

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ACERTA PHARMA B.V.,
Patent Owner.

Case IPR2023-00478
Patent 10,272,083 B2

PETITION FOR *INTER PARTES* REVIEW

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1003	Declaration of Sylvia Hall-Ellis, Ph.D.
1004	Prosecution History of U.S. Patent No. 10,272,083 (Application No. 15/112,968)
1005	U.S. Patent No. 9,758,524 to Barf, et al. (“Barf”)
1006	PCT International Publication No. WO2013/010868 to Barf, et al. (“Barf-PCT”)
1007	U.S. Provisional Application No. 61/509,397 to Barf, et al. (“Barf Provisional”)
1008	Bruce D. Cheson, et al., <i>Advancements in the Treatment of B-Cell Malignancies</i> (International Conference on Malignant Lymphoma), CLINICAL ADVANCES IN HEMATOLOGY & ONCOLOGY, Vol. 11, Issue 9, Supplement 12 (Sept. 2013) (“Cheson”)
1009	Ranjana H. Advani, et al., <i>Bruton Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) Has Significant Activity in Patients With Relapsed/Refractory B-Cell Malignancies</i> , J. CLINICAL ONCOLOGY, 31(1):88-94 (Jan. 2013) (“Advani”)
1010	John C. Byrd, et al., <i>Acalabrutinib (ACP-196) in Relapsed Chronic Lymphomatic Leukemia</i> , N. ENGL. J. MED. 374(4):323-32 (Jan. 2016) (“Byrd”)
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1015	M. Dreyling, et al., <i>How to manage mantle cell lymphoma</i> , LEUKEMIA 28:2117-31 (2014) (“Dreyling”)
1016	IMBRUVICA™ (ibrutinib) Prescribing Information (2014)
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1019	Claire V. Hutchinson, et al., <i>Breaking good: the inexorable rise of BTK inhibitors in the treatment of chronic lymphocytic leukaemia</i> , BRITISH J. OF HAEMATOLOGY 166:12-22 (2014) (“Hutchinson”)
1020	Jennifer R. Brown, et al., <i>Phase I Study Of Single Agent CC-292, a Highly Selective Bruton’s Tyrosine Kinase (BTK) Inhibitor, In Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)</i> , BLOOD 122(21):1630 (2013) (“Brown”)
1021	Daniel W. Pierce, et al., <i>Target Engagement, Pathway Inhibition, and Efficacy Of The Bruton’s Tyrosine Kinase (Btk) Inhibitor CC-292</i> , BLOOD 122(21):4169 (2013) (“Pierce”)
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1026	International Conference on Harmonisation; Dose-Response Information to Support Drug Registration; Guideline; Availability, 59 Fed. Reg. 55,972 (Nov. 9, 1994)
1027	U.S. Food and Drug Administration, <i>Guidance for Industry - S9 Nonclinical Evaluation for Anticancer Pharmaceuticals</i> (March 2010) (“S9 Guidance”)
1028	U.S. Food and Drug Administration, <i>Guidance for Industry - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers</i> (July 2005) (“MSSD Guidance”)
1029	Erica K. Evans, et al., <i>Inhibition of Btk with CC-292 Provides Early Pharmacodynamic Assessment of Activity in Mice and Humans</i> , J. PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 346:219-228 (Aug. 2013) (“Evans”)

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1032	Sarah Brumskill, et al., <i>Conference Scene: Recent developments in the understanding and treatment of hematological malignancies</i> , INT’L J. HEMATOLOGIC ONCOLOGY, Vol. 2, No. 5, published online at https://doi.org/10.2217/ijh.13.52 (Oct. 8, 2013) (“Brumskill”)
1033	Toshio Yoshizawa, et al., <i>ONO-4059—a Potent and Selective Reversible Bruton’s Tyrosine Kinase (Btk) Inhibitor: Single Agent, Twice Daily (BD) Dosing and Dosing with Food Results in Sustained, High Trough Levels of ONO-4059, Translating into 100% Tumour Remission in a TMD-8 Xenograft Model</i> , BLOOD, 124(21):4502 (2014) (“Yoshizawa”)
1034	Plaintiffs’ Initial Infringement Contentions to Defendant Sandoz Inc., C.A. No. 22-154-GBW-SRF (Consolidated) (D. Del. Sept. 26, 2022)
1035	CALQUENCE® (acalabrutinib) Prescribing Information (2017)
1036	Jan de Jong, et al., <i>Effect of CYP3A perpetrators on ibrutinib exposure in healthy participants</i> , PHARMACOLOGY RESEARCH & PERSPECTIVES, Vol. 3, Issue 4 (2015) (“de Jong”)
1037	Dominique Levêque, <i>Evaluation of Fixed Dosing of New Anticancer Agents in Phase I Studies</i> , ANTICANCER RESEARCH 28:3075-78 (2008) (“Levêque”)
1038	ZYDELIG® (idelalisib) Prescribing Information (2014)
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1041	LYNPARZA™ (olaparib) Prescribing Information (2014)
1042	Betty Y. Chang, et al., <i>Egress of CD191CD51 cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients</i> , BLOOD 122(14):2142 (2013) (“Chang”)
1043	Yan Bao, et al., <i>Tyrosine Kinase Btk Is Required for NK Cell Activation</i> , J. Biological Chemistry 287(28):23769 (2012)

GLOSSARY OF ABBREVIATIONS

BCR.....	B-cell receptor
BID, b.i.d., BD	twice a day (<i>bis in die</i>)
BTK, Btk	Bruton's Tyrosine Kinase
CLL	chronic lymphocytic leukemia
EC50, IC50.....	half-maximal effective/inhibitory concentration
FDA.....	U.S. Food and Drug Administration
MCL	mantle-cell lymphoma
MPEP	Manual of Patent Examining Procedure
NHL.....	non-Hodgkin's lymphoma
NK	natural killer [cells]
nM	nanomolar
ORR.....	overall response rate
PCT	Patent Cooperation Treaty
PI3K	phosphoinositide 3-kinase
POSA.....	person of ordinary skill in the art
QD	once a day (<i>quaque die</i>)
μM.....	micromolar
SLL.....	small lymphocytic leukemia

I. INTRODUCTION

Petitioner requests *inter partes* review of claims 8-12 and 19-20 of U.S. Patent No. 10,272,083 (the “’083 patent”). These claims are directed to treating mantle-cell lymphoma (“MCL”) by orally administering 100 mg twice daily of acalabrutinib, a known inhibitor of Bruton’s Tyrosine Kinase (“BTK”). As shown below and by Petitioner’s expert, Dr. Fruehauf (EX1002), all challenged claims would have been obvious to a person of ordinary skill in the art (“POSA”) by the ’083 patent’s effective filing date on January 21, 2015, based on two grounds.

First, all challenged claims would have been obvious over Barf (EX1005) and Cheson (EX1008). *Infra* §X.A. Barf is an issued patent with an effective filing date in 2011, whose sole independent claim recites a method of treating MCL with acalabrutinib. EX1005, 150:2-32. Barf’s claim 12 narrows this method by reciting a dosing range that overlaps with the ’083 patent’s claimed 100 mg dose (*id.*, 151:14-16), triggering “a presumption of obviousness.” *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004). Moreover, a POSA would have arrived at the claimed dose through routine experimentation by conducting a dose-finding study focused on maximizing BTK occupancy, which was successfully done for previous BTK inhibitors. EX1002 ¶¶15, 127-42.

Administering the claimed dose twice daily would have been obvious over Cheson’s teaching that “BTK inhibitors are being evaluated in a twice-daily

schedule in an attempt to overcome the synthesis of new BTK molecules,” which “appeared to be more effective” in clinical trials. EX1008, 4, 10; EX1002 ¶16.

Second, to the extent Patent Owner attempts to disqualify Barf as prior art, all challenged claims would have been obvious over Barf-PCT (EX1006) and Cheson. *Infra* §X.B. Barf-PCT is the international application counterpart to Barf, published in 2013. EX1006, 1. Thus, Barf-PCT provides the same disclosures as Barf—including acalabrutinib, treating MCL, and the overlapping dosing range. *Id.*, 35:16-36:2, 22:15-16, 20:24-25; EX1002 ¶17.

During prosecution, the Examiner repeatedly found the claims *prima facie* obvious and allowed them only after the applicants alleged unexpected results. *Infra* §IV.C. As shown below, however, the alleged results were neither probative nor unexpected. *Infra* §X.C. Thus, the Examiner’s basis for allowance was incorrect, and the challenged claims are unpatentable.

Patent Owner is currently asserting these claims against generic drug makers of acalabrutinib, including Petitioner. Instituting review and canceling the challenged claims will thus promote the Office’s objective to ensure that the patent “system, as a whole, does not unnecessarily delay generic and biosimilar competition, which provide cost savings to Americans when they purchase pharmaceutical products.” 87 Fed. Reg. 60,130, 60,131 (Oct. 4, 2022).

II. MANDATORY NOTICES

Under 37 C.F.R. §42.8(b), Petitioner states as follows:

1. ***Real party-in-interest.*** For purposes of this Petition only, the real party-in-interest is Sandoz Inc.

2. ***Related matters.*** The '083 patent has been asserted in the following civil actions: *Acerta Pharma BV v. Cipla Ltd.*, No. 1-22-cv-00162 (D. Del.); *Acerta Pharma BV v. MSN Pharms. Inc.*, No. 1-22-cv-00163 (D. Del.); *Acerta Pharma BV v. Sandoz Inc.*, No. 1-22-cv-00164 (D. Del.); *Acerta Pharma BV v. Alembic Pharms. Ltd.*, No. 1-22-cv-00154 (D. Del.); *Acerta Pharma BV v. Natco Pharma Ltd.*, No. 1-22-cv-00155 (D. Del.).

No prior IPR petition for the '083 patent has been filed.

The '083 patent is related to U.S. Patent No. 11,090,302.

3. ***Lead and back-up counsel.*** Petitioner identifies the following:

- *Lead counsel:* Jovial Wong (Reg. No. 60,115)
- *Back-up counsel:* Charles B. Klein*
- *Back-up counsel:* Eimeric Reig-Plessis*
- *Back-up counsel:* Sharon Lin*

* Counsel to seek *pro hac vice* admission.

4. ***Service information.*** Petitioner identifies the following:

- *Email address:* acalabrutinibIPR@winston.com

- *Mailing address:* Winston & Strawn LLP
1901 L Street NW
Washington, DC 20036
- *Telephone number:* 202-282-5867
- *Fax number:* 202-282-5100

Please address all correspondence to lead counsel at the address shown above. Petitioner consents to electronic service at the above-listed email address.

