

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 B2

Before SHERIDAN K. SNEDDEN, SUSAN L. C. MITCHELL, and
TINA E. HULSE, *Administrative Patent Judges*.

HULSE, *Administrative Patent Judge*.

DECISION
Granting Institution of Post-Grant Review
35 U.S.C. § 324

I. INTRODUCTION

BeiGene USA, Inc. and BeiGene, Ltd. (collectively, “Petitioner”) filed a Petition requesting a post-grant review of claims 1–8, 12, and 20 of U.S. Patent No. 11,672,803 B2 (Ex. 1001, “the ’803 Patent”). Paper 2 (“Pet.”). Pharmacyclics LLC (“Patent Owner”) filed a Preliminary Response. Paper 6 (“Prelim. Resp.”). With our authorization, Petitioner filed a Reply to Patent Owner’s Preliminary Response (Paper 7, “Prelim. Reply”), and Patent Owner filed a Sur-Reply (Paper 8, “Prelim. Sur-Reply”).

We have authority under 35 U.S.C. § 324(a), which provides that a post-grant review may not be instituted “unless . . . the information presented in the petition . . . , if such information is not rebutted, would demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” Upon considering the arguments and evidence presented by the parties, we determine Petitioner has shown that it is more likely than not that at least one of the claims challenged in the Petition is unpatentable.

A. *Real Parties-in-Interest*

Petitioner identifies itself as the real party-in-interest. Pet. 3.

Patent Owner identifies itself as a real party-in-interest and states that it is a wholly owned subsidiary of AbbVie Inc. and the sole assignee of the ’803 Patent. Paper 4, 1. Patent Owner also states that Janssen Biotech, Inc. is the exclusive licensee of the ’803 Patent. *Id.*

B. *Related Proceedings*

Petitioner and Patent Owner identify *Pharmacyclics LLC v. BeiGene USA, Inc.*, Case No. 1:23-cv-00646 (CFC) (D. Del.) filed on June 13, 2023,

as a related matter.¹ Pet. 4; Paper 4, 1. Patent Owner also states that U.S. Patent Application Nos. 18/180,064 and 18/171,254, which are pending, claim the benefit of the application that led to the '803 Patent. Paper 4, 1.

C. The '803 Patent

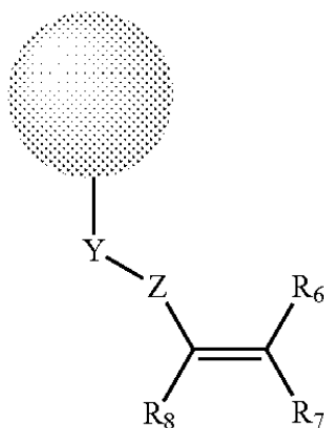
The '803 Patent, entitled “Use of Inhibitors of Brutons Tyrosine Kinase (BTK),” issued from U.S. Patent Application No. 16/926,280 (“the '280 Application”), which was filed July 10, 2020. Ex. 1001, codes (54), (21), (22). The '803 Patent claims the benefit of the filing dates of a series of applications, the earliest of which is U.S. Patent Application No. 13/153,317 (“the '317 Application”), filed on June 3, 2011. *Id.*, code (63). The '803 Patent also claims the benefit of the filing dates of various provisional applications, the earliest of which was filed on June 3, 2010. *Id.*, code (60).

The '803 Patent relates to methods for treating a cancer, such as a hematological malignancy, by administering an irreversible Bruton's tyrosine kinase (“BTK”) inhibitor (“BTKI”) until disease progression, unacceptable toxicity, or individual choice. Ex. 1001, Abstract, 1:37–2:1, 3:24–46. The '803 Patent explains that BTK is a key signaling enzyme expressed in all hematopoietic cell types except T lymphocytes and natural killer cells. *Id.* at 1:37–40. BTK is a key regulator of B-cell development, activation, signaling, and survival and plays a role in a number of other hematopoietic cell signaling pathways. *Id.* at 1:40–59. According to the '803 Patent, BTKIs can induce mobilization of lymphoid cells (or, in some cases, cause lymphocytosis, i.e., an increase in lymphocytes) in solid

¹ The district court proceeding has been stayed until resolution of this post-grant proceeding. Pet. 55.

hematological malignancies, which increases their exposure to additional cancer treatments and their availability for biomarker screening. *Id.* at 11:16–22.

In some embodiments, the '803 Patent describes BTKIs that form an irreversible covalent bond with a cysteine sidechain of BTK, a BTK homolog, or a BTK tyrosine kinase cysteine homolog. Ex. 1001, 3:18–21. The BTKIs described in the '803 Patent “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.” *Id.* at 45:56–60. The '803 Patent also discloses structures of various BTKIs, including Formulas (A)–(F). *Id.* at 47:5–80:36. For example, Formula (E) is reproduced below:



Formula (E) depicts the structure of an irreversible BTKI with a ball that represents “a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog.” Ex. 1001, 62:15–17. According to the '803 Patent, “[i]n some embodiments, the [ball] is a substituted fused biaryl moiety selected from [eight different structures].” *Id.* at 62:44–63:20.

The Specification also includes Examples 6, 10–12, 14, and 15, which describe clinical trials and/or other testing to determine the efficacy of a BTKI in chronic lymphocytic leukemia (“CLL”) and small lymphocytic leukemia (“SLL”) patients. *Id.*, Examples 6, 10–12, 14, 15; Ex. 1005 ¶¶ 118–135. For example, the Specification states in Example 6 that there was an initial rapid reduction in nodal disease and spleen size with a corresponding rise in the circulating lymphocyte count (i.e., lymphocytosis). *Id.* at 135:30–34. At the same time, patients reported symptomatic improvement, and over time, the initial rise in lymphocytes returns to pre-treatment levels. *Id.* at 135:39–41.

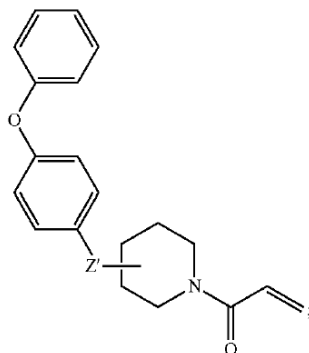
The Specification states that “[c]onsidering the age of the individuals typically diagnosed with CLL and SLL, there is a need in the art for a simple and effective treatment of the disease with minimum side-effects that do not impede on the patient’s quality of life.” *Id.* at 36:18–22. According to the ’803 Patent, “[t]he instant invention fulfills this long standing need in the art.” *Id.* at 36:22–23.

D. Illustrative Claim

Petitioner challenges claims 1–8, 12, and 20 of the ’803 Patent, of which claims 1 and 8 are independent. Claim 1 is illustrative and is reproduced below:

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.

Ex. 1001, 151:34–152:4.

E. The Asserted Grounds of Unpatentability

Petitioner challenges claims 1–8, 12, and 20 of the '803 Patent based on the grounds set forth in the table below.

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1–8, 12, 20	112(a)	Written Description
1–8, 12, 20	112(a)	Enablement
1–8, 12, 20	102(a)	Byrd ²
1–8, 12, 20	103	Byrd and IMBRUVICA Label ³

Petitioner also relies on the Declaration of Hollis Showalter, Ph.D. (Ex. 1003) and the Declaration of Steven Rosen, M.D. (Ex. 1005).

² Byrd et al., *Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia*, 369 N. ENGL. J. MED. 32–42 (2013) (Ex. 1009, “Byrd”).

³ Highlights of Prescribing Information for IMBRUVICA® (ibrutinib) capsules, for oral use (2016) (Ex. 1058, “IMBRUVICA Label”).

II. ANALYSIS OF POST-GRANT ELIGIBILITY

As a preliminary matter, we must determine whether the '803 Patent is eligible for post-grant review. Before we can make that determination, however, we must address the level of ordinary skill in the art and certain claim construction issues.

A. *Person of Ordinary Skill in the Art*

Petitioner asserts that a person of ordinary skill in the art ("POSA") would be

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 at least another member having at least a Ph.D. in chemistry, organic chemistry, or related field with training as a medicinal chemist.

Pet. 57 (citing Ex. 1003 ¶ 136; Ex. 1005, ¶¶ 172–75). Petitioner contends that "[t]he Challenged Claims are unpatentable, however, under any definition of a POSA, including any differing definition(s) that Patent Owner advances." *Id.* (citing Ex. 1005 ¶ 176).

Patent Owner does not contest Petitioner's definition of the level of ordinary skill in the art for purposes of its Preliminary Response. Prelim. Resp. 20.

