an irreversible BTKI in the context of a complex cellular proteome via fluorescent labeling. EX1055.002. A POSA in 2011 would have also recognized this approach to assess the selectivity and irreversibility of BTK inhibition. *See id.*

214. Lastly, I understand from Dr. Scott that in June 2011, physicochemical properties such as molecular weight, octanol/water partition coefficient, number of H-bond donors/acceptors, and polar surface area could have been calculated and/or predicted from a compound’s chemical structure. *See* EX2012, ¶32. I understand from Dr. Scott that it was routine to calculate these

properties on compounds to be synthesized to help prioritize compounds with the potential for good PK properties. *See id.*

215. Considering these disclosures in the '803 Patent and the understanding of a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method, it is my opinion that, starting from ibrutinib, only routine experimentation would have been needed to identify compounds of the Challenged Claims and confirm their irreversible inhibition of BTK. Therefore, it is my opinion that *Wands* factor 1 supports that a POSA would have been able to make and use the irreversible BTK inhibitors in the claimed method.

C. Petitioner's Expert Inflates the Breadth of the Compounds Within the Claimed Genus (*Wands* Factor 8)

216. Dr. Showalter opines that the Challenged Claims are directed to potentially billions of species and that testing and/or screening would have been required to predict which species that satisfy the structural requirements of the claims would also meet the requirements for irreversible and Cys481 covalent binding. EX1003, ¶233 (citing EX1003, Section VIII); *see also* EX1003, ¶¶259-270. I disagree with Dr. Showalter. As I have explained, Dr. Showalter's opinions on breadth focus on the breadth of the potential *Z'-scaffolds in isolation* (*see* EX1003, Section VIII), and Dr. Showalter improperly inflates the number of

potential Z'-scaffolds by ignoring the "common sense" that a POSA would apply.

See supra §X.A.3.b(3); EX1003, ¶176.

217. Dr. Showalter's analysis of the numerical breadth of the compounds suitable for use in the claims methods fails to incorporate either (1) a POSA's knowledge in 2011 from the '803 Patent and art regarding the structure of the kinase active site and its hinge region generally or (2) a POSA's knowledge in 2011 from the '803 Patent and art of the BTK active site specifically and the available crystal structure that revealed the binding mode of a close reversible analogue of ibrutinib, B43, to BTK (PDB: 3GEN, EX2001)). *See supra* §§VI.D, VII.A-VII.B; *see also supra* §X.A.3.b(3).

218. As I have explained, proper consideration of a POSA's knowledge about the kinase hinge region in June 2011 from the '803 Patent and art would limit the scope of acceptable compounds to those that have a Z'-scaffold that functions as a hinge-binding element and makes the necessary one to three H-bonds with the BTK hinge region. *See supra* §§VI.D.3, VII.A.4, X.A.2. Moreover, as discussed in §X.A.3.b(3), by focusing on the potential Z'-scaffolds in isolation, Dr. Showalter **ignores** the required substituents on Z', namely, the linker-warhead and the phenoxyphenyl group. *See* EX1003, Section VIII. In 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have understood that the linker-warhead needed to be oriented

generally towards Cys481 in order to covalently bind and that the phenoxyphenyl group needed to be oriented to bind within the hydrophobic back pocket. *See supra* §X.A.3.b(3); *see also supra* §X.A.1-X.A.2. And in 2011, a POSA would have further understood that these required substituents on Z'—and their orientations and the potential steric hindrance that results from adding the substituents—would **limit** the scope of acceptable Z'-scaffolds. *See supra* §X.A.3.b(3); *see also supra* §X.A.2.b. Dr. Showalter does not account for whether the Z'-scaffolds that he identified would actually satisfy the need for H-bonds to the hinge **and** the ability for the phenoxyphenyl to occupy the hydrophobic back pocket and for the linker-warhead to covalently bind to Cys481. *See* EX1003, Section VIII (§§141-178).

219. Furthermore, as I have explained, in 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have leveraged the teachings of the '803 Patent, existing structural information regarding BTK and its ligand interactions (*e.g.*, Marcotte (PDB: 3GEN)), and existing information regarding the hinge-binding elements of other kinase inhibitors, for use in virtual docking and modeling. *See supra* §X.A.3.b(3); *see also supra* §§VII.B.2, X.A.2.b. In 2011, a POSA would have used virtual docking to predict which Z'-scaffolds for ibrutinib-like BTKIs would satisfy the need for H-bonds to the hinge **and** the ability for the phenoxyphenyl to occupy the hydrophobic back pocket and for the linker-warhead to covalently bind to Cys481.

These virtual docking and modeling tools would have ruled out inappropriate compounds. *See supra* §§X.A.3.b(3), XI.B. Therefore, by viewing Z' in isolation, Dr. Showalter inflates the breadth of the potential Z'-scaffolds.