III. REQUIREMENTS FOR REVIEW

Under 37 C.F.R. §42.104, Petitioner certifies:

- a. *Grounds for standing.*** The '083 patent is available for IPR.

Petitioner is not barred or estopped from requesting review of any claim on any ground. All fees may be charged to Deposit Account No. 50-1814.

- b. *Identification of challenge.*** As explained further below, Petitioner requests cancelation of claims 8-12 and 19-20 under the following grounds:

Ground	Claims	Basis ¹	References
1	8-12, 19-20	103	Barf, Cheson
2	8-12, 19-20	103	Barf-PCT, Cheson

IV. THE '083 PATENT

A. Specification

The '083 patent is titled “Methods of treating chronic lymphocytic leukemia and small lymphocytic leukemia using a BTK inhibitor.” EX1001. The “Background of the Invention” explains that BTK is a “protein kinase expressed in B cells” whose function “is well established.” EX1001, 1:14-18. Citing prior art, the specification admits that “[t]he reported role for BTK in the regulation of proliferation and apoptosis [i.e., death] of B cells indicates the potential for BTK inhibitors in the treatment of B cell lymphomas,” and “BTK inhibitors have thus been developed as potential therapies.” *Id.*, 1:28-32.

Like the title, the specification focuses on “B cell chronic lymphocytic leukemia (CLL)” (*id.*, 1:34) and “[s]mall lymphocytic leukemia (SLL)” (*id.*, 1:45).

¹ The '083 patent was filed in 2015 and claims priority to provisional applications filed in 2014 (EX1001, 1), after the effective date of March 16, 2013, for the Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287-88 (2011). Thus, this Petition applies the AIA version of Title 35.

The specification discloses treatments for these conditions by administering a compound of “Formula (II),” i.e., acalabrutinib. *Id.*, 2:37-47. The only recited clinical data is from a study on CLL. *Id.*, 7:24-61, Figs. 2-8. The patent contains no *in vivo* or clinical data on MCL. EX1002 ¶43.

The specification does not ascribe any significance to any particular doses, recognizing that “[t]he amounts of BTK inhibitors administered” may vary in “the discretion of the prescribing physician.” EX1001, 42:29-33. The patent states that “an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day,” with exemplary ranges spanning 1-500 mg. *Id.*, 42:33-34, 43:12-38. As to frequency, the patent states that dosing may occur as rarely as “once a month” or as often as “six times per day.” *Id.*, 42:50-62.

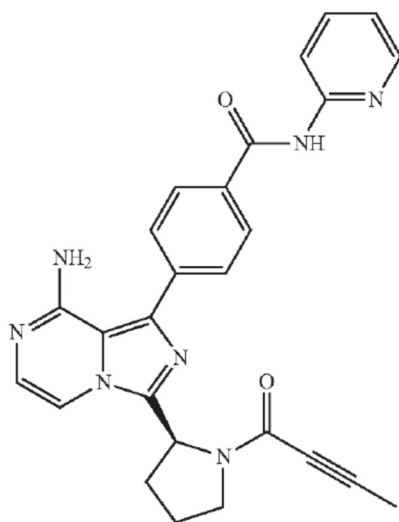
The only mention of dosing for MCL is in a list including 10 other conditions. *Id.*, 4:1-33. For these conditions, the patent recites administration “once daily at a dose selected from the group consisting of 100 mg, 175 mg, 250 mg, and 400 mg” or “twice daily at a dose of 100 mg.” *Id.*, 4:16-17, 4:33. No data is provided for these dosing regimens to treat MCL. EX1002 ¶45.

B. Claims

The '083 patent has two independent claims: 1 and 8. Claim 1 and its dependent claims, which Petitioner is not challenging, recite “treating chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL).” EX1001,

99:2-3. Claim 8 is the sole independent claim challenged in this Petition and recites a method of treating MCL:

8. A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of orally administering, to the human subject, a dose of 100 mg twice daily of a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II):



or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.

Id., 100:39-65.

The challenged dependent claims exclude hydrates or solvates (claim 9), recite intended effects of certain treatment durations (claim 10), limit MCL to certain morphologies (claim 11), add combination therapy with an anti-CD20 antibody (claim 12), require the free form of acalabrutinib (claim 19), or require a salt form (claim 20).

C. Prosecution history

None of the originally filed claims were specific to treating MCL. Like its issued version, claim 1 recited a treatment for CLL/SLL. EX1004, 4. The only other independent claim (originally numbered 9) was a Markush claim reciting “[a] method of treating a hematological malignancy” that only mentioned MCL as one of 11 conditions. *Id.*, 5.

The Examiner rejected the claims as obvious over U.S. Patent Application Publication No. 2013/0338172 (“Smyth ’172”) and Barf-PCT, which the Examiner called “Johannes” or “868.” EX1004, 908. The Examiner relied on Smyth ’172, which describes an oral formulation of ibrutinib (another BTK inhibitor) because it “is similar to the compound of the instant claims and is used to treat similar disorders.” *Id.*, 909. The Examiner relied on Barf-PCT for acalabrutinib’s structure, stating (erroneously) that “[t]he compound of example 1 is identical to that of the instant claimed formula (II).” *Id.* The Examiner found “[i]t would have been obvious to include the compound of the 868 into the formulation of the 172 as the compound[s] have the same cores and treat the same conditions.” *Id.*

In response, the applicants amended both independent claims to recite “a human subject suffering” from the recited conditions. *Id.*, 989, 991. For claim 9 (which issued as claim 8), “hematological malignancy” was changed to “mantle

cell lymphoma (MCL).” *Id.*, 991. For both claims, the applicants added the dosing regimen, “100 mg twice daily.” *Id.*, 989-91.

In their remarks, the applicants revealed a reason for their newfound focus on MCL and the claimed regimen: On October 31, 2017—nearly four years from the earliest claimed priority date—FDA approved acalabrutinib (CALQUENCE®) 100 mg twice daily to treat MCL. *Id.*, 994. Thus, the applicants amended then-claim 9 to recite what is, in essence, “the dosing regimen specified in the approved label for CALQUENCE®”—a regimen that was not previously claimed. *Id.*, 995.

Addressing the obviousness rejection, the applicants conceded that acalabrutinib is disclosed in Barf-PCT, but they correctly noted that this disclosure is in “Example 6,” not Example 1 as the Examiner mistakenly found. *Id.*, 997. As for Smyth ’172, the applicants did “not agree” that ibrutinib and acalabrutinib “have the same core or are similar compounds.” *Id.* Citing three structural differences, the applicants argued that “[a]lthough the compounds have activity as BTK inhibitors, they are not structurally similar and, therefore, have distinct pharmacological properties.” *Id.*

The applicants further argued that even if the compounds were structurally similar, the dosing for ibrutinib would not lead a POSA to the claimed regimen. *Id.*, 998-1000. The applicants explained that ibrutinib (IMBRUVICA®) was FDA-approved in the prior art to treat MCL at a higher, once-daily dose of 560 mg. *Id.*,

998-99. Thus, the applicants argued that, under the Examiner's theory starting from ibrutinib, a POSA would not expect success given "the larger dose, once daily treatment for IMBRUVICA®." *Id.*, 1000. According to the applicants, "[i]t was unexpected that acalabrutinib could be orally administered twice daily at a significantly lower dose (100 mg BID) than ibrutinib," and a POSA "considering the '172 application would not have expected the lower amount BID dosing of acalabrutinib to be sufficient to provide for full BTK occupancy...." *Id.*, 1002.

The applicants cited certain clinical data, but only for CLL. First, they cited Example 2 in the specification on treating CLL with once-daily acalabrutinib. *Id.*, 1000-01. Second, they cited Byrd (EX1010), which included twice-daily dosing but only in patients with "relapsed CLL." EX1004, 1001.

The Examiner was unpersuaded and entered a final rejection, citing Smyth '172, Barf-PCT, and a third reference, Evarts (U.S. Patent Application Publication No. 2014/0179673). *Id.*, 1034. The Examiner's reliance on Barf-PCT was unchanged and included the same erroneous citation to Example 1 (instead of Example 6) for acalabrutinib's structure. *Id.* Instead of citing Barf-PCT for acalabrutinib's dosing (EX1006, 20:24-25), the Examiner cited Evarts as disclosing 100-150 mg doses for other BTK inhibitors (EX1004, 1035).

The applicants focused their response on unexpected results. *Id.*, 1077-79. Because the Examiner continued to rely on Smyth '172 as a primary reference,

they repeated that “[i]t was unexpected that acalabrutinib could be orally administered twice daily (BID) and at a significantly lower dose (100 mg BID)” than ibrutinib. *Id.*, 1077. They also provided a more detailed discussion of Byrd, which compared four once-daily cohorts (ranging 100-400 mg) to a single twice-daily cohort (100 mg) in CLL patients. *Id.*, 1078-79.

While acknowledging that “BTK target occupancy was complete (99 to 100%) four hours after dosing for all cohorts,” the applicants cited a difference in degree of BTK occupancy “immediately before administration of the next dose (at trough).” *Id.*, 1079. The applicants argued that this numerical difference in trough BTK occupancy was an “unexpected benefit.” *Id.* Further, to contrast this result with ibrutinib, they quoted Byrd’s statement that “twice-daily dosing of ibrutinib ... may not be possible owing to the potential for drug accumulation given the ibrutinib half-life of 4 to 13 hours.” *Id.*, 1078.

This time, the Examiner was persuaded and allowed the claims with the following Reasons for Allowance:

While other BTK inhibitor compounds, are known in the prior art, they differ [sic] chemically from [sic] heinstant [sic] invention. Further the 100 mg, twice daily oral dosage in [sic] unexpectadtly [sic] superior for BTK inhibition without increase [sic] toxicity. The closets [sic] chemical compound in the prior art is ibrutinib, but the half0life [sic] is such that a twice daily dosage would not be effective.

Id., 1382.

V. EFFECTIVE FILING DATE

The effective filing date of the challenged claims is January 21, 2015, the filing date of International Application PCT/IB2015/000645. EX1001, 1(22).

Although the '083 patent claims priority to three provisional applications filed in 2014, none describes treating MCL by administering 100 mg of acalabrutinib twice daily, as required by the challenged claims. EX1002 ¶65.