Although defining a person of ordinary skill in the art as a "team" of individuals is not conventional, because Patent Owner does not dispute the definition at this stage of the proceeding, we adopt Petitioner's definition as it appears to be consistent with the prior art's demonstration of the level of ordinary skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art

itself reflects an appropriate level and a need for testimony is not shown” (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Construction

The Board applies the same claim construction standard that would be used to construe the claims in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.200(b) (2021). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

1. “Method for Treating” and “Therapeutically Effective Amount”

Claims 1 and 8 recite a “method for treating” CLL or SLL comprising administering a “therapeutically effective amount” of a BTKI. Ex. 1001, claims 1 and 8.

Petitioner argues that the preamble of the Challenged Claims should be construed as limiting. Pet. 42–45. Petitioner also argues that the preamble should be construed “in combination with the term ‘therapeutically effective amount’ to limit the scope of the Challenged Claims to the use of certain irreversible BTKIs that both (1) effectively treat CLL/SLL (‘efficacy’), and (2) do so without causing undue adverse side effects (‘safety’).” *Id.* at 42 (citing Ex. 1005 ¶¶ 164–68); *see also id.* at 45–47. Petitioner contends, “if a particular irreversible BTKI cannot be administered to effectively and safely treat CLL/SLL at any amount, then administering that BTKI does not practice the claims.” *Id.* at 46.

Patent Owner “agrees that the preamble is limiting as a statement of the intentional purpose for which the method is performed—treating patients with CLL or SLL.” Prelim. Resp. 18. But Patent Owner disagrees with

Petitioner’s construction of “therapeutically effective amount,” because it is an “attempt to rewrite an express definition in the specification” and adds a safety requirement that is not recited in the definition of “therapeutically effective amount” in the Specification. *Id.* at 19. Patent Owner contends “therapeutically effective amount” should be construed according to its express definition in the Specification to mean “a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms [of a] B-cell lymphoproliferative disorder (BCLD) . . . [or] reduction and/or alleviation of the signs, symptoms, or causes of BCLD.” *Id.* (citing Ex. 1001, 24:58–63). Notwithstanding its proposed construction, Patent Owner posits that “a precise construction of ‘therapeutically effective amount’ is not necessary to resolve the dispute here” and “[e]ven under Petitioner’s flawed construction of ‘therapeutically effective amount,’ Petitioner fails to meet its burden to warrant institution.” *Id.* at 20.

Having considered the parties’ respective arguments at this stage of the proceeding, we agree that the preamble is limiting as a statement of intentional purpose. *See Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1342 (Fed. Cir. 2021) (stating the Federal Circuit “has not hesitated to hold preambles limiting when they state an intended purpose for methods of using a compound”). Moreover, we find Patent Owner has the better position that the term “therapeutically effective amount” should be construed according to its express definition in the Specification and not according to the separate and distinct definition of “effective amount,” as Petitioner suggests. That is, we decline to import a safety limitation to the term “therapeutically effective amount” that only appears in the definition for “effective amount.” *Compare* Ex. 1001, 24:58–62 *with id.* at 24:66–25:2

(referencing “undue adverse side effects” in the definition of “effective amount” but not “therapeutically effective amount”). Thus, we construe the term “therapeutically effective amount” to mean “a sufficient amount of an agent of a compound being administered which will relieve to some extent one or more of the symptoms [of] B-cell lymphoproliferative disorder (BCLD).”

2. *Remaining Claim Terms*

Petitioner offers constructions for the terms “optionally substituted fused heterocyclic ring system” and “irreversible” BTKI, proposing constructions consistent with the express definitions set forth in the Specification. *See* Pet. 42 (citing Ex. 1001, 14:36–44 (definition of “ring” and “ring system”), 14:51–52 (definition of “fused”), 15:66–16:21 (definition of “heterocycle”), 19:57–20:7 (definition of “optionally substituted” or “substituted”), 26:23–25 (definition of “irreversible”)).

Petitioner also asserts that the limitation reciting administering a BTKI “on a continuous daily regimen . . . wherein lymphocytosis is not considered progression of the CLL or SLL” in claims 1 and 8 (i.e., the “lymphocytosis limitation”) should be given patentable weight “because it is functionally related to the substrate—*i.e.*, there must be lymphocytosis after which administration continues, and Patent Owner relied on it for patentability.” *Id.* at 47 (citing Ex. 1002, 558; Ex. 1005 ¶¶ 169–71); *see also Praxair Distrib., Inc. v. Mallinckrodt Hosp. Prod. IP Ltd.*, 890 F.3d 1024, 1033 (Fed. Cir. 2018) (stating a limitation claiming information involving a mental step will receive patentable weight “only if the limitation is functionally related to the substrate” on which the mental step is applied).

For purposes of the Preliminary Response, Patent Owner “does not contest Petitioner’s proposed constructions for ‘optionally substituted fused

heterocyclic ring system’ and ‘irreversible’ BTKIs” and agrees “that the lymphocytosis limitation is entitled to patentable weight because it requires the physical action of continuing to administer to the individual the BTKI after lymphocytosis.” Prelim. Resp. 18.

Because Patent Owner does not contest Petitioner’s constructions of “optionally substituted fused heterocyclic ring system,” “irreversible” BTKI, and the lymphocytosis limitation, and because Petitioner’s constructions are consistent with the Specification and the applicable law, we apply Petitioner’s proposed constructions of those claim limitations in this Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

C. Eligibility for Post-Grant Review

Having determined the level of skill in the art and the relevant constructions of the claims, we now determine whether the ’803 Patent is eligible for post-grant review. Section 6(d) of the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (Sept. 16, 2011) (“AIA”) sets forth the post-grant review provisions, which apply only to patents subject to the first-inventor-to-file provisions of the AIA. AIA § 6(f)(2)(A) (stating the provisions of Section 6(d) “shall apply only to patents described in section 3(n)(1)”). Post-grant reviews are only available for patents that issue from applications “that contain[] or contained at any time . . . a claim to a claimed invention that has an effective filing date . . . on or after” March 16, 2013. AIA § 3(n)(1). Moreover, “[a] petition for a post-grant review may only be filed not later than the date that is 9 months after the date of the grant of the patent or of the issuance of a reissue patent (as the case may

be).” 35 U.S.C. § 321(c). Petitioner has the burden of demonstrating eligibility for post-grant review. *See Mylan Pharms. Inc. v. Yeda Rsch. & Dev. Co.*, PGR2016-00010, Paper 9 at 10 (PTAB Aug. 15, 2016).

The ’803 Patent issued on June 13, 2023, and Petitioner filed the Petition on November 1, 2023. Ex. 1001, code (45). Thus, it is undisputed that the Petition was filed less than nine months after the date the patent was granted.

The parties’ dispute lies in the effective filing date of the challenged claims. Petitioner asserts that the ’803 Patent is eligible for post-grant review because at least one of the challenged claims is only entitled to the July 10, 2020, filing date of the ’280 Application, which led to the ’803 Patent. Ex. 1001, code (22); Pet. 55–56, 60–96. Patent Owner disagrees and asserts that each of the challenged claims is entitled to the benefit of the filing date of non-provisional U.S. Patent Application No. 13/153,317 (“the ’317 Application”), filed on June 3, 2011. Prelim. Resp. 21.

As explained below, on this record, we agree with Petitioner that the challenged claims are eligible for post-grant review.

1. Legal Standards

To be eligible for post-grant review, Petitioner has the burden to show that the effective filing date of at least one claim of the ’803 Patent is on or after March 16, 2013. *See US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17 at 9–12 (PTAB Jan. 29, 2016). To claim the benefit of an earlier filing date of a U.S. patent application under 35 U.S.C. § 120, as Patent Owner asserts here, the claimed invention must be disclosed “in the manner provided by § 112(a) (other than the requirement to disclose the best mode)” in the earlier application. *See* 35 U.S.C. § 120. In other words, the claimed invention must have adequate

written description support and be enabled in an ancestor application filed before March 16, 2013.

The test for written description support is “whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date” based on an “objective inquiry into the four corners of the specification.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The written description requirement is satisfied when the specification “set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed.” *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 928 (Fed. Cir. 2004).