220. In addition to inflating breadth of the compounds in terms of numerical breadth, Dr. Showalter's analysis inflates breadth in terms of relevant structural diversity. As described in detail *supra* in §X.A.3.b(1) and §X.A.3.b(2), Dr. Showalter focuses on irrelevant structural distinctions between the Z'-scaffolds of compounds for use in the claims (*e.g.*, Dr. Showalter's "four subgenera" of various combinations of aromatic versus non-aromatic 5 and 6 membered rings). EX1003, ¶233. A POSA in 2011 would have instead focused on the ability of the Z'-scaffold to form the appropriate one to three H-bonds with the hinge structure of BTK while orienting the phenoxyphenyl into the back-pocket of the BTK active site and directing the linker-warhead towards Cys481. *See supra* §X.A.1-X.A.2, X.A.3.b(3). Thus, it is my opinion that Dr. Showalter's analysis inflates the breadth of the compounds within the genus in terms of their **relevant** structural diversity.

221. Additionally, in his breadth opinion, Dr. Showalter fails to incorporate the context of the claim requirement that the compound be an orally-dosed irreversible BTK inhibitor and the "common sense" that a POSA would apply. EX1003, ¶176. To arrive at his large figure of potential Z'-scaffolds, Dr. Showalter opines that multiple substituents can be added to the ring system—even

opining that “the number of substitutions permitted by ‘optionally substituted’ *can be potentially infinite*.” EX1003, ¶162 (emphasis added). However, as I have explained, Dr. Showalter’s opinion defies rational drug design and common sense. *See supra* §X.A.3.b(3). A POSA in 2011 would have known that the Z’ of the kinase inhibitor would *not* have been substituted to the degree that Dr. Showalter suggests—and certainly not “infinite[ly]” substituted. *See id.* As I have explained, adding too many substituents to the ring system would be nonsensical because this would lead to potential steric clash and an inappropriately-sized small molecule for oral administration (*i.e.*, Lipinski’s rule of five would be violated). *See supra* §X.A.3.b(3); EX2012, ¶¶45-46; *see also* EX2012, ¶¶41-44. Because Dr. Showalter’s irrational and nonsensical substitutions opinion underlies his Z’ calculations, Dr. Showalter incorrectly inflates the breadth of potential Z’-scaffolds.

222. For the reasons above, it is my opinion that *Wands* factor 8 does not support that a POSA in 2011 would be unable to use the irreversible BTKIs in the claimed method.

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

223. Dr. Showalter admits that the POSA would be highly skilled. *See* EX1003, ¶253 (“In the field of covalent Btk inhibition, the level of skill was relatively high.”). However, Dr. Showalter fails to adequately address a POSA’s

sophisticated knowledge and the state of the prior art in June 2011, as taught by the '803 Patent and art. *See* EX1003, ¶¶253-258; *see also* EX1003, ¶¶259-270. I disagree with Dr. Showalter's assertions that the art and nature of the invention were unpredictable and that not much was known in the state of the prior art. EX1003, ¶253. I further disagree with Dr. Showalter's assertion that the state of the art for hinge-binding scaffolds, including the Z'-scaffold of the claims, was "highly unpredictable" in 2011 and that it remains so today. EX1003, ¶254.

224. As I have explained, in June 2011, a POSA reading the '803 Patent to identify ibrutinib-like irreversible BTKIs for use in the claimed method would have a sophisticated understanding of the structure of ibrutinib-like BTKIs. *See supra* §§VI.D, VII.A-VII.B. As described in further detail *supra* in §VI.D and §VII.A-VII.B, in June 2011, based on the teachings of the '803 Patent and consistent art, the structure-function relationship for ibrutinib-like BTKIs was well understood. Indeed, as described in further detail *supra* in §VII.B.2, in June 2011, a POSA would have been aware of significant structural information regarding the BTK active site, including the binding mode for a BTKI that shares the phenoxyphenyl and scaffold required by the claims (Marcotte). *See* EX2001.0003-0005 (PDB: 3GEN).

225. As I have explained, consistent with the teachings of the '803 Patent, Marcotte's structural information would have provided a POSA in 2011 with data

to visualize ibrutinib-like BTKIs through virtual docking in the then-available BTK structure and recognize which bind and irreversibly inhibit BTK. *See supra* §VII.B.2.