Provisional Application Nos. 61/974,665 (April 3, 2014) and 62/035,777 (August 11, 2014) describe treating lymphoma by administering a BTK inhibitor combined with a PI3K inhibitor. *Id.* ¶66; EX1012; EX1013. Neither discloses twice-daily administration of 100 mg acalabrutinib to treat MCL. *Id.* Provisional Application No. 61/929,742 (January 21, 2014) is a phase I dose-escalation protocol for acalabrutinib in CLL patients. *Id.* ¶67; EX1011. It does not disclose a twice-daily dose of 100 mg acalabrutinib, let alone for MCL. *Id.* On the contrary, it states that “ACP-196 [i.e., acalabrutinib] is intended to be administered orally once daily” in subjects with CLL/SLL. EX1011, 32, 28. Thus, none of the cited

provisional applications provides written-description support for the challenged claims. EX1002 ¶68.²

VI. LEVEL OF ORDINARY SKILL

A POSA for purposes of the challenged claims would have been an oncologist with at least a medical degree (M.D.) and five years' clinical experience treating lymphomas/leukemias and/or researching treatments for them. *Id.* ¶70. A POSA would have had experience designing, conducting, or participating in clinical trials on oncology drugs and would have been familiar with the state of the art regarding the clinical development and use of BTK inhibitors. *Id.* Dr. Fruehauf meets this definition today and as of January 21, 2015. *Id.* ¶71.

VII. CLAIM CONSTRUCTION

For purposes of this Petition only, Petitioner proposes the following constructions under 37 C.F.R §42.104(b)(3).

² Petitioner's grounds references predate the earliest provisional filing of January 21, 2014, so this Petition would establish obviousness even if the claims were entitled to this priority date. Petitioner cites background references published between January 21, 2014, and January 21, 2015, which provide additional corroborating support but are not necessary to the grounds.

A. “A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of orally administering, to the human subject” (claim 8)

Claim 8’s preamble should be construed as limiting as to the intentional purpose for which the method must be performed, but without requiring any particular level of efficacy or result of the intended treatment.

The Federal Circuit considered similar preambles in *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329 (Fed. Cir. 2003), and *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001). In both cases, like claim 8 here, the claims recited methods of treating a human with a medical condition:

Claim in <i>Jansen</i>	Claim in <i>Rapoport</i>	’083 patent claim 8
“A method of <i>treating</i> or preventing macrocytic-megaloblastic anemia <i>in humans</i> ... which comprises administering a daily oral dosage of a vitamin preparation <i>to a human in need thereof</i> ”	“A method for <i>treatment</i> of sleep apneas comprising administration of a therapeutically effective amount of a Formula I azapirone compound ... <i>to a patient in need of such treatment...</i> ”	“A method of <i>treating</i> a mantle cell lymphoma (MCL) <i>in a human subject suffering therefrom</i> comprising the step of orally administering, <i>to the human subject...</i> ”

Jansen, 342 F.3d at 1330; *Rapoport*, 254 F.3d at 1056; EX1001, claim 8 (emphases added). In both *Jansen* and *Rapoport*, the Federal Circuit held the preamble limiting because it “sets forth the objective of the method,” and the “recitation of a

patient or a human ‘in need’ gives life and meaning to the preambles’ statement of purpose.” *Jansen*, 342 F.3d at 1333 (citing *Rapoport*, 254 F.3d at 1061). The Federal Circuit held “[t]he preamble is therefore a statement of the intentional purpose for which the method must be performed.” *Id.* As in *Jansen* and *Rapoport*, claim 8’s preamble recites a purpose, “treating a mantle cell lymphoma (MCL).” And, like *Jansen* and *Rapoport*’s patient “in need,” claim 8’s “human subject suffering therefrom” gives life and meaning to that purpose.

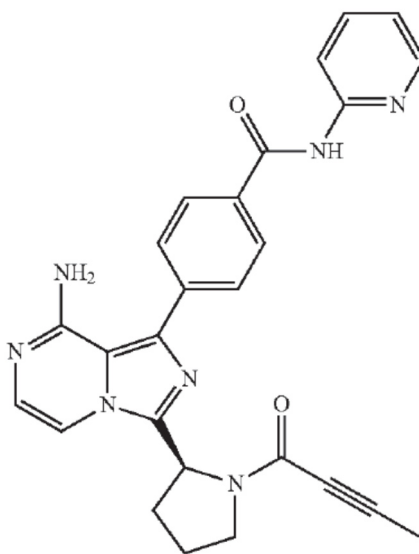
In *Jansen*, a limiting construction was “bolstered by an analysis of the prosecution history” because “the ‘treating or preventing ...’ phrase and the ‘to a human in need thereof’ phrase were added to gain allowance.” 342 F.3d at 1333. Similarly, here, “in a human subject suffering therefrom” and “the human subject” were added after prior-art rejections. EX1004, 991, 994-95.

Thus, claim 8’s preamble is “a statement of the intentional purpose for which the method must be performed.” *Jansen*, 342 F.3d at 1333. Beyond requiring the claimed method to be performed for the purpose (i.e., with intent) of treating MCL, however, there is no basis to import any efficacy requirement or result of the intended treatment. Notably, the specification does not provide any *in vivo* or clinical data showing that acalabrutinib is effective for treating MCL, let alone with the claimed dosing regimen. EX1002 ¶74.

An instructive decision by now-Federal-Circuit-Judge Stark is *Novartis Pharmaceuticals Corp. v. Accord Healthcare Inc.*, 387 F. Supp. 3d 429 (D. Del. 2019). There, Judge Stark construed preambles reciting methods for treating multiple sclerosis (“MS”) in patients “in need thereof.” *Id.* at 435. Applying *Jansen* and other cases, Judge Stark held the preambles limiting but rejected the patentee’s attempt to add “an additional limitation, that the claims also ‘require an actual effect.’” *Id.* at 435-37. Judge Stark explained: “While the general purpose of the invention is to achieve a safe and effective manner of treating MS, such efficacy is not a limitation of the claims.” *Id.* at 438. The same is true here. Nothing requires reading any efficacy limitation into the claims, which merely require *intent* to treat MCL. EX1002 ¶74.

B. “a compound of Formula (II):...” (claims 8-9)

Claims 8 and 9 refer to “a compound of Formula (II)” with the structure:



EX1001, 100:43-62, 100:67-101:19. The recited “Formula (II)” compound should be construed as acalabrutinib.

During prosecution, the applicants represented that “[t]he compound of Formula (II) as specified in independent Claims 1 and 9 [which issued as claim 8] is ... acalabrutinib.” EX1004, 994. The applicants explained that now-claim 8 “specifies a method of treating mantle cell lymphoma (MCL) in a human subject by orally administering 100 mg of acalabrutinib twice daily to the subject...” *Id.*, 995. Thus, the compound of claims 8-9 is acalabrutinib. EX1002 ¶77.

C. “wherein the Mantle Cell Lymphoma (MCL) increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, and about 56 days” (claim 10)

Unlike the preamble discussed above, the “wherein” clause in dependent claim 10 is not limiting and merely recites an intended result. Thus, this clause lacks patentable weight. *See Minton v. Nat’l Ass’n of Secs. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) (“A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.”); Manual of Patent Examining Procedure (“MPEP”) §2111.04 (9th ed. June 2020) (“wherein” and “whereby” clauses “raise a question as to the limiting effect of the language in a claim”).

Unlike the preamble, claim 10’s “wherein” clause was not added to overcome rejections during prosecution; substantially the same language was in the

original claims. EX1004, 6 (claim originally numbered 12). The applicants did not alter this claim except to limit the “hematological malignancy” to MCL, for consistency with the claims from which it depends. *Id.*, 991. Nor did the applicants rely on the recited results to distinguish prior art. Thus, the results in this “wherein” clause lack patentable weight for obviousness purposes.

VIII. TECHNICAL BACKGROUND

MCL is a form of B-cell, non-Hodgkin’s lymphoma (“NHL”), a cancer in which malignant cells form in the lymph system. EX1002 ¶80; EX1014 (Pileri), 1. B-cells are white blood cells involved in the immune system. EX1002 ¶80. Other forms of B-cell NHL include CLL and SLL. *Id.*

Traditionally, treatments for MCL centered on chemotherapy. *Id.* ¶81. More recently, targeted anti-cancer agents have been introduced. *Id.*; EX1008 (Cheson), 11-13. While MCL’s prognosis was long viewed as poor, by 2014, newer therapies meant it was “no longer a hopeless disease,” as therapies “dramatically improved.” EX1015 (Dreyling), 1. Among the new “molecular targeted approaches” were BTK inhibitors, which showed “durable single-agent efficacy in relapsed or refractory MCL” and “excellent tolerability.” *Id.*, 10.

The first clinically developed BTK inhibitor is ibrutinib, which FDA approved for MCL in 2013. EX1004, 998; EX1016. As explained in Advani, which was published in 2013 and reports ibrutinib’s phase I dose-escalation trial:

“Signaling from the B-cell antigen receptor (BCR) regulates multiple cellular processes, including proliferation, differentiation, apoptosis, and cell migration, and is essential for normal B-cell development and survival.” EX1009, 7; EX1003 ¶¶50-57. “The BCR pathway is implicated in the pathogenesis of several B-cell malignancies, including ... mantle-cell lymphoma.” EX1009, 7. BTK “is a signaling molecule positioned early within the BCR signaling cascade” and “is a uniquely attractive target for selective B-cell inhibition.” *Id.*

Advani explains that ibrutinib is “a selective and irreversible small-molecule BTK inhibitor” with a half-maximal inhibitory concentration (IC₅₀) of 0.5 nM, i.e., the concentration required for 50% inhibition of its maximum effect on BTK. *Id.*; EX1002 ¶83. A related concept is half-maximal effective concentration (EC₅₀), which for purposes of this proceeding is identical to IC₅₀ when referring to drugs whose effect is inhibition. EX1002 ¶83.

Advani reports that ibrutinib was tested at weight-based, daily doses in five cohorts of 1.25, 2.5, 5, 8.3, and 12.5 mg/kg. EX1009, 8. “BTK occupancy >95% was observed in dose level cohorts II to V (2.5 to 12.5 mg/kg per day), and each of these cohorts had similar response rates, consistent with efficacy deriving from BTK inhibition.” *Id.*, 12. Although ibrutinib was later marketed with a 560 mg dose (EX1016), FDA recognized in its reviews dated 2013–2014 that Advani’s “Phase 1 study suggested that maximum ORR [i.e., overall response rate] and

maximum occupancy was achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg),” so drugmakers “should [] consider exploring lower doses in future development programs.” EX1017, 5.