The specification does not have to provide exact or verbatim textual support for the claimed subject matter at issue. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996). Moreover, “the written description requirement does not demand either examples or an actual reduction to practice.” *Ariad Pharms.*, 589 F.3d at 1352. “[A]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention.” *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003). Furthermore, “[a] specification may . . . contain a written description of a broadly claimed invention without describing all species that [the] claim encompasses.” *Id.*

That said, the Federal Circuit explains that written description of a genus requires more than a “broad outline of a genus’s perimeter”:

[W]ritten description of a broad genus requires description of not only the outer limits of the genus but also of either a representative number of members of the genus or structural features common to the members of the genus, in either case with

enough precision that a relevant artisan can visualize or recognize the members of the genus.

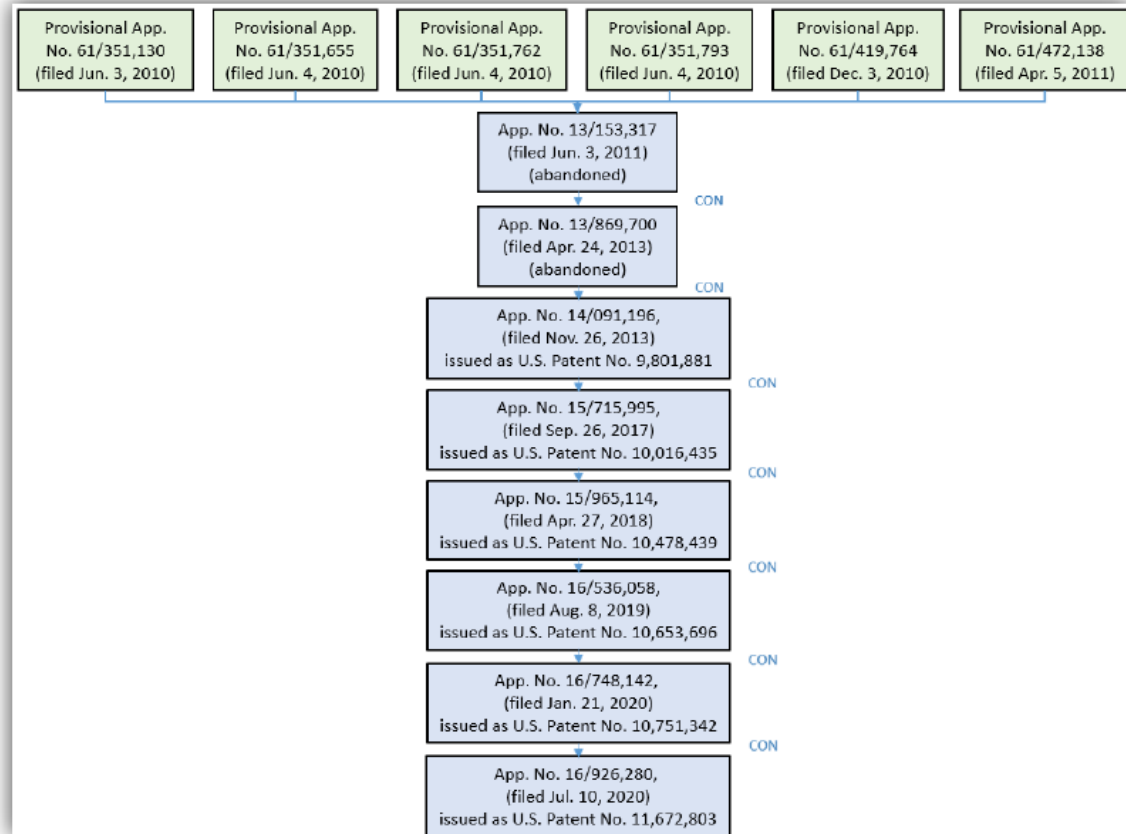
Regents of the Univ. of Minn. v. Gilead Sciences, Inc., 61 F.4th. 1350, 1356 (Fed. Cir. 2023). “For genus claims, . . . we have looked for blaze marks within the disclosure that guide attention to the claimed species or subgenus.” *Id.*

The written description inquiry is a question of fact, is context specific, and must be determined on a case-by-case basis. *Ariad Pharms.*, 598 F.3d at 1351 (citing *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575; *Capon v. Eshhar*, 418 F.3d 1349, 1357–1358 (Fed. Cir. 2005)). “[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Id.* (citing *Capon*, 418 F.3d at 1357–58). Factors used to evaluate the sufficiency of a disclosure include: 1) “the existing knowledge in the particular field”; 2) “the extent and content of the prior art”; 3) “the maturity of the science or technology”; and 4) “the predictability of the aspect at issue.” *Id.* (citing *Capon*, 418 F.3d at 1359).

“Patent claims are awarded priority on a claim-by-claim basis based on the disclosure in the priority applications.” *Lucent Techs., Inc., v. Gateway, Inc.*, 543 F.3d 710, 718 (Fed. Cir. 2008) (citations omitted). We address below whether the challenged claims have written description support in an ancestor application filed before March 16, 2013.

2. *Analysis of Written Description Support*

The ’803 Patent issued from the ’280 Application, filed on July 10, 2020. Ex. 1001, codes (21), (22). The patent family tree provided by Petitioner is reproduced below:



Pet. 61. The family tree shows that the '280 Application claims priority to six non-provisional applications—U.S. Application Nos. 16/748,142; 16/536,058; 15/965,114; 15/715,995; 14/091,196; and 13/869,700—and the earliest-filed non-provisional application, the '317 Application. *Id.*, code (63). The parties agree that the specifications of those non-provisional applications are substantively identical to the '803 Patent Specification. Pet. 61; Prelim. Resp. 5 n.1. As such, both Petitioner and Patent Owner cite to the Specification of the '803 Patent in their written description discussions instead of the '317 Application. Pet. 61 n.5; Prelim. Resp. 21 (addressing PGR eligibility in conjunction with its response to the written description challenge of the '803 Patent). For ease of reference, we do the same in this Decision with the understanding that all citations to the '803 Patent

Specification also apply to citations to the ancestral non-provisional application specifications.

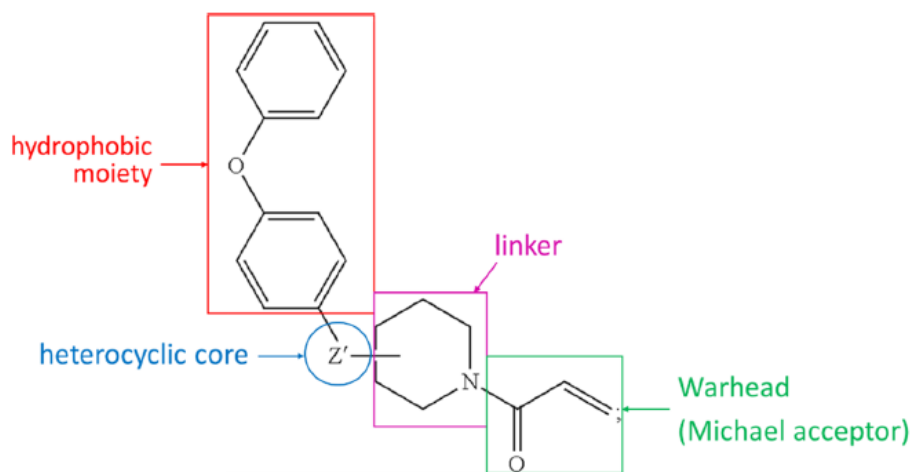
Petitioner asserts that the Specification fails to provide adequate written description support for the full scope of the challenged claims. Pet. 65–81. Patent Owner disagrees and contends “at least the ’317 Application provides sufficient § 112 support for the challenged claims.” Prelim. Resp. 21.

Having considered the parties’ respective arguments, we find on this record that Petitioner has shown sufficiently that the Specification does not adequately describe the full scope of the challenged claims.