226. Dr. Showalter's declaration *completely ignores* both the structural information available for the BTK active site and ibrutinib-like BTKI binding (*e.g.*, Marcotte (EX2001) and PDB: 3GEN). *See* EX1003, ¶¶254-257; *see also* EX1003, ¶¶238-242; *supra* §VII.B.2; EX2018, 46:12-20 (Dr. Showalter admitting that Marcotte is not cited in his Declaration). Indeed, as noted above, Petitioner successfully predicted binding of a zanubrutinib analog by modeling in the Marcotte structure. *See* EX2039, Fig. 1 (.0003-0004); EX2018, 128:16-130:6; *see also supra* §X.A.3.a.

227. In addition, I specifically disagree with Dr. Showalter's assertion that there was a "lack of development of BTKI scaffolds, including the Z'-structure." EX1003, ¶256. Dr. Showalter specifically fails to address a POSA's understanding from the teachings of the '803 Patent and art of kinase inhibitor hinge-binding elements, *i.e.*, scaffolds including the Z'-scaffold, in 2011. As detailed *supra* in §VI.D.3 and §VII.A.4, a POSA in 2011 would have recognized the need for kinase inhibitors to form one to three H-bonds with the kinase hinge region. As I have explained, a POSA reading the '803 Patent would have understood that the Z'-scaffold was responsible for forming these critical H-bonds. *See supra* §X.A.2.a.

Additionally, a POSA reading the '803 Patent in 2011 to identify additional Z'-scaffolds as directed in Formula E would have been aware of scaffold “swapping” of kinase hinge-binding elements or the replacement of hinge-binding elements of a known inhibitor with those from another kinase inhibitor. *See supra* §VII.B.1.

228. Moreover, I disagree with Dr. Showalter's assertions that the art and nature of the invention were unpredictable. EX1003, ¶25. As I have detailed *supra* in §X.A.3.a, Dr. Showalter's *own cited references* actually *support* that the structure-activity relationship for ibrutinib-like BTKIs and hinge-binding in 2011 *was* well-known and predictable. For example, in a section titled “***Empirical Rules to Predict Hinge Binding Orientation***,” Ghose explains that it is “***straightforward***” to identify the moieties of a kinase inhibitor most likely to be involved in hinge binding. EX1052.019 (emphases added). Ghose further explains that hinge binding could be “categorized in terms of the ligand core structure and ***a few simple empirical rules***.” EX1052.020 (emphasis added). And Ghose also teaches that because “[m]ost parts of the ATP binding site show limited movement,” “through an analysis of the binding modes of different types of kinase ligands, ***one can anticipate the binding mode of a related ligand*** with ‘kinase inhibitor features.’” EX1052.002 (emphasis added). As another example, Garuti confirms the specification's teaching regarding the structure-function relationship for covalent inhibitors that interact with BTK's Cys481 in June 2011. *See supra*

§X.A.3.a. Specifically, Garuti teaches that “important parameters” include “the corrected orientation of the Michael acceptor toward the cysteine and a short distance” to the cysteine side chain. EX1049.001. And Garuti further explains that hinge-binding interactions place the warhead in the correct position to bind with the cysteine residue of the kinase. *Id.*

229. Therefore, it is my opinion that *Wands* factors 5-7 support that a POSA would have been able to make and use the irreversible BTKIs necessary for the claimed method and that the Challenged Claims are therefore enabled.

E. Petitioner’s Expert Points to Irrelevant Differences Among Species Suitable for Use in the Claimed Methods

230. Dr. Showalter identifies irrelevant differences among the species suitable for use in the claimed methods. Specifically, Dr. Showalter points to compounds within the claimed genus that have different attachment points of the linker structure or chirality of the linker attachment, and opines that such differences lead to variation in preclinical potency. *See* EX1003, ¶¶71-73. However, these compounds all have IC₅₀ values in the nM range, showing that they are all potent inhibitors of BTK. While Dr. Showalter emphasizes the differences between the IC₅₀ values of the compounds, such differences do not evidence unpredictability of the compounds’ activities—all are able to irreversibly inhibit BTK by binding covalently to Cys481. *See* EX1003, ¶¶71-73 (citing EX1060, Tbl. 3 (.003); EX1053, Tbl. 6 (.005)).

231. Accordingly, Dr. Showalter's reliance on such differences fails to demonstrate that the compounds are not useful for the claimed method. Rather, these examples support enablement of the claims—demonstrating that compounds of the claimed genus irreversibly inhibit BTK.

F. No Separate Analysis of Dependent Claims

232. Dr. Showalter does not provide a separate analysis regarding the enablement of the limitations recited in the dependent claims, but rather relies solely on his analysis for independent claims 1 and 8. *See* EX2018, 185:17-186:14. Therefore, the dependent claims are fully enabled for all the same reasons as independent claims 1 and 8.

XII. CONCLUSION

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true. Further, I am aware that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001. I declare under penalty of perjury that the foregoing is true and correct.

Executed on 6 AUG 2024 (date), in Boston, MA (city, state).



Michael J. Eck