By January 2015, two other BTK inhibitors were in clinical use for cancer: CC-292 and ONO-4059. EX1018 (Akinleye), 3; EX1019 (Hutchinson), 4. Both had similar IC₅₀s for BTK of <0.5 nM and 2.2 nM, respectively. *Id.*; EX1002 ¶86. CC-292 was tested at daily doses of 750 and 1000 mg, including as divided doses of 375 and 500 mg twice daily, which “may show better nodal responses” than once-daily dosing. EX1019 (Hutchinson), 7; *see also* EX1020 (Brown), 3; EX1021 (Pierce), 2. ONO-4059 was tested at lower doses ranging from 20-320 mg, with “responses ... seen at all dose levels.” EX1019 (Hutchinson), 7; EX1022 (Rule), 2 (reporting responses at 40, 80, 160 mg); EX1002 ¶¶87-88.

As shown below, the prior art discloses a fourth BTK inhibitor—known today as acalabrutinib—and its use to treat MCL.

IX. GROUNDS REFERENCES³

A. Barf (EX1005)

1. Prior-art status

Barf is prior art because it is an issued patent that “names another inventor and was effectively filed before the [’083 patent’s] effective filing date.” 35 U.S.C. §102(a)(2). Barf names eight inventors; only one (Tjeerd Barf) is named on the ’083 patent. EX1005; EX1001. Thus, Barf “names another inventor.” MPEP §2154.01(c) (“any difference in inventive entity ... satisfies the ‘names another inventor’ requirement”; “in the case of joint inventors, only one joint inventor needs to be different for the inventive entities to be different”).

Barf claims priority to Provisional Application No. 61/509,397 (EX1007 (“Barf Provisional”)), filed on July 19, 2011, before the ’083 patent’s effective filing date of January 21, 2015. EX1005, 1(60). A prior-art patent “shall be considered to have been effectively filed, with respect to any subject matter described in the patent ... as of the filing date of the earliest [priority] application

³ In addition to these references, Petitioner relies on background art, which “can legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness.” *Ariosia Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015).

that describes the subject matter.” 35 U.S.C. §102(d)(2). As shown below in parentheses citing EX1007, Barf Provisional supports all portions of Barf cited in this Petition, satisfying §102(d)(2).

In pre-AIA cases, the Federal Circuit and Board also required petitioners relying on provisional filing dates to show the cited application provides written-description support for at least one claim of the prior-art patent. *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1382 (Fed. Cir. 2015); *Ex Parte Mann*, No. 2015-003571, 2016 WL 7487271, at *6 (PTAB Dec. 21, 2016). The Federal Circuit declined to consider whether this requirement applies under the AIA (*Dynamic Drinkware*, 800 F.3d at 1381 n.2), and the Office has clarified that, in AIA cases, “whether a patent ... is actually entitled to priority or benefit with respect to any of its claims is not at issue in determining the date the patent ... was ‘effectively filed’ for prior art purposes.” MPEP §2154.01(b).

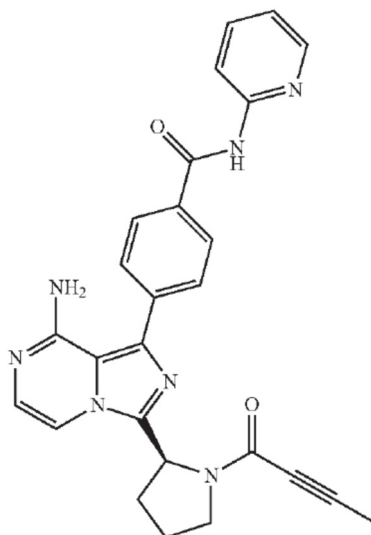
Nevertheless, some non-precedential panel decisions have assumed *Dynamic Drinkware* applies in AIA cases. *E.g., Found. Med., Inc. v. Guardant Health, Inc.*, IPR2019-00652, Paper 12 at 15-17 (PTAB Aug. 19, 2019). Here, the portions of Barf that Petitioner relies on include Barf’s claims, which are supported by Barf Provisional as shown below. Thus, to the extent *Dynamic Drinkware* applies, at least one claim of Barf is entitled to Barf Provisional’s filing date.

2. Exemplary disclosures

Barf teaches that “[t]he reported role for Btk in the regulation of proliferation and apoptosis of B cells indicates there is potential for Btk inhibitors in the treatment of B cell lymphomas.” EX1005, 2:3-6 (EX1007, 2:8-9). Barf describes a prior need for inhibitors that are selective for BTK because “an inhibitor that inhibits multiple or all kinases of the Src-family kinases simultaneously may cause serious adverse effects.” EX1005, 2:50-52 (EX1007, 2:38-39). To meet this need, Barf discloses “6-5 membered fused pyridine ring compounds,” “pharmaceutical compositions comprising these compounds and [] their use in therapy.” EX1005, 2:58-61 (EX1007, 3:4-5).

Barf has only one independent claim, which requires treating MCL in a human by administering an effective amount of acalabrutinib:

1. A method of treating Mantle Cell Lymphoma (MCL) in a human subject, the method comprising administering to the human subject a compound which is (S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



or a pharmaceutically acceptable salt thereof, in an amount effective to treat the MCL in the human subject.

EX1005, 150:2-31. Claims 2 and 4 recite a pharmaceutical composition of acalabrutinib and its “oral administration.” *Id.*, 150:33-34, 150:39-41. Claim 12 narrows claim 1’s “amount effective to treat the MCL in the human subject” to the range, “0.0001-25 mg per kg body weight.” *Id.*, 151:14-16.

Claims 1, 2, 4, and 12 of Barf are supported by Barf Provisional. EX1002 ¶93. Example 6 of Barf Provisional discloses the chemical name and structure in Barf’s claim 1 (i.e., acalabrutinib). EX1007, 37:8-11. Barf Provisional discloses that “[p]roliferative diseases that can be treated or prevented include ... mantle cell lymphoma (MCL).” *Id.*, 23:35-37. Barf Provisional discloses pharmaceutical compositions “[f]or oral administration.” *Id.*, 21:5-9. Barf Provisional discloses that “a dosage for humans preferably contains 0.0001-25 mg per kg body weight.”

Id., 21:37-38. Thus, Barf's claims 1, 2, 4, and 12 are entitled to Barf Provisional's filing date, July 19, 2011. EX1002 ¶93.

Barf's Table 1 reports the EC50 for BTK of Barf's covered compounds:

TABLE 1	
EC50 Btk activity values	
EC50	Example
≥1 μM	91,
≥100 nM	52, 53, 54, 55, 68, 72, 74, 85, 86, 87, 88, 90, 92, 93, 94, 104
<1 μM	
≥10 nM	2, 4, 5, 7, 11, 24, 40, 41, 50, 51, 56, 57, 58, 59, 60, 69, 70, 71, 73, 80, 81, 82, 83,
<100 nM	84, 89, 95, 96, 97, 98, 99, 103, 105, 106, 112, 113, 114, 119
<10 nM	1, 3, 6, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 61, 62, 63, 64, 65, 66, 67, 75, 76, 77, 78, 79, 100, 101, 102, 107, 108, 109, 110, 111, 115, 116, 117, 118, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133

EX1005, col. 145 (EX1007, 97).

Example 6 (i.e., acalabrutinib) has the lowest EC50 of <10 nM, placing it among the most potent compounds. *Id.*; EX1002 ¶95; EX1005, 36:12-40 (EX1007, 37:38-11). Example 6 also has a much higher EC50 (≥1 μM) for other kinases (Lck, Src, FynT, and Lyn), confirming it is highly selective for BTK.

EX1005, cols. 146-49 (Tbls. 2-5) (EX1007, 98-101); EX1002 ¶95.

B. Barf-PCT (EX1006)

Barf-PCT is an international patent application publication from 2013, which is prior art under §102(a)(1). EX1006, 1(43). Barf is a division of an application published as Barf-PCT. EX1005, 1(62). Like Barf, Barf-PCT claims

priority to Barf Provisional. EX1006, 1(30). Thus, Barf and Barf-PCT share the same material disclosure; only their claims are different. EX1005; EX1006.

As in Barf, Example 6 of Barf-PCT discloses acalabrutinib. EX1006, 35:16-36:2. Barf-PCT discloses “[p]roliferative diseases that can be treated or prevented include ... mantle cell lymphoma (MCL).” *Id.*, 22:15-16. Barf-PCT discloses “oral administration.” *Id.*, 19:32-33. Barf-PCT discloses “a dosage for humans preferably contains 0.0001-25 mg per kg body weight.” *Id.*, 20:24-25. And Barf-PCT discloses the same EC50s for Example 6 (acalabrutinib), showing its high selectivity for BTK. *Id.*, 94-98 (Tbls. 1-5); EX1002 ¶97.

C. Cheson (EX1008)

As shown by Petitioner’s expert librarian, Sylvia Hall-Ellis, Ph.D., Cheson (EX1008) is an authentic copy of a journal supplement for *Clinical Advances in Hematology & Oncology*, a periodical published at least since 2003 and held by 65 libraries worldwide. EX1003 ¶¶42-49. A date stamp from the Mirand Library at the Roswell Park Cancer Institute, where this copy of Cheson was found, indicates that the journal containing Cheson was processed on September 27, 2013, whereupon it became available to the public. *Id.* ¶43; EX1008, 1. Thus, Cheson was publicly available as a printed publication under §102(a)(1). EX1003 ¶¶44-49.

Cheson discloses “[s]everal BTK inhibitors are being evaluated in clinical trials; the furthest in development is ibrutinib.” EX1008, 4. Although “[i]brutinib

is administered orally once daily,” Cheson notes “[o]ther BTK inhibitors are being evaluated in a twice-daily schedule in an attempt to overcome the synthesis of new BTK molecules within those cells.” *Id.* Specifically, “[t]he BTK inhibitor CC-292” has completed “[a] phase 1 dose-escalation study.” *Id.*, 10. “A twice-daily dosing schedule was evaluated to address the potential production of new BTK that could have occurred between daily doses,” and “twice-daily dosing appeared to be more effective, perhaps with more rapid responses.” *Id.*

X. ANALYSIS OF GROUNDS FOR TRIAL

A. Ground 1: Claims 8-12 and 19-20 would have been obvious over Barf and Cheson.

1. Claim 8

As explained below under headings (a) and (b), Barf expressly teaches all of claim 8’s limitations except the dosing regimen of 100 mg twice daily. As explained under heading (c), the claimed regimen would have been obvious to a POSA over Barf and Cheson.

a. “A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of”

Barf’s claim 1 recites “[a] method of treating Mantle Cell Lymphoma (MCL) in a human subject.” EX1005, 150:2-4; *supra* §IX.A. Thus, Barf discloses the preamble in claim 8 of the ’083 patent. EX1002 ¶106; *see also Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1289, 1295 (Fed. Cir. 2010), *vacated on*

other grounds, 374 F. App'x 35 (Fed. Cir. 2010), *reinstated in-relevant-part*, 649 F.3d 1276, 1296 (Fed. Cir. 2011) (“The claims of a prior art patent are part of its disclosure.”) (invalidating claims over prior-art patent’s claims).

b. “orally administering, to the human subject, ... a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II) ... or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.”