3. *Structural Limitations of Claims 1 and 8*

a) *Technical Background of the Structure of Irreversible BTKIs*

Petitioner states that irreversible BTKIs generally comprise four components: (1) a hydrophobic moiety, (2) a heterocyclic core (optionally substituted), (3) a linker, and (4) a warhead, as shown by the following annotated structure of the challenged claims:

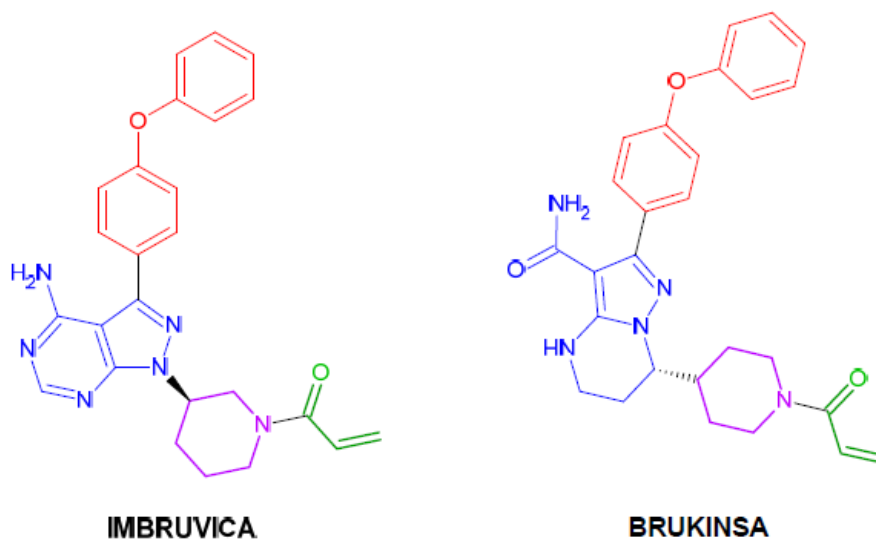


annotated structure of the Challenged Claims

Pet. 9 (citing Ex. 1003 ¶¶ 93–94). The annotated structure of the challenged claims shows a phenoxyphenyl hydrophobic moiety in a red box, a Z' -

structure heterocyclic core in a blue circle, a piperidine linker in a purple box, and a warhead (i.e., a Michael acceptor, which forms the covalent bond to BTK).

Two examples of irreversible BTKIs are IMBRUVICA (ibrutinib), marketed by Patent Owner, and BRUKINSA (zanubrutinib), marketed by Petitioner. Both are FDA approved to treat CLL/SLL and have the following structures, annotated in the same color scheme as the annotated structure above:

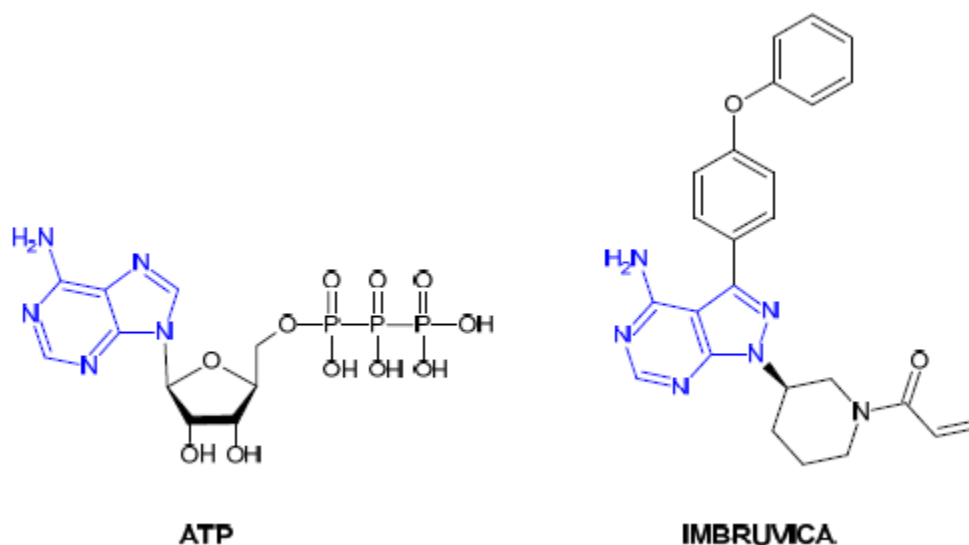


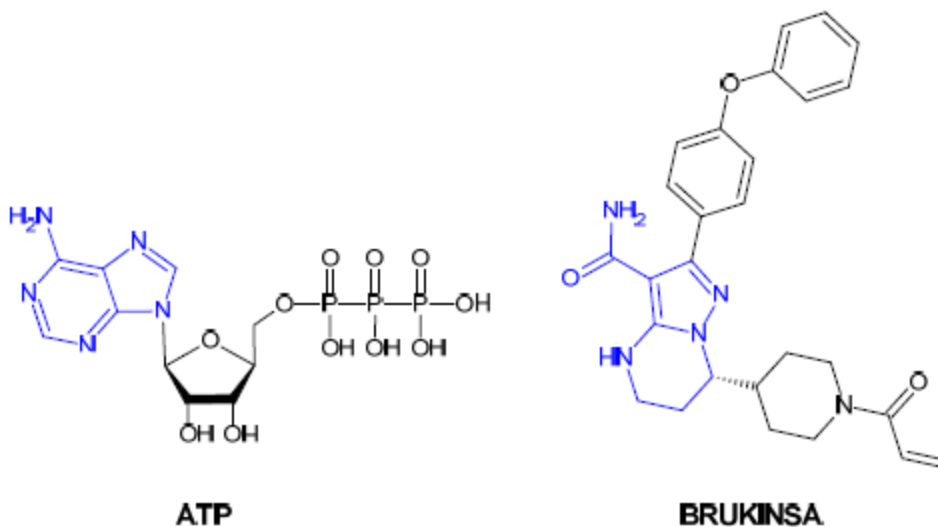
Pet. 10 (citing Ex. 1003 ¶¶ 39); Ex. 1003 ¶¶ 34, 38. The annotated structures show IMBRUVICA and BRUKINSA have the same phenoxyphenyl hydrophobic moiety in red and the same warhead in green, but different Z'-structures in blue and differently oriented piperidine linkers in purple.

Petitioner asserts that there are a number of differences between IMBRUVICA and BRUKINSA, including: (1) the aromaticity of the fused heterocyclic ring system (i.e., IMBRUVICA's ring system is biaryl and BRUKINSA's is non-biaryl); (2) the heteroatom pattern of the ring system (i.e., IMBRUVICA has four N heteroatoms and BRUKINSA has three N heteroatoms at different positions); (3) the substitution pattern on the ring

system (i.e., IMBRUVICA has an amino substitution at C4 of its 6-membered ring, whereas BRUKINSA has an amide substitution at the C3 position of its 5-membered ring); and (4) the linker (i.e., in IMBRUVICA the linker is connected to the N1 atom of the ring system at C3 of the piperidine group, and in BRUKINSA the linker is connected to C7 of the ring system via C4 of the piperidine group). Pet. 10–12 (citing Ex. 1003 ¶¶ 39–48).

Petitioner also states that IMBRUVICA is designed to mimic adenine (the ring system of adenosine triphosphate (ATP)) so that IMBRUVICA can bind to BTK in a mode analogous to adenine. *Id.* at 13 (citing Ex. 1003 ¶¶ 49–55). BRUKINSA, on the other hand, does not attempt to mimic adenine, as its ring system is non-aromatic and has no amino substitution. *Id.* at 14 (citing Ex. 1003 ¶¶ 49, 52). The annotated structures comparing ATP to IMBRUVICA and BRUKINSA are reproduced below:





The annotated structures depict the adenine of ATP in blue and the Z'-structures of IMBRUVICA and BRUKINSA in blue. The adenine of ATP and the Z'-structure of IMBRUVICA are both aromatic with an amino substitution at the C4 position of the 6-membered ring. Pet. 13 (citing Ex. 1003 ¶¶ 54, 55). The Z'-structure of BRUKINSA, on the other hand, has an amide substitution on the 5-membered ring and the phenoxyphenyl hydrophobic moiety is projected from a different position on the 5-membered ring with the linker located on the non-aromatic 6-membered ring. Pet. 14 (citing Ex. 1003 ¶¶ 49, 52).

Petitioner also notes that in a 2021 survey of reported irreversible BTKIs, six BTKIs have a 5:6 fused heterocyclic ring system, like the challenged claims. Pet. 15 (citing Ex. 1003 ¶¶ 49–52; Ex. 1071 at 6). Of those six BTKIs, five are adenine mimetics like IMBRUVICA, and BRUKINSA is the only BTKI that is not. *Id.* (citing Ex. 1003 ¶¶ 49–52, 67).

b) Whether the Specification Describes the Full Scope of the Structural Limitations of Claims 1 and 8

Petitioner asserts that the Specification does not describe the full scope of the “Structural Limitations” of independent claims 1 and 8, which require:

the [recited] skeletal structure, “wherein Z’ is an optionally substituted fused heterocyclic ring system comprising from 2–4 nitrogen heteroatoms” and “wherein the optionally substituted fused heterocyclic ring system consists a 5-membered ring comprising at least one nitrogen heteroatom fused to a 6-membered ring comprising at least one nitrogen heteroatom.”

Pet. 28 (citing Ex. 1003 ¶¶ 92–95). According to Petitioner, the Structural Limitations cover four subgenera defined by the aromaticity of the ring system of the Z’-structure. *Id.* at 58 (citing Ex. 1003 ¶¶ 143–147). The four subgenera of Z’-structures are:

- An aromatic 5-membered ring fused to an aromatic 6-membered ring (“biaryl”)
- An aromatic 5-membered ring fused to a non-aromatic 6-membered ring (“5-aro, 6-non-aro”)
- A non-aromatic 5-membered ring fused to an aromatic 6-membered ring (“5-non-aro, 6-aro”)
- A non-aromatic 5-membered ring fused to a non-aromatic 6-membered ring (“bi-non-aromatic”)

Id. (citing Ex. 1003 ¶ 144). Within each of the subgenera, Petitioner asserts there are at least hundreds of possible ring systems, and each of those hundreds of ring systems can have optional substitutions selected from 21 broad categories, and each of those categories include numerous possible substitutions. *Id.* at 59 (citing Ex. 1003 ¶¶ 148–174). Accordingly, Petitioner’s expert, Dr. Showalter, states that the “number of structural species encompassed by these Structural Limitations is at least in the billions.” Ex. 1003 ¶ 142.

Petitioner further notes that the only compounds expressly disclosed by the Specification that satisfy the Structural Limitations are IMBRUVICA and its positional/chiral isomers. Pet. 29 (citing Ex. 1001, 65:10–25, 71:1–20, 77:10–25, 79:50–65, 80:1–15, 80:37–57 (compounds 4, 9, 13, 14); Ex. 1003 ¶ 102). Petitioner asserts that Formulas (A)–(D) and (F) cover only compounds with the Z'-structure of IMBRUVICA. Moreover, each of those Formulas together with the eight specific ring system embodiments of Formula (E) all teach adenine mimetics. *Id.* at 29 (citing Ex. 1003 ¶¶ 99, 107–109, 111). Notably, according to Petitioner, the Specification “does not describe any BTKI resembling BRUKINSA.” *Id.* at 65 (citing Ex. 1003 ¶¶ 194–208).

Petitioner argues that the Specification fails to disclose structural features common to all members of the genus sufficient to visualize the full scope of the challenged claims. Pet. 66 (citing Ex. 1003 ¶¶ 39–48, 98–117, 190–207). In addition, Petitioner argues there are no blaze marks in the Specification that would guide a POSA from the overly broad, generic structure of Formula (E) to the full scope of the Structural Limitations of the claims. *Id.* at 68–69 (citing Ex. 1003 ¶¶ 112–114, 208). Nor does the Specification provide a representative number of species to show possession of the full scope of the Structural Limitations, as disclosure of a limited number of BTKIs that all belong to the biaryl subgenus does not represent the three non-biaryl subgenera, including BRUKINSA.⁴ *Id.* at 70 (citing Ex. 1003 ¶ 210).

⁴ Although the Specification includes a non-biaryl moiety as an embodiment of the ball of Formula (E) (i.e., “E4”), Petitioner asserts that a POSA would disregard E4 as an error because the Specification identifies it as an example of a “biaryl moiety.” Pet. 67 n.8 (citing Ex. 1003 ¶¶ 115 n.2, 190–191, n.6).

At this stage of the proceeding, we are persuaded that Petitioner has shown that it is more likely than not that the Specification fails to provide written description support for the full scope of the Structural Limitations of claims 1 and 8 for the reasons stated in the Petition. For example, we are persuaded that Petitioner has shown, on this record, that the genus of claimed compounds is large and includes four structurally distinct subgenera. But the Specification's description of representative species is relatively small, disclosing only a limited number of BTKIs that are all within the biaryl subgenus of compounds. Pet. 70 (citing Ex. 1003 ¶¶ 210). Thus, because the Specification does not disclose compounds from any of the three non-biaryl subgenera, including BRUKINSA, we are persuaded that the Specification fails to describe a representative number of compounds "to reflect the structural diversity of the claimed genus." See *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300–01 (Fed. Cir. 2014) (finding lack of written description support where specification failed to describe a species representative of a structurally distinct antibody that fell within the scope of the claimed genus).

Similarly, we are persuaded that Petitioner has shown sufficiently that the Specification fails to describe structural features common to all members

Patent Owner disagrees, arguing the Specification does not limit the use of "biaryl" to the explicit disclosure of the structures and the definition of "aryl" does not exclude structures that are partially non-aromatic. Prelim. Resp. 33–34 n.4. On this record, we find Petitioner has the better position, as the Specification prefaces the structures with "In some embodiments, [the ball] is a substituted fused biaryl moiety *selected from*" and we accept, at this stage of the proceeding, Dr. Showalter's definition of "biaryl" as both the 5- and 6-membered rings are aromatic. Ex. 1001, 62:44–45; Ex. 1003 ¶ 41. That said, the parties are invited to address this issue further during trial.

of the genus that would allow a POSA to visualize the full scope of the challenged claims. For example, although the claims broadly cover non-biaryl ring structures like BRUKINSA that are not adenine mimetics, the Specification describes only BTKIs with biaryl ring structures that act as adenine mimetics. *See* Pet. 67; Ex. 1003 ¶¶ 190–207. Thus, we are persuaded on this record that Petitioner has shown sufficiently that the Specification fails to disclose common structural features or blaze marks that would enable a POSA to visualize the members of the genus. *See Univ. of Minn.*, 61 F.4th at 1358.

In response, Patent Owner first asserts that Petitioner misapplies the relevant written description law, noting that the claims are directed to methods of treatment as opposed to a class of compounds. Prelim. Resp. 40. Patent Owner cites the Board’s decision in *Merck Sharp & Dohme Corp. v. Genentech, Inc.*, PGR2021-00039, Paper 10 at 21–23 (PTAB July 24, 2021) for the proposition that the Board denied institution where the petition “improperly focused on the support for [the] genus of compounds for use in the claimed methods rather than the methods themselves.” Prelim. Resp. 41. The *Merck* decision is distinguishable, however, because there was evidence in the record that numerous examples of the claimed compounds were known and used in the art to treat cancer, as recited in the claims. PGR2021-00039, Paper 10 at 20. Similarly, we are not persuaded—on this record—that *Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629 (E.D. Tex. 2017) (Bryson, J.), *aff’d*, 739 F. App’x 643 (Fed. Cir. 2018) (“*UroPep*”) applies to the facts of this case, as the jury there heard undisputed evidence that hundreds of examples of the claimed compounds were known in the art and that the field of specific selective inhibitors was “pretty mature.” *Id.* at 645–46. In contrast, here, Petitioner’s

expert notes that as of 2021 (let alone 2011), there were only six reported irreversible BTKIs with a 5:6 fused heterocyclic ring system that were approved or under clinical and pre-clinical investigation. Ex. 1003 ¶ 49. Thus, unlike in *Merck* and *UroPep*, there were not hundreds of known BTKIs falling within the scope of the claims at the time of the invention, and thus the knowledge in the art in the field of BTKIs with the claimed structure was arguably not “mature” at the time of the invention. Accordingly, Petitioner’s focus on the breadth of the claimed compounds as opposed to the claimed method is not fatal to the Petition, as Patent Owner asserts.

Patent Owner also asserts that Petitioner mischaracterizes the known structure-activity relationship for irreversible BTKIs, criticizing Petitioner’s reliance on certain references its expert relies on. Prelim. Resp. 57–62 (citing Ex. 1003 ¶¶ 60, 65, 76, 240, 242, 254–256, 279; Ex. 1052; Ex. 1049; Ex. 1036; Ex. 1055; Ex. 1060). According to Patent Owner, none of the references Petitioner relies on supports Petitioner’s contention that substitutions to the Z’ structure can unpredictably affect the binding of the BTKI. *Id.* And, in fact, Patent Owner asserts that Ghose,⁵ cited by Dr. Showalter, teaches the opposite, stating that it is “straightforward to identify the moieties [of a kinase inhibitor] most likely to be involved in hinge binding” and that hinge binding could be “categorized in terms of the ligand core structure and a few simple empirical rules.” Prelim. Resp. 58 (citing Ex. 1052.019–020).

⁵ Ghose et al., *Knowledge Based Prediction of Ligand Binding Modes and Rational Inhibitor Design for Kinase Drug Discovery*, 51 J. MED. CHEM. 5149–71 (2008) (Ex. 1052, “Ghose”).

Patent Owner also notes that Petitioner fails to identify any structure falling within the scope of the claims that does not bind to BTK or form a covalent bond. Prelim. Resp. 64. Patent Owner asserts that this is not surprising given the common structural features of the genus that drives BTK inhibition and covalent binding. *Id.* at 65.