Barf’s claim 1 continues that the recited method of treating MCL comprises “administering to the human subject a compound which is” acalabrutinib (i.e., the same structure in claim 8 of the ’083 patent) “or a pharmaceutically acceptable salt thereof.” EX1005, 150:4-30; EX1002 ¶108. Barf’s claim 4 narrows claim 1 by requiring “oral administration.” EX1005, 150:39-41. Moreover, oral administration would have been obvious as the most convenient route of administration and was used exclusively for the only three BTK inhibitors in clinical use for oncology in the prior art—i.e., ibrutinib, CC-292, and ONO-4059. EX1002 ¶109; EX1009, 7; EX1020, 2; EX1022, 1.

Thus, Barf’s claims 1 and 4 meet every limitation in claim 8 of the ’083 patent except “a dose of 100 mg twice daily.” EX1002 ¶111.

c. “a dose of 100 mg twice daily”

As shown below, it would have been obvious to (i) administer a dose of 100 mg acalabrutinib; and (ii) administer this dose twice daily.

i. A 100 mg dose would have been obvious.

The 100 mg dose would have been obvious for two related but independent reasons. First, as discussed below, it falls within a range disclosed by Barf. Second, a POSA would have arrived at this dose through routine experimentation.

(1) Barf discloses and claims a range that encompasses the claimed dose.

Barf's claim 12 specifies that claim 1's "amount effective to treat the MCL" is "0.0001-25 mg per kg body weight." EX1005, 150:30-31, 151:14-16. A POSA developing a drug for clinical use would have converted this weight-based range to fixed doses, which was preferred for oral drugs. EX1002 ¶115. The prior art confirms that "trials of agents given orally were mainly conducted with a fixed dose," which "is far more convenient than that adjusted to body size" and can "reduce medication errors." EX1037 (Levêque), 2. Moreover, "it has never been proven that dosing of anticancer drugs according to ... body weight leads to improvement of therapeutic outcomes in adult patients when compared to fixed dosing," especially for "targeted therapies" like Tyrosine Kinase inhibitors, which were "administered at a fixed dose." *Id.*, 3; EX1002 ¶116.

For converting weight-based doses, a standard assumption in the prior art is an average human weight of 70 kg. EX1002 ¶118; EX1017, 5, 20 (FDA using 70 kg to convert weight-based doses for ibrutinib). Based on that weight, Barf's range provides a fixed dose of 0.007-1750 mg, which encompasses the '083 patent's

claimed dose of 100 mg, as well as the daily dose of 200 mg when administered twice daily. EX1002 ¶118. This remains true if other common weight conversions are used, such as 60 kg (0.006-1500 mg) or 80 kg (0.008-2000 mg). *Id.*

Where “there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness.” *Iron Grip*, 392 F.3d at 1322. This presumption applies even if there are other differences between the claims and prior art. *Valeant Pharms. Int’l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 30, 32 (Fed. Cir. 2020) (reversing holding that “overlapping ranges only establish a prima facie case of obviousness when the only difference between the prior art is the ‘range or value,’” and applying presumption where claim “overlaps with the [] range in the record art,” even though “none of the references disclose the same drug as the one claimed”); *see also Fresenius Kabi USA, LLC v. Chugai Seiyaku Kabushiki Kaisha*, IPR2021-01288, Paper 30 at 38 (PTAB Feb. 23, 2022) (applying “presumption of obviousness” for claimed fixed dose after converting weight-based dosing range in prior art by “70 kg ‘typical’ weight”).

Thus, “the burden of production falls upon the patentee to come forward with evidence of teaching away, unexpected results or criticality, or other pertinent objective indicia indicating that the overlapping range would not have been obvious.” *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) (quotation omitted). Petitioner is unaware of any teaching away

from the claimed 100 mg dose (or 200 mg daily). Although the applicants alleged unexpected results during prosecution, the alleged results were neither probative nor unexpected, as shown below in §X.C.1. Petitioner is unaware of any other secondary considerations and reserves the right to rebut any alleged considerations or teaching away Patent Owner may allege.

The presumption of obviousness is reinforced because Barf is an issued patent, whose claims are presumed enabled. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). Barf's applicants overcame written-description and enablement rejections during prosecution by amending the claims to specifically require treating MCL. EX1023, 566-67, 43-44, 46, 23. Thus, the Office has already found Barf's claims enabled, which confirms a reasonable expectation of success for its dosing range. *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (patent "must enable [POSA] to practice the full scope of the claimed invention"; "when a range is claimed, there must be reasonable enablement of the scope of the range").

Although the presumption of obviousness is sufficient to render the 100 mg dose obvious, additional information about other BTK inhibitors in the prior art would have narrowed the range of possibilities and steered a POSA toward this dose. EX1002 ¶121. FDA's 2013 Good Review Practice provides that "[c]omparisons of an investigational drug's potency and activity with that of other

well-characterized drugs of the same class may also be useful in determining the starting dose.” EX1024, 14. Here, by January 2015, three irreversible BTK inhibitors were known to have been clinically tested for treating cancers: ibrutinib, CC-292, and ONO-4059. EX1019 (Hutchinson), 2, 4, Tbl. 1; EX1018 (Akinleye), 3, Tbl. 1; EX1002 ¶122. The prior art reported the following EC50s for BTK and dosing ranges that produced clinical responses with these compounds:

Compound	EC50 (BTK)	Effective dosing range
Ibrutinib	0.5 nM	Maximal BTK occupancy and responses seen at doses from 2.5-12.5 mg/kg (175-875 mg for 70 kg). EX1009 (Advani), 9-12.
CC-292	<0.5 nM	Responses seen at 750-1000 mg once-daily and 375-500 mg twice-daily. EX1019 (Hutchinson), 7.
ONO-4059	2.2 nM	Responses seen at 20-320 mg. <i>Id.</i>

EX1002 ¶122. Thus, three BTK inhibitors for leukemia/lymphoma were successfully used at doses ranging from 20-1000 mg, which falls within Barf’s range. *Id.* ¶123. Because these compounds had the same biological target (BTK) and a potency within the range reported for acalabrutinib (<10 nM), a POSA practicing Barf would have started by investigating doses within this narrowed 20-1000 mg range, which encompasses the claimed 100 mg dose. *Id.*

This narrowed range is consistent with Barf's own teachings, which would have funneled the POSA away from both the highest and lowest ends of the disclosed range and toward the effective range of 20-1000 mg for other BTK inhibitors. *Id.* ¶124. First, Barf teaches that acalabrutinib (Example 6) is among the most potent covered compounds for inhibiting BTK, with a relatively low EC50 of <10 nM, whereas multiple other compounds had much higher EC50s, below 100 nM or 1 µM. EX1005, col. 145 (Tbl. 1) (EX1007, 97); EX1005, 36:12-40 (EX1007, 37:8-11); EX1002 ¶124. Thus, a POSA would have assumed that the highest end of Barf's range was intended for less potent compounds with higher EC50s. EX1002 ¶124. *Cf. Boehringer Ingelheim Pharms. Inc. v. Mylan Pharms. Inc.*, 803 F. App'x 397, 402 (Fed. Cir. 2020) (for compound with "lowest IC50 value," POSA would be "looking at the lowest end of the dose range").

Second, Barf teaches that, "[i]n general[,] parenteral [i.e., non-oral] administration requires lower dosages than other methods of administration which are more dependent upon absorption." EX1005, 17:60-63 (EX1007, 21:36-37). A POSA would have understood that some amount of drug may be lost (i.e., not absorbed) when administered orally, requiring higher doses than intravenous administration, which delivers the drug directly into the bloodstream. EX1002 ¶125. Thus, a POSA would have assumed that the lowest end of Barf's range was intended for intravenous or other parenteral administration. *Id.*

In short, Barf's own guidance and reported data on other BTK inhibitors would have led a POSA to investigate doses ranging from 20-1000 mg, which fell within Barf's claimed range. *Id.* ¶126. Thus, with no probative secondary considerations, the claimed 100 mg dose would have been obvious. *Id.*

(2) A POSA practicing Barf would have arrived at a 100 mg dose by conducting a routine dose-finding study.

As an independent basis for obviousness, a POSA practicing Barf's method would have arrived at the claimed dose by conducting a routine dose-finding study based on FDA guidance, which provided a roadmap for determining the optimal dose of a BTK inhibitor like acalabrutinib. EX1002 ¶127; *Genzyme Therapeutic Prods. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1365 (Fed. Cir. 2016) (affirming obviousness where "all that remained to be achieved over the prior art was the determination that a specific dose within a previously suggested dose range ... would have been safe and effective," requiring "no more than routine processes"); *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (prior-art patent's "specification is enabling in part because those skilled in the art would know how to conduct a dose response study to determine the appropriate amounts to be used") (citation omitted).

Dose-finding studies have long been routine in the pharmaceutical industry, and BTK inhibitors are no exception. EX1002 ¶128. The prior art recognizes that

“therapeutically effective amounts may be determined by routine experimentation, including but not limited to a dose escalation clinical trial.” EX1025 (Verner), 24:41-43; EX1002 ¶128. Since 1994, FDA has issued guidelines for designing such trials to “help identify an appropriate starting dose.” EX1026, 1. These trials “should be an integral component of drug development” and “can usually be accomplished with no loss of time and minimal extra effort.” *Id.*, 2.