Finally, Patent Owner argues that the Specification provides sufficient blaze marks to the claimed BTKIs. *Id.* at 66–71. Patent Owner asserts that the Specification “provides clear preferences for precise key components of these inhibitors—the phenoxyphenyl and linker-warhead—leaving as partially generic in the claim only the Z’ structure with specific structural constraints (5:6 ring requiring certain heteroatoms) and an understood structure-function relationship.” *Id.* at 68.

There is no dispute that the Specification describes the phenoxyphenyl hydrophobic moiety and the linker-warhead of IMBRUVICA. But the parties dispute the sufficiency of the generic disclosure of the Z’ structure and how well understood the structure-function relationship was in the art in 2011. Petitioner asserts that the “[structure-activity relationship] between the Z’-structure and the function of covalently binding Btk is not fully understood even today, especially for compounds that do not include close structural similarity to adenine.” Pet. 16 (citing Ex. 1003 ¶ 54). Patent Owner, on the other hand, asserts that “there was ‘sufficiently known correlation’ between heterocyclic core structure and hinge-binding function.” Prelim. Resp. 70 (citing Ex. 1052.019-020).

Given the highly fact-dependent nature of written description analyses, most of Patent Owner’s arguments reflect factual disputes that are better addressed at trial with the benefit of further expert testimony that has been subject to cross-examination. On this record, however, in light of the

breadth of the claims and the limited variety of compounds described by the Specification, we are persuaded that Petitioner has shown sufficiently at this stage of the proceeding that the Specification does not adequately disclose common structural features or provide sufficient blaze marks that a POSA in 2011 would visualize the full scope of the claims, including the non-biaryl subgenera of the Structural Limitations and the compounds like BRUKINSA that do not mimic adenine.

Thus, at this stage of the proceeding, we find Petitioner has shown sufficiently that it is more likely than not that the two challenged independent claims 1 and 8 lack written description support in the Specification as of 2011.⁶

4. *Conclusion*

Because we find that at least claims 1 and 8 of the challenged claims lack written description support in any parent application filed before March 15, 2013, we need not address whether the parent applications also fail to enable the claims to determine that the '803 Patent is eligible for post-grant review.

III. ANALYSIS OF GROUNDS

A. *Written Description Support for the Challenged Claims*

Petitioner asserts claims 1–8, 12, and 20 of the '803 Patent fail to meet the written description requirement. Pet. 96; *see also id.* at 64–81. Patent Owner opposes. Prelim. Resp. 39–72.

⁶ Petitioner also argues the Specification fails to provide written description support for various other limitations of the claims. Pet. 71–80. Because we find the Specification fails to adequately describe the full scope of the Structural Limitations, we need not address those additional limitations for purposes of this Decision.

As explained above, we find—on this record—that Petitioner has shown sufficiently that the Specification, which is substantively identical to the '317 Application, fails to provide adequate written description support for the challenged claims. Accordingly, for the same reasons stated above with respect to post-grant review eligibility, we find Petitioner has shown it is more likely than not that the challenged claims are unpatentable for lack of written description support. *See supra* Section II.C.

B. Enablement of the Challenged Claims

Petitioner asserts claims 1–8, 12, and 20 of the '803 Patent fail to meet the enablement requirement. Pet. 96–97; *see also id.* at 81–95. Patent Owner opposes. Prelim. Resp. 72–86. At this stage of the proceeding, we find Petitioner has shown sufficiently that the Specification fails to enable the full scope of the claims.

Under 35 U.S.C. § 112(a), the specification must enable a person skilled in the art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Moreover, the Supreme Court reaffirmed that “the specification must enable the full scope of the invention as defined by its claims,” allowing for “a reasonable amount of experimentation.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610–12 (2023). To determine whether undue experimentation would be required, we may consider the following “*Wands* factors”: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Id.*

We address the parties' respective arguments with respect to each of the *Wands* factors below.

1. *The breadth of the claims*

Petitioner asserts that the claims are very broad, which favors a finding of no enablement. Pet. 82 (citing Ex. 1003 ¶¶ 233, 234; Ex. 1005 ¶¶ 233, 234).

Patent Owner states Petitioner inflates the breadth of the claims, asserting that Petitioner ignores that the claims are limited to “small organic molecules” with specific Structural Limitations. Prelim. Resp. 84. Patent Owner argues that although the claims hypothetically include numerous different compounds, a POSA would understand how to identify operative embodiments. *Id.*

At this stage of the proceeding, we agree with Petitioner that the claims are very broad, even considering the limitations to “small organic molecules” with specific Structural Limitations. As explained above, there are four subgenera of Z'-structures and numerous possible substitutions encompassed by the claims. To the extent the parties dispute how much experimentation would be necessary to identify which compounds to use in the claimed methods, the parties may explore that issue further during trial with the support of expert testimony.

2. *The quantity of experimentation necessary*

Petitioner asserts that as of 2020, extensive testing would be required for a POSA to (1) “synthesize the billions of species that meet the Structural Limitations and determine which of those species would also satisfy the

Functional Limitation⁷ requiring covalently binding to Cys481 or another residue” (Pet. 96, citing Ex. 1003 ¶¶ 276–280; Ex. 1005 ¶¶ 303–307); (2) “determine which of those potentially billions of species would effectively and safely treat CLL/SLL” (Pet. 97, citing Ex. 1003 ¶¶ 276–280); and (3) “determine which of those potentially billions of species would satisfy the lymphocytosis limitation” (Pet. 97, citing Ex. 1003 ¶¶ 303–307).

Patent Owner responds, stating Petitioner inflates the quantity of experimentation necessary to practice the claims by requiring experimentation necessary to establish a therapeutically effective dose sufficient for regulatory approval. Prelim. Resp. 80. Patent Owner notes that regulatory approval is not the standard for enablement. *Id.* Rather, Patent Owner asserts that given the “significant available BTK structural information” available, a POSA would be able to identify appropriate Z'-structures that would bind the hinge region of BTK and confirm BTK binding and inhibition using routine experimentation. *Id.* at 82.

On this record, we agree with Patent Owner that regulatory approval is not the standard for enablement. *See United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1370 (Fed. Cir. 2023) (noting that failed safety study “may be an issue for the FDA,” but it is not an issue for enablement of a “therapeutically effective” dose). Moreover, as explained above, we do not import a safety limitation to the construction of “therapeutically effective amount.” *See supra* Section II.B.1.

⁷ Petitioner defines the “Functional Limitations” of the claims as requiring the BTKI to be irreversible and/or form a covalent bond with Cys481 of a BTK; to treat CLL or SLL by administering a “therapeutically effective amount” and resulting in “lymphocytosis.” Pet. 28–29.

That said, at this stage of the proceeding, we are persuaded that Petitioner has shown sufficiently that significant trial and error experimentation would have been required to confirm whether candidates that satisfy the Structural Limitations would covalently bond Cys481 given the challenging nature of the tests and the sheer breadth of the claims. Pet. 83–84 (citing Ex. 1003 ¶¶ 235–246).

3. *The amount of direction or guidance presented and the presence or absence of working examples*

Petitioner asserts that the Specification discloses limited guidance and limited working examples for each of the Functional Limitations. Pet. 88–90. That is, according to Petitioner, the Specification never describes any specific structural features that would result in covalently binding Cys481 or describes any tests or data demonstrating such binding. *Id.* at 88 (citing Ex. 1003 ¶¶ 247–252). Petitioner notes the Specification provides limited guidance and working examples regarding the clinical trials involving IMBRUVICA, but does not provide any examples or guidance with respect to any other claimed species. *Id.* at 89 (citing Ex. 1003 ¶¶ 255–260). Finally, Petitioner asserts the Specification provides no guidance regarding which of the potentially billions of candidates other than IMBRUVICA satisfy the Structural Limitations and other Functional Limitations such as the lymphocytosis limitation. *Id.* at 90 (citing Ex. 1003 ¶¶ 261–264).

Patent Owner asserts that the Specification provides working examples of the method of irreversibly inhibiting BTK, which leads to treating CLL/SLL and lymphocytosis. Prelim. Resp. 79 (citing Examples 6, 10, 11, 14).

We find Petitioner has made a sufficient showing at this stage of the proceeding. The working examples identified by Patent Owner involving

ibrutinib only enable a POSA “to achieve a small subset of the claimed range.” *MagSil Corp. v. Hitachi Global Storage Techs.*, 687 F.3d 1377, 1384 (Fed. Cir. 2012). According to Petitioner, the Specification fails to describe any specific structural features that would result in covalently binding Cys481 and fails to describe tests or data demonstrating covalent binding to Cys481. Pet. 88 (citing Ex. 1003 ¶¶ 247–252). Thus, we find Petitioner has shown sufficiently on the record before us that this factor favors a finding of nonenablement.

4. *The predictability or unpredictability of the art, the nature of the invention, state of the prior art, and relative skill of those in the art*

Petitioner asserts that each of these factors favors a finding of no enablement, as the nature of the invention was unpredictable and little was known in the art as of July 2020. Pet. 90 (citing Ex. 1003 ¶¶ 253–258). Petitioner asserts that even today, the effect of the Z'-structure on BTK binding activity is unpredictable. *Id.* (citing Ex. 1003 ¶ 254). Moreover, according to Petitioner, the field of CLL/SLL treatment, including the dosing regimens and whether it would result in lymphocytosis is highly unpredictable. *Id.* at 91–92 (citing Ex. 1003 ¶¶ 265–276).

Patent Owner disagrees, arguing that the POSA would have been highly skilled and the state of the art is sophisticated, given the knowledge in the art of kinase design and the specific information available about BTK structure and modeling available. Prelim. Resp. 85–86.

At this stage of the proceeding, notwithstanding Patent Owner's factual disagreement, Petitioner and its expert have shown sufficiently on this record that the art remains unpredictable today, including the effect of the Z'-structure on BTK binding activity. Pet. 90. (Ex. 1003 ¶¶ 253–258).

5. *Conclusion as to enablement*

Having considered Petitioner's arguments regarding the various *Wands* factors, at this stage of the proceeding, we find on balance that Petitioner has shown sufficiently that a POSA would not have been able to practice the full scope of the claimed invention in 2020 without undue experimentation.

That said, like written description, enablement is a highly fact-dependent issue that will benefit from further expert testimony and evidence at trial. The key issues at trial for enablement will be the state of the art in 2020 and whether a POSA would have understood how to make and use the full scope of the claimed invention given the development in the field of BTK inhibitors at that time. As the Federal Circuit has repeatedly instructed, the Specification need not describe "how to make and use every possible variant of the claimed invention, when a range is claimed, there must be reasonable enablement of the scope of the range." *McRo, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 (Fed. Cir. 2020).

C. *Unpatentability over Byrd*

Petitioner asserts claims 1–8, 12, and 20 of the '803 Patent are anticipated by Byrd. Pet. 97–103. Additionally, Petitioner asserts claim 5 is unpatentable as obvious over Byrd and the IMBRUVICA Label. *Id.* at 103–104.

In the Preliminary Response, Patent Owner does not address Petitioner's Grounds 3 and 4 beyond arguing that Byrd is not prior art because Byrd was "published in 2013, after the June 2011 filing date of the non-provisional application to which the '803 Patent claims priority." Prelim. Resp. 86. For the reasons discussed above, we determine that the claims of the '803 Patent are not entitled to claim the benefit of the June

2011 filing date of the '317 Application. *See supra* Section II.C.

Accordingly, we determine on the record before us that Petitioner has shown sufficiently that Byrd is prior art to the '803 Patent.

Having considered the evidence and argument presented in the Petition, we determine Petitioner has shown it is more likely than not that the recited claims are unpatentable by or over Byrd.

1. Byrd (Ex. 1009)

Byrd is a journal article entitled, “Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia.” Ex. 1009, 1.⁸ Byrd discusses the results of “a phase 1b–2 multicenter study to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of ibrutinib (PCI-32765), a first-in-class, oral covalent inhibitor of BTK designed for treatment of B-cell cancers, in patients with relapsed or refractory CLL or small lymphocytic lymphoma.” *Id.* According to Byrd, ibrutinib is a “potent inhibitor (50% inhibitory concentration, 0.5 nM) that covalently binds to the cysteine-481 amino acid of the BTK enzyme.” *Id.* at 2.

In Byrd’s study, patients received a fixed daily dose of 420 or 840 mg of ibrutinib “on a continuous schedule until the onset of disease progression or unacceptable toxicity.” Ex. 1009, 3. Over the course of the study, safety of the treatments, overall response rate, progression-free survival, pharmacodynamics, and pharmacokinetics were assessed. *Id.* Byrd reports that ibrutinib administered to patients orally once daily “was associated with a high frequency of durable remissions in patients with relapsed or refractory

⁸ Citations to Ex. 1009 use the Bates stamped page numbers located on the bottom right corner of each page.

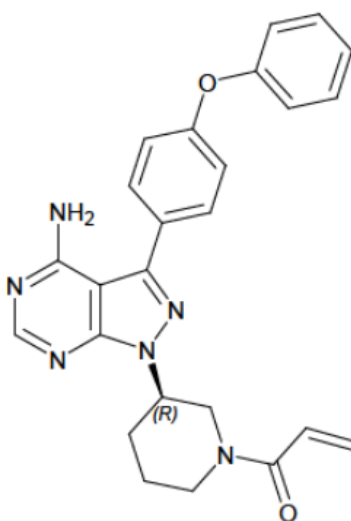
CLL and small lymphocytic lymphoma, including patients with high-risk genetic lesions.” *Id.* at 2.

2. *The IMBRUVICA Label (Ex. 1058)*

The IMBRUVICA Label is a document describing prescribing information for “IMBRUVICA® (ibrutinib) capsules, for oral use.”

Ex. 1058, 1. The IMBRUVICA label explains that ibrutinib is a small-molecule inhibitor of Bruton’s tyrosine kinase (BTK) that forms a covalent bond with a cysteine residue in the BTK active site. *Id.* at 18–19.

According to the IMBRUVICA Label, ibrutinib has the structure reproduced below. *Id.*



The IMBRUVICA Label indicates that IMBRUVICA is for treating Mantle cell lymphoma (MCL), Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL), and Waldenström’s macroglobulinemia (WM). *Id.* at 1. The IMBRUVICA Label indicates that the drug should be orally administered at a dosage of 560 mg once daily for patients with MCL, and orally administered at a dosage of 420 mg once daily for patients with CLL/SLL and WM. *Id.*

3. *Ground 3: Alleged Anticipation by Byrd*

Anticipation requires that “each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citation omitted). “To establish inherency, the extrinsic evidence ‘must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.’” *Id.* (citation omitted). Moreover, to anticipate, a prior art reference must “disclose[] within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim.” *Net MoneyIN, Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008).

Petitioner asserts that Byrd discloses each limitation of claim 1. Pet. 97–100. For example, Petitioner asserts that Byrd discloses a method for treating CLL/SLL by orally administering a fixed daily dose of 420 mg ibrutinib on a continuous schedule until the onset of disease progression or unacceptable toxicity. *Id.* at 97–98 (citing Ex. 1009.001, 3; Ex. 1005 ¶¶ 309–313). Byrd also identifies ibrutinib as a “covalent inhibitor of BTK” (Ex. 1009.007) and states that ibrutinib caused lymphocytosis, which is “not a sign of progressive disease” (Ex. 1009.007, .038). Pet. 98 (citing Ex. 1003 ¶¶ 314–319). Petitioner asserts that Byrd discloses IMBRUVICA as an irreversible BTKI, and a POSA would have known IMBRUVICA’s structure, which satisfies the recited Structural Limitations. Pet. 99 (citing Ex. 1005 ¶¶ 320–323; Ex. 1003 ¶¶ 34–37).

Having considered the evidence and argument cited by the Petition, we are persuaded at this stage of the proceeding that Petitioner has shown it

is more likely than not that Byrd discloses each limitation of claim 1. *See* Pet. 97–100.

We have also considered Petitioner’s evidence and argument with respect to claims 2–7 and 12, which depend from claim 1, as well as independent claim 8 and its dependent claim 20, and find that Petitioner has shown sufficiently that Byrd anticipates those claims, as well, for the reasons stated in the Petition. Pet. 100–103 (citing Ex. 1005 ¶¶ 327–362).