“Most phase 1 clinical trials are characterized by progressive dose escalation with sponsors collecting safety information on each dose experience.” EX1024 (FDA Good Review Practice), 20. For safety reasons, a POSA would have selected “a low starting dose” and practiced “cautious dose escalation.” *Id.*, 21; EX1002 ¶130. Applying standard FDA guidelines, a POSA would have calculated a safe starting dose using preclinical toxicology studies and animal-to-human conversion tables. EX1002 ¶131; EX1027, 7 (“nonclinical studies can facilitate dose selection, schedule, and escalation during Phase 1 studies”); EX1028, 4 (outlining procedures “for deriving the maximum recommended starting dose (MRSD) for first-in-human clinical trials,” including “calculations used to generate the MRSD from animal data”); *Boehringer*, 803 F. App’x at 402 (“a skilled artisan would have a reasonable expectation of arriving at the claimed ... dosages through routine experimentation” since “dose ranging studies are conducted starting with a low dose, and sequentially moving through increasing doses”).

After determining a starting dose through routine animal studies, a POSA would have gradually titrated doses in humans and selected a dose for development based on BTK occupancy and clinical responses. EX1002 ¶134. Cheson teaches that, for a BTK inhibitor, “use of a dose that attains full occupancy appears to be important for obtaining maximal antitumor activity.” EX1008, 7. Likewise, a POSA would have known BTK occupancy was used to evaluate doses in clinical trials for ibrutinib and CC-292. EX1002 ¶134; EX1009 (Advani), 12 (describing “probe for BTK measuring active-site occupancy” that “allows for dose escalation based ... on an optimal biologic dose, where target binding could be demonstrated”); EX1029 (Evans), 8 (“direct quantification of Btk engagement ... will reduce uncertainty about the dose required for target inhibition and enable selection of the optimal pharmacological dose and dosing schedule”).

Specifically, a POSA would have selected the lowest non-toxic dose that achieves maximal BTK occupancy. EX1002 ¶136. For traditional chemotherapies, which are cytotoxic (i.e., kill cells), “patients [we]re treated with increasing doses of the drug until dose limiting toxicity is observed” (EX1030 (Barf 2012), 14), which is known as the “maximum tolerated dose (MTD)” (EX1031 (Mahipal), 2). By 2014, however, the industry had shifted away from exclusively seeking the MTD, particularly with “targeted agents” such as BTK inhibitors, for which “the biologically effective dose is now frequently used rather

than the MTD.” *Id.*; EX1002 ¶137. For BTK inhibitors, the prior art teaches that “a modest excess of exposure with respect to the dose where full target occupancy is observed should be more than sufficient.” EX1030 (Barf 2012), 14. Moreover, the prior art indicates that, “[c]learly, one should be able to design and synthesize suitable probes for diagnosis and target occupancy purposes with modest efforts.” *Id.* Thus, evaluating BTK occupancy in a dose-finding trial would have been obvious and routine to a POSA. EX1002 ¶137.

FDA endorsed this approach during ibrutinib’s development, noting in its 2013-2014 clinical pharmacology reviews that the lowest dose with “maximum BTK occupancy and maximum response” is “likely [to] be efficacious.” EX1017, 10. Although ibrutinib was marketed at a higher dose, FDA encouraged “exploring lower doses in future development programs.” *Id.*, 5; *see also id.*, 11-12, 20, 55. That is consistent with FDA’s longstanding recognition that “drugs have often been initially marketed at what were later recognized as excessive doses.” EX1026, 2. Moreover, a POSA would have expected lower doses to provide reduced side effects, lower risk of drug-drug interactions, reduced costs, and pills that are easier to swallow and formulate. EX1002 ¶139; *Boehringer*, 803 F. App’x at 402 (motivations for lower dose include “(1) being a smaller, easier to swallow tablet; (2) being easier to formulate in combination pills; (3) having a lower risk of drug to drug interactions; and (4) reducing the risk of side effects.”).

This obvious and FDA-endorsed approach of selecting the lowest dose that provides maximal BTK occupancy would have led a POSA directly to the claimed 100 mg dose. EX1002 ¶140. Indeed, in the dose-finding study for acalabrutinib, “BTK occupancy was complete (99 to 100%)” at the starting dose of 100 mg. EX1010 (Byrd), 5. Moreover, the phase I protocol in Provisional Application No. 61/929,742 admits that this starting dose of 100 mg was determined by following known FDA’s guidelines and conducting “[s]tandard” studies:

The starting ACP-196 dose of 100 mg was selected based on Food and Drug Administration (FDA) Guidances: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (MSSD), and Nonclinical Evaluation for Anticancer Pharmaceuticals (ICH S9) (FDA 2005 and 2010). Standard GLP 28-day nonclinical systemic toxicity studies in rats and dogs were conducted in support of this trial.... [In rats], the 100 mg/kg/day was selected to conservatively represent the HNSTD [highest non-severely toxic dose]. Following the S9 guidance and using conversion factors from the MSSD guidance, the conversion factor for mg/kg to mg/m² for rodents is 6, which converts to 600 mg/m² in rats. The starting human dose for oncology would be one-tenth the HNSTD, 60 mg/m², or approximately 100 mg for a 60-kg subject with a body surface area of 1.6 m².

EX1011, 28 (emphasis added).

Although acalabrutinib's phase-I trial is not prior art, post-filing evidence can confirm that "the experimentation needed to arrive at the claimed dosages was nothing more than routine." *Merck*, 874 F.2d at 809. In *Merck*, the Federal Circuit considered whether a claim reciting doses for two compounds was obvious over a prior-art patent that disclosed the same compounds but not their doses. *Id.* at 806-09. In holding the doses obvious, the Federal Circuit relied on evidence that "the dose response ... procedures followed by" the patentee, including "animal and human studies," were obvious to conduct. *Id.* at 809. "Reached by means of routine procedures, and producing only predictable results, the recited dosages therefore do not distinguish the claims of the [asserted] patent from the ... [prior-art] patent," whose "specification is enabling in part because those skilled in the art would know how to conduct a dose response study to determine the appropriate amounts to be used." *Id.* (citation omitted).

The same is true here. Barf's dosing range is presumed enabled because a POSA would have determined acalabrutinib's optimal dose using routine procedures endorsed by FDA. EX1002 ¶141. Standard animal studies and conversion tables would have led a POSA directly to the 100 mg starting dose, and routine testing for BTK occupancy would have confirmed this dose was optimal. *Id.* Because the claimed dose was determined through routine experimentation, it would have been obvious to a POSA. *Id.*

Although a POSA would have selected the 100 mg dose as optimal, this dose would be obvious even assuming a POSA would move forward with a higher dose for commercial development. *Id.* ¶142. Simply by conducting a dose-escalation study that *includes* the 100 mg starting dose, a POSA would be practicing the claimed dose in at least one “human subject,” which is all the claimed method requires. *Id.* Because it was at least obvious to include this dose in a phase-I trial, it would have been obvious to a POSA. *Id.*

ii. Twice-daily dosing would have been obvious.

One of the first considerations for a POSA conducting a dose-finding study would have been the frequency of dosing. *Id.* ¶143. Barf teaches that doses within its range “may be presented as one dose or multiple subdoses administered at appropriate intervals throughout the day.” EX1005, 17:63-66 (EX1007, 21:38-39). Thus, Barf encompasses twice-daily administration. EX1002 ¶143.

A POSA practicing Barf would have been motivated to administer acalabrutinib twice daily based on Cheson, which teaches that “BTK inhibitors are being evaluated in a twice-daily schedule in an attempt to overcome the synthesis of new BTK molecules within those cells.” EX1008, 4; EX1002 ¶144. Cheson explains that, for CC-292, “[a] twice-daily dosing schedule was evaluated to address the potential production of new BTK that could have occurred between daily doses.” *Id.*, 10. This strategy had promising results: “In early follow-up,

twice-daily dosing appeared to be more effective, perhaps with more rapid responses,” while remaining “well tolerated.” *Id.*; EX1002 ¶144.

The same rationale and results were reported in other publications, which confirmed CC-292 was being tested twice daily to counteract BTK’s resynthesis during the day. EX1032 (Brumskill), 3 (“The half-life of CC-292 is 2 h and BTK resynthesis occurs after 12 h, therefore b.i.d. dosing maintains BTK inhibition.”). In a phase-I study, patients dosed “BID showed continued lymph node size reduction over time” (EX1020 (Brown), 3), and “residual free Btk levels were lower with the BID schedule, offering a rationale for an early trend towards more rapid nodal responses, lymphocytosis, and partial responses” (EX1021 (Pierce), 2). *See also* EX1002 ¶145; EX1019 (Hutchinson), 4 (“Data with AVL-292/CC-292 ... twice daily dosing suggests improved nodal responses”).

Likewise, ONO-4059 was tested twice-daily preclinically to prolong BTK inhibition. EX1002 ¶146. Yoshizawa “hypothesized that the efficacy of ONO-4059 could be further enhanced by increasing the drug trough concentration”—i.e., the drug’s blood levels before the next dose is administered—using twice-daily dosing. EX1033, 1. Yoshizawa concluded that “a more frequent dosing regimen such as BD [twice-daily] may be a more effective treatment” than once-daily dosing that “warrants further investigation in the clinical setting.” *Id.*, 2.

Thus, a POSA would have included twice-daily administration in a dose-finding study for acalabrutinib to ensure inhibition of BTK synthesized during the day. EX1002 ¶148. Because both second-generation BTK inhibitors being tested for cancers—CC-292 and ONO-4059—showed promising results with twice-daily dosing, a POSA would have viewed any dose-finding study limited to once-daily administration as incomplete for failing to include a regimen that could result in more continuous BTK inhibition. *Id.* Thus, a POSA would have included a twice-daily cohort in a dose-finding study for acalabrutinib. *Id.*

Investigating twice-daily administration would have been routine and uncontroversial to a POSA. *Id.* ¶149. Many targeted oncology therapies FDA-approved at the time were dosed twice daily. *Id.*; e.g., EX1038 (idelalisib); EX1039 (nilotinib); EX1040 (ruxolitinib); EX1041 (olaparib). Moreover, FDA guidelines teach that drugmakers should consider “a comparison of [a] long dose interval regimen with the same dose in a more divided regimen, looking, where this is feasible, for persistence of desired effect throughout the dose interval and for adverse effects associated with blood level peaks.” EX1026, 2.