4. *Ground 4: Alleged Obviousness of Claim 5 over Byrd and the IMBRUVICA Label*

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness when presented. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

As explained above, we find Petitioner has shown sufficiently that Byrd discloses each limitation of claim 5. *See supra* Section III.C.3. To the extent it is unclear that the $AUC_{(0-24)}$ of administering 420 mg ibrutinib per day is $>100 \text{ ng}\cdot\text{h}\cdot\text{ml}$, as disclosed in Figure S1 of Byrd, Petitioner asserts that the IMBRUVICA label expressly states that the AUC in patients at 420 mg is $680\pm517 \text{ ng}\cdot\text{h}/\text{ml}$. Pet. 103 (citing Ex. 1058.001; Ex. 1005 ¶¶ 365–367). Petitioner asserts that a POSA “would have looked to the Label to

confirm that the method of Byrd resulted in the claimed AUC because Byrd and the Label are directed to the same dosing regimen.” *Id.*

On this record, we find Petitioner has shown sufficiently that claim 5 of the ’803 Patent would have been unpatentable as obvious over Byrd and the IMBRUVICA Label.

IV. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 325(d)

Lastly, we address Patent Owner’s request that we exercise our discretion to deny institution under 35 U.S.C. § 325(d). Prelim. Resp. 21–38. For the reasons discussed below, we decline to do so.

A. Legal Standards

Under § 325(d), we have discretion to deny a petition that presents the same or substantially the same prior art or arguments as previously presented to the Office. *See* 35 U.S.C. § 325(d).

In performing an analysis under § 325(d), the Board uses a two-part framework:

(1) We consider whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and

(2) If either condition of the first part of the framework is satisfied, we consider whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6, 8 (PTAB Feb. 13, 2020) (precedential).

To help us evaluate the *Advanced Bionics* framework, we consider a number of non-exclusive factors, as set forth in our decision in *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at

17–18 (PTAB Dec. 15, 2017) (precedential) (“the *Becton, Dickinson* factors”):

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
- (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, IPR2017-01586, Paper 8 at 17–18.

According to *Advanced Bionics*, *Becton, Dickinson* factors (a), (b), and (d) relate to whether the same or substantially the same art or arguments previously were presented to the Office, and factors (c), (e), and (f) relate to whether the petitioner has demonstrated a material error by the Office.

Advanced Bionics, IPR2019-01469, Paper 6, 9–11.

B. Analysis

Patent Owner argues that we should exercise our discretion to deny institution under § 325(d) because the Examiner extensively considered § 112 support for the challenged claims during prosecution of the ’803 Patent. On this record, we are not persuaded that we should exercise our discretion under § 325(d) in this proceeding to deny institution of a trial.

I. Brief Summary of Relevant Prosecution History

During prosecution of the '803 Patent, the Examiner issued a rejection under § 112 in the Office Action dated June 6, 2022, for claims directed to methods of using irreversible BTKIs without structural limitations. Ex. 1002, 433, 436–452. The Examiner stated the claims to irreversible inhibitors of Btk included any chemical compounds, peptides, molecules, macromolecules, etc. that can irreversibly bind to BTK, but stated that the Specification does not describe all irreversible inhibitors of BTK to show possession of the invention. *Id.* at 447–48. In response, Applicants amended the claims to recite certain Structural Limitations and argued that the Specification describes the structure of BTK, the degree of interaction of the claimed BTKIs with Cys481 of BTK, and a POSA would be able to determine which BTKIs that fall within the present genus would bind to BTK at this position and would thereby be irreversible. *Id.* at 556–557; *see also id.* at 578 (stating after an Examiner interview that the claims “have been amended to specify a particular genus of small molecule, irreversible Btk inhibitors having **the particular chemical structure**”) (emphasis in original).

The Examiner, however, maintained the § 112 rejection in the Office Action dated December 27, 2022, stating “Applicants do not have support for all the fused heterocyclic ring systems as claimed.” *Id.* at 588, 593. The Examiner stated that “Applicants have support for the broadest definition of Z', in page 79 with a fused biaryl moiety of the following [identifying the eight embodiments of Formula (E)].” *Id.* at 593–594. The Applicants amended the claims after Final Rejection to specify the size of the rings and the amount of nitrogen heteroatoms in each ring. *Id.* at 629, 638.

The Examiner then issued a Notice of Allowance on May 17, 2023, entering an Examiner's Amendment to change the term "optionally substituted fused heterocyclic ring system comprises" to "optionally substituted fused heterocyclic ring system consists [of]." *Id.* at 656–57.

2. *Step 1: whether the same or substantially the same art or arguments previously were presented to the Office*

We first consider whether the same or substantially the same art or arguments previously were presented to the Office. *Advanced Bionics*, Paper 6, 8. Petitioner's Grounds 1 and 2 challenge the patentability of the '803 Patent based on a lack of written description support and enablement under 35 U.S.C. § 112(a). Patent Owner contends that both of these issues were addressed during prosecution, because the Examiner "issued two extensive office actions, detailing both written description and enablement rejections," "considered five responses and supplemental submissions from Pharmacyclics concerning the patentability of the claims," "engaged in five interviews, including multiple interviews discussing § 112 support and claim amendments to the genus of BTKIs in the claims," and ultimately granted the claims after considering a series of amendments by the Applicant. Prelim. Resp. 22–24 (citing Ex. 1002, 358–62, 421, 423–30, 432–70, 548, 550–60, 570–80, 587–615, 628–40, 656–57, 660).

Patent Owner asserts that because the Examiner issued multiple § 112 rejections based on the breadth of the claimed compound genus that "substantially the same arguments were previously presented to the Office." Prelim. Resp. 27. We disagree. Although it is true the written description rejections were based on the breadth of the claims, each rejection was aimed at a specific issue not present here. The first rejection focused on the scope of the term "irreversible inhibitor of [BTK]," which included chemical

compounds, peptides, molecules, macromolecules, etc. *Id.* at 447–48. The second rejection focused on how the term “optionally substituted fused heterocyclic ring system” could include three or more rings of unlimited size. *Id.* at 593–94. Although the Examiner considered the written description support of several different claim terms during prosecution, we agree with Petitioner in that it appears from the prosecution history of the ’803 Patent that the Examiner may not have considered the aromaticity of the heterobicyclic core (i.e., the four subgenera), the substitution patterns, and the heteroatom patterns. Pet. 50 (citing Ex. 1003 ¶ 142).

That the Examiner did not consider those aspects of the claims is evident in the Examiner’s written description rejection in a related U.S. Patent Application for substantively similar claims, which does not appear in the prosecution history of the ’803 Patent. *See* Ex. 2005. As Petitioner notes, the Examiner’s rejection mirrors several arguments made in the Petition, including the breadth of the four subgenera of possible ring systems for the Z-structures and the unpredictability of the Z-structure on whether the BTKI will covalently bind BTK and inhibit BTK irreversibly. Prelim. Reply 2 (citing Ex. 1100.0007–11, 22–24). From this express consideration of these written description issues in the related application with no commensurate consideration in the prosecution history of the ’803 Patent, we find this to be strong evidence that the Examiner did not consider these specific written description issues during prosecution of the ’803 Patent.

We, therefore, find Patent Owner has not satisfied the first prong of *Advanced Bionics* and we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d). Moreover, as explained above, we find Petitioner has shown sufficiently on this record that it is more likely than not

that the challenged claims lack § 112 written description support. *See supra* Section III.A.

Because we determine that we will not exercise our discretion to deny institution with respect to Ground 1 and trial should be instituted on this ground, we need not address Patent Owner’s contentions that we should exercise our discretion to deny institution of Grounds 3 and 4. That is because, under the Supreme Court’s decision in *SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348 (2018), if we institute trial on one ground, we must institute this post-grant review on all grounds raised in the Petition. *See* 37 C.F.R. § 42.208(a) (“When instituting post-grant review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim.”); *see also* Guidance on the impact of *SAS* on AIA trial proceedings, *available at* <https://www.uspto.gov/patents/ptab/trials/guidance-impact-sas-aia-trial> (“If the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition.”).

V. CONCLUSION

For the foregoing reasons, we determine that Petitioner has shown that it is more likely than not that at least one of the challenged claims of the ’803 Patent is unpatentable. Accordingly, we institute a post-grant review of claims 1–8, 12, and 20 of the ’803 Patent.

Our determination in this Decision is not a final determination on the patentability of the challenged claims and, thus, leaves undecided any factual issues necessary to determine whether sufficient evidence supports Petitioner’s contentions by a preponderance of the evidence in the final written decision. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting in the context of an *inter partes* review that “there is a significant difference between a petitioner’s burden to establish a

‘reasonable likelihood of success’ at institution, and actually proving invalidity by a preponderance of the evidence at trial”) (quoting 35 U.S.C. § 314(a) and comparing § 316(e)).

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 324(a), a post-grant review of claims 1–8, 12, and 20 of the ’803 Patent is *instituted* with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 324(c) and 37 C.F.R. § 42.4(b), post-grant review of the ’803 Patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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