A POSA would have understood that administering a given amount of drug as a single daily dose results in higher peak plasma levels and lower trough levels than the same amount divided into two doses, which provides more consistent plasma drug concentration. EX1002 ¶151. Having more consistent plasma drug

concentration through twice-daily dosing avoids both excessive peak concentrations (likely to cause adverse effects) and sub-optimal trough concentrations (insufficient for therapeutic benefit). *Id.* A POSA would have been motivated to investigate twice-daily dosing to avoid this possibility, especially if acalabrutinib turned out to have a short half-life, which had been seen with CC-292 and would have been routinely determined as one of the first steps in drug development. *Id.*; EX1032 (Brumskill), 3 (“The half-life of CC-292 is 2 h and BTK resynthesis occurs after 12 h, therefore b.i.d. dosing maintains BTK inhibition.”); EX1024 (FDA Good Review Practice), 26.

At a minimum, twice-daily dosing was obvious to try. The only three irreversible BTK inhibitors with clinical data reported for lymphoma/leukemia in the prior art (ibrutinib, CC-292, ONO-4059) were dosed once or twice daily. EX1002 ¶154. Ibrutinib—developed first and without the benefit of promising data on CC-292 and ONO-4059—was tested once-daily. EX1009 (Advani), 7. CC-292 was tested once and twice daily, which provided better results. EX1019 (Hutchinson), 7. ONO-4059 was tested once-daily, but a preclinical study on twice-daily dosing suggested “further investigation in the clinical setting.” EX1033 (Yoshizawa), 2. Moreover, FDA discouraged more frequent administration: “Dosing more often than twice per day appears to lead to poorer patient compliance and is unattractive to patients.” EX1024, 26. Thus, there were

only two reasonable options: once and twice daily, which is “a finite number of identified, predictable solutions.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007); EX1002 ¶154.

Accordingly, a POSA would have arrived at the claimed dosing regimen of 100 mg acalabrutinib twice daily, rendering claim 8 obvious. EX1002 ¶155.

2. Claim 9

Claim 9 limits the claimed BTK inhibitor to acalabrutinib “or a pharmaceutically acceptable salt thereof,” narrowing claim 8 by omitting hydrates and solvates. This claim is obvious for the same reasons as claim 8: Barf discloses and claims acalabrutinib and its pharmaceutically acceptable salt. *Supra* §X.A.1; EX1002 ¶158; EX1005, 150:2-31 (EX1007, 37:8-11).

3. Claim 10

Claim 10 depends from claim 9 and adds: “wherein the Mantle Cell Lymphoma (MCL) increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, and about 56 days.”

As discussed, this “wherein” clause merely recites intended results and lacks patentable weight under §103. *Supra* §VII.C.

To the extent claim 10 requires administering acalabrutinib for the recited durations, that would have been obvious over Cheson, which teaches that the BTK

inhibitor ibrutinib was clinically administered “26 months,” encompassing all recited durations. EX1008, 9; *see also id.*, 10 (24 months in Fig. 6), 14 (24 months in Fig. 8; “response rate appeared to improve ... beyond 12 months”); EX1002 ¶161. CC-292 was also tested in 28-day cycles. EX1020 (Brown), 2. Moreover, MCL is considered incurable, so a POSA would have continued administering a BTK inhibitor indefinitely. EX1002 ¶162. That was standard practice for ibrutinib, and a POSA would have done the same with acalabrutinib. *Id.*

The recited outcome of such administration is an inherent result that cannot distinguish the prior art. “[I]nherency may supply a missing claim limitation in an obviousness analysis” where it is “the ‘natural result’ of the combination of prior art elements.” *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194-95 (Fed. Cir. 2014). “[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting” outcome. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012).

In parallel litigation, Patent Owner has asserted that claim 10 is infringed by administering acalabrutinib for 26.6 months. EX1034, 4. For the claimed result, Patent Owner relies on data in the ’083 patent purporting to show it inherently occurs. *Id.* Thus, under Patent Owner’s infringement theory, the claimed increase in monocytes and NK cells is an inherent result.

Even if claim 10 were construed to require the result of increasing monocytes and NK cells in peripheral blood, a POSA would have reasonably expected this result. EX1002 ¶165. It was well known that inhibiting BTK causes cancer cells to detach from bone marrow and enter peripheral blood. *Id.*; EX1042 (Chang), 1 (“MCL cells are mobilized into the peripheral blood of patients treated with the BTK inhibitor ibrutinib”). It was also known that, once in the peripheral blood, these cells undergo programmed cell death because they are no longer “well protected and nurtured” in the bone marrow. EX1042, 10; EX1002 ¶165.

A POSA would have reasonably expected other cells that signal through the BTK pathway to also detach from the bone marrow and enter peripheral blood. EX1002 ¶166; EX1042, 2 (“many MCL patients had rapid increases of CD5+ B lymphocytes in the peripheral blood (PB) following ibrutinib treatment”). Because monocytes and NK cells both signal through the BTK pathway, a POSA would have reasonably expected acalabrutinib—a BTK inhibitor—to increase monocyte and NK cell levels in the peripheral blood. EX1002 ¶166; EX1043 (Bao), 1 (“Btk is required for activation of NK cells” and “involved in the regulation of Toll-like receptor-triggered innate response of macrophages”).

Thus, claim 10 would have been obvious. EX1002 ¶167.

4. Claim 11

Claim 11 recites: “The method of claim 9, wherein the MCL is selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL.”

Claim 11 is obvious for the same reasons as claims 8-9. EX1002 ¶169. A POSA would have known that the first three recited morphologies relate to disease progression, with mantle-zone MCL progressing to nodular and then diffuse MCL, while blastoid MCL is an aggressive variant. EX1014 (Pileri), 2. A POSA would have administered acalabrutinib to treat all these subtypes, which involve the same BCR signaling pathway. *Id.*; EX1002 ¶170. The full scope of Barf’s claims, which are not limited to any MCL subtype, are presumed enabled and confirm a reasonable expectation of success. *Amgen*, 314 F.3d at 1355.

Moreover, in parallel litigation, Patent Owner asserts that marketing generic acalabrutinib would infringe this claim (EX1034, 4-5), even though the FDA-approved labeling for acalabrutinib does not mention any subtypes and relates generally to patients with “mantle cell lymphoma (MCL) who have received at least one prior therapy” (EX1035, 1). Thus, under Patent Owner’s theory that MCL includes these subtypes, this claim is obvious over Barf, which similarly claims treating MCL generally. EX1005, 150:2-3; EX1002 ¶171.

5. Claim 12

Claim 12 recites: “The method of claim 9, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, velutuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.”

This limitation is obvious over Cheson, which teaches combining a BTK inhibitor with rituximab. EX1002 ¶174. Cheson explains: “The addition of other agents such as rituximab or bendamustine to ibrutinib has been shown to reduce the duration of lymphocytosis.” EX1008, 4; EX1002 ¶174. Cheson reports initial results of a clinical trial combining ibrutinib and rituximab, which “appeared to reduce the lymphocytosis ... compared with ibrutinib alone” and “was well tolerated.” EX1008, 9. Barf also notes anti-CD20 agents treat B-cell disorders (EX1005, 1:66-2:2 (EX1007, 2:5-7)) and covers combinations with other drugs (EX1005, 17:10-11 (EX1007, 21:3-4)).

Thus, a POSA would have been motivated to administer a BTK inhibitor like acalabrutinib together with rituximab to reduce lymphocytosis, rendering claim 12 obvious. EX1002 ¶175.

6. Claim 19

Claim 19 requires acalabrutinib's "free form." This claim is obvious for the same reasons as claims 8-9. *Id.* ¶177.

Barf's claim 1 covers treating MCL by administering acalabrutinib "or a pharmaceutically acceptable salt," indicating the claim covers the free base. EX1005, 150:2-31 (emphasis added); EX1002 ¶178. Moreover, Barf teaches its compounds "can be in the form of a free base," rendering claim 19 obvious. EX1005, 26:40-42 (EX1007, 28:16-17); EX1002 ¶¶178-79.

7. Claim 20

Claim 20 requires a "pharmaceutically acceptable salt of" acalabrutinib. This claim is obvious for the same reasons as claims 8-9. EX1002 ¶181. Barf's claim 1 covers acalabrutinib "or a pharmaceutically acceptable salt thereof," rendering claim 20 obvious. EX1005, 150:2-31; *see also id.*, 26:40-51 (EX1007, 28:16-22) (describing salt forms); EX1002 ¶181-82.

B. Ground 2: Claims 8-12 and 19-20 would have been obvious over Barf-PCT and Cheson.

The challenged claims are obvious over Barf-PCT and Cheson for substantially the same reasons as in Ground 1. EX1002 ¶183.

1. Claim 8

- a. “A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of”**

Barf-PCT teaches that, by administering its compounds, “[p]roliferative diseases that can be treated or prevented include ... mantle cell lymphoma (MCL).” EX1006, 22:15-16. Barf-PCT provides that such compounds may be administered to humans. *Id.*, 20:24-25. Thus, Barf-PCT teaches a method of treating MCL in a human subject suffering therefrom. EX1002 ¶187.

- b. “orally administering, to the human subject, ... a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II) ... or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.”**

Barf-PCT teaches its compounds may be formulated “[f]or oral administration.” EX1006, 19:32-33. As the ’083 applicants admitted in prosecution, Barf-PCT teaches acalabrutinib in Example 6. *Id.*, 35:16-36:2; EX1004, 997. Thus, Barf-PCT teaches orally administering, to the human subject, the BTK inhibitor acalabrutinib (i.e., Formula (II)). EX1002 ¶188.

Because the ’083 patent “does not claim the [acalabrutinib] compound itself, but rather methods of using the compound[,] [t]his case therefore does not require lead compound analysis,” i.e., motivation to select acalabrutinib. *Novartis Pharm. Corp. v. W.-Ward Pharm. Int’l Ltd.*, 923 F.3d 1051, 1060 (Fed. Cir. 2019) (“To the

extent the district court required a showing that a [POSA] would have selected [the claimed compound] over other prior art compounds, it erred.”).

Regardless, a POSA would have been motivated to select acalabrutinib to treat MCL. EX1002 ¶189. Barf-PCT teaches a preference for selective BTK inhibitors because “an inhibitor that inhibits multiple or all kinases of the Src-family kinases simultaneously may cause serious adverse effects.” EX1006, 2:32-33. Barf-PCT shows that acalabrutinib (Example 6) is highly selective for BTK, with an $EC_{50} < 10$ nM but a much higher $EC_{50} \geq 1$ μ M for other kinases. *Id.*, 94-98 (Tbls. 1-5). Thus, it would have been obvious to administer acalabrutinib to a human subject to treat MCL. EX1002 ¶190.

c. “a dose of 100 mg twice daily”

Barf-PCT teaches “a dosage for humans preferably contains 0.0001-25 mg per kg body weight.” EX1006, 20:24-25. This is the same range claimed by Barf and renders a 100 mg dose obvious for the same reasons. *Supra* §X.A.1.c.i.(1); EX1002 ¶192. Again, when converted to fixed doses, this range includes 100 mg, creating a presumption of obviousness. *Id.*; *Iron Grip*, 392 F.3d at 1322.

Moreover, for the same reasons discussed in Ground 1, a POSA would have narrowed this range by focusing on the known 20-1000 mg dosing range that was effective for three other BTK inhibitors. *Supra* §X.A.1.c.i.(1). Barf-PCT’s guidance is consistent with this narrowed range for the same reasons discussed for

Barf. EX1002 ¶193. First, Barf-PCT shows acalabrutinib is among the most potent compounds with the lowest EC50 for BTK, so a POSA would have deprioritized the highest end of Barf-PCT's range intended for less potent compounds. *Id.*; EX1006, 94 (Tbl. 1). Second, Barf-PCT teaches "parenteral administration requires lower dosages than other methods of administration," so a POSA would have deprioritized the lowest end of Barf-PCT's range. EX1006, 20:23-24; EX1002 ¶194. A POSA also would have conducted a routine dose-finding study and selected the lowest dose of acalabrutinib that achieves maximal BTK occupancy, leading directly to 100 mg. *Supra* §X.A.1.c.i.(2).

Administering this dose twice daily would have been obvious given Barf-PCT's teaching of "multiple subdoses administered at appropriate intervals throughout the day" (EX1006, 20:25-26) and Cheson's teaching that "BTK inhibitors are being evaluated in a twice-daily schedule in an attempt to overcome the synthesis of new BTK molecules within those cells," which "appeared to be more effective" than once-daily dosing (EX1008, 4, 10). EX1002 ¶196; *supra* §X.A.1.c.ii. Thus, claim 8 would have been obvious. EX1002 ¶197.

2. Claim 9

Claim 9 limits the claimed BTK inhibitor to acalabrutinib "or a pharmaceutically acceptable salt thereof," omitting hydrates or solvates. This claim is obvious for the same reasons as claim 8; Barf-PCT discloses acalabrutinib

and its pharmaceutically acceptable salt. *Supra* §X.B.1; EX1002 ¶200; EX1006, 35:16-36:2, 17:15-18:5.

3. Claim 10

As discussed in Ground 1, the “wherein” clause added by claim 10 merely recites intended results of certain treatment durations and lacks patentable weight. *Supra* §VII.C. To the extent claim 10 requires administering acalabrutinib for the recited durations, that would have been obvious over Cheson for the reasons discussed in Ground 1. *Supra* §X.A.3; EX1002 ¶203; EX1008, 9. The recited outcome of such administration is an inherent result that cannot distinguish prior art. *TWI*, 773 F.3d at 1194-95. Regardless, the result would have been reasonably expected as shown above. *Supra* §X.A.3; EX1002 ¶¶165-66, 205.

Thus, claim 10 would have been obvious. EX1002 ¶¶206-08.

4. Claim 11

Claim 11 is obvious for the same reasons discussed in Ground 1. EX1002 ¶210; *supra* §X.A.4. Based on Barf-PCT’s teaching that acalabrutinib inhibits BTK and treats MCL, a POSA would have administered acalabrutinib to treat all recited morphologies, which involve the same BCR signaling targeted by BTK inhibition, rendering claim 11 obvious. EX1002 ¶¶211-12; EX1014 (Pileri), 2.

5. Claim 12

Claim 12 recites combination therapy with anti-CD20 antibodies, including rituximab. For the same reasons as Ground 1, this limitation is obvious over

Cheson, which teaches combination therapy of a BTK inhibitor with rituximab. EX1002 ¶214; *supra* §X.A.5; EX1008, 4 (“The addition of other agents such as rituximab or bendamustine to ibrutinib has been shown to reduce the duration of lymphocytosis.”), 9. Moreover, Barf-PCT notes anti-CD20 agents treat B-cell disorders (EX1006, 2:1-3) and covers combinations with other drugs (*id.*, 19:29), rendering claim 12 obvious. EX1002 ¶¶215-16.

6. Claim 19

Claim 19 requires acalabrutinib’s “free form.” This claim is obvious for the same reasons as claims 8-9. Barf-PCT’s compounds “can be in the form of a free base,” rendering claim 19 obvious. EX1006, 26:31-32; EX1002 ¶¶217-20.

7. Claim 20

Claim 20 requires a “pharmaceutically acceptable salt of” acalabrutinib. This claim is obvious for the same reasons as claims 8-9. Barf-PCT’s compounds may be “in the form of a pharmaceutically acceptable salt” and lists exemplary salts, rendering claim 20 obvious. EX1006, 26:31-37; EX1002 ¶¶221-22.

C. There are no probative secondary considerations.

Petitioner is unaware of any probative secondary considerations of nonobviousness and reserves the right to rebut any alleged considerations during trial. Nevertheless, Petitioner preliminary addresses alleged unexpected results raised in prosecution and the specification.

1. The results submitted during prosecution fail to demonstrate probative unexpected results.

As discussed above (§IV.C), the applicants argued (1) it was unexpected that acalabrutinib could be dosed at a “significantly lower dose” than ibrutinib and achieve full BTK occupancy; and (2) it was unexpected twice-daily dosing would sustain BTK occupancy longer than once-daily dosing. EX1004, 1002, 1077, 1079. These alleged results are neither probative nor unexpected.

a. A daily dose of 200 mg acalabrutinib (100 mg BID) does not produce probative unexpected results.

During prosecution, as detailed above (§IV.C), the Examiner’s primary reference (Smyth ’172) related to ibrutinib, which the Examiner deemed “similar” to acalabrutinib because both compounds “have the same cores.” EX1004, 909, 1034. The Examiner assumed a POSA would have started with a method of treatment using ibrutinib and substituted the known structure of acalabrutinib for ibrutinib. *Id.* In response, the applicants did “not agree” ibrutinib is structurally similar to acalabrutinib (*id.*, 997) but alternatively argued that a POSA starting from ibrutinib would not have used the claimed dose because ibrutinib was marketed at a higher, once-daily dose of 560 mg (*id.*, 998-99).

In this context, where ibrutinib is considered the starting point, the applicants argued “[i]t was unexpected that acalabrutinib could be orally administered twice daily at a significantly lower dose (100 mg BID) than ibrutinib

and provide continuous and improved BTK target occupancy (greater than 95% over a period of 24 hours) relative to ibrutinib.” *Id.*, 1002. According to the applicants, a POSA “considering the [ibrutinib] ’172 application would not have expected the lower amount BID dosing of acalabrutinib to be sufficient to provide for full BTK occupancy by acalabrutinib.” *Id.*; *accord id.*, 1077.

This alleged result of “full BTK occupancy” at a daily dose of 200 mg (100 mg BID) acalabrutinib is not a probative unexpected result, for two reasons.

First, “to properly evaluate whether a superior property was unexpected,” a patentee must demonstrate “what properties were expected.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (patentee’s “evidence must fail because the record is devoid of any evidence of what the skilled artisan would have expected.”). The applicants, however, provided no evidence that a POSA would assume acalabrutinib requires the same dose as ibrutinib to achieve the same BTK occupancy. EX1002 ¶230. On the contrary, they denied a POSA would equate acalabrutinib and ibrutinib. EX1004, 997-98, 1077. Nor did they provide any evidence of what doses a POSA *would* expect were required.

The applicants relied on ibrutinib’s marketed dose to rebut the Examiner’s obviousness theory, which relied on an ibrutinib reference as a starting point. *Id.*, 909, 1034. By contrast, this Petition starts from a dosing range for *acalabrutinib* disclosed in Barf and Barf-PCT, which does not depend on any structural similarity

with ibrutinib. Any reliance on ibrutinib is in the context of practicing Barf's range in view of data on other BTK inhibitors, including CC-292 and ONO-4059. *Supra* §X.A.1.c.i.(1). Petitioner is not simply assuming acalabrutinib would be administered at the same dose as ibrutinib.

Because the applicants' arguments about ibrutinib were specific to rebutting the Examiner's theory and relied on a comparison that the applicants themselves rejected, they are irrelevant to this Petition and fail to show a POSA would expect acalabrutinib to require ibrutinib's higher, FDA-approved dose. For this reason alone, the applicants failed to show probative unexpected results.

Second, even assuming a POSA would expect acalabrutinib to require the same dose as ibrutinib to achieve the same BTK occupancy, it was not unexpected that a 200 mg daily dose would achieve greater-than-95% BTK occupancy. EX1002 ¶232. The equivalent result was reported for ibrutinib. *Id.* Advani discloses that 2.5 mg/kg ibrutinib achieved "BTK occupancy >95%." EX1009, 12. For the common conversion of 70 kg, this equates to 175 mg, and for a North American average of 80 kg, equates to 200 mg. EX1002 ¶232. That acalabrutinib achieves the same BTK occupancy (>95%) at substantially the same daily dose (175-200 mg/day) as ibrutinib is thus neither superior nor unexpected. *Id.*

Given the maximal occupancy reported with ibrutinib at doses as low as 175-200 mg/day, it is immaterial that ibrutinib was marketed at a higher dose. *Id.*

¶233. As recognized in FDA guidelines, “drugs have often been initially marketed at what were later recognized as excessive doses.” EX1026, 2. FDA reached that same conclusion for ibrutinib. In its 2013-2014 reviews (EX1017), FDA repeatedly recommended lower doses for ibrutinib, citing Advani:

- “[T]he proposed dose is 2.4-fold higher than the lowest dose that resulted in maximum BTK occupancy and maximum clinical response. Dose-response relationship for ORR and BTK occupancy from Phase 1 study suggested that maximum ORR and maximum occupancy was achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg).... *The sponsor should thus consider exploring lower doses in future development programs.*” EX1017, 5.
- “[A] lower dose would likely be efficacious.... Evaluate lower doses of ibrutinib in future clinical development as *data from the Phase 1 trial showed that maximum BTK occupancy and maximum response were achieved at doses of ≥ 2.5 mg/kg.*” *Id.*, 10; *see also id.*, 11-12.
- “In the phase 1 dose escalation trial, full and sustained ($> 90\%$ at 24 hours) occupancy of the BTK active site was reached at ibrutinib doses ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg). *Therefore, doses lower than the selected doses are expected to have sustained occupancy of the BTK active site in vivo....*” *Id.*, 20; *see also id.*, 55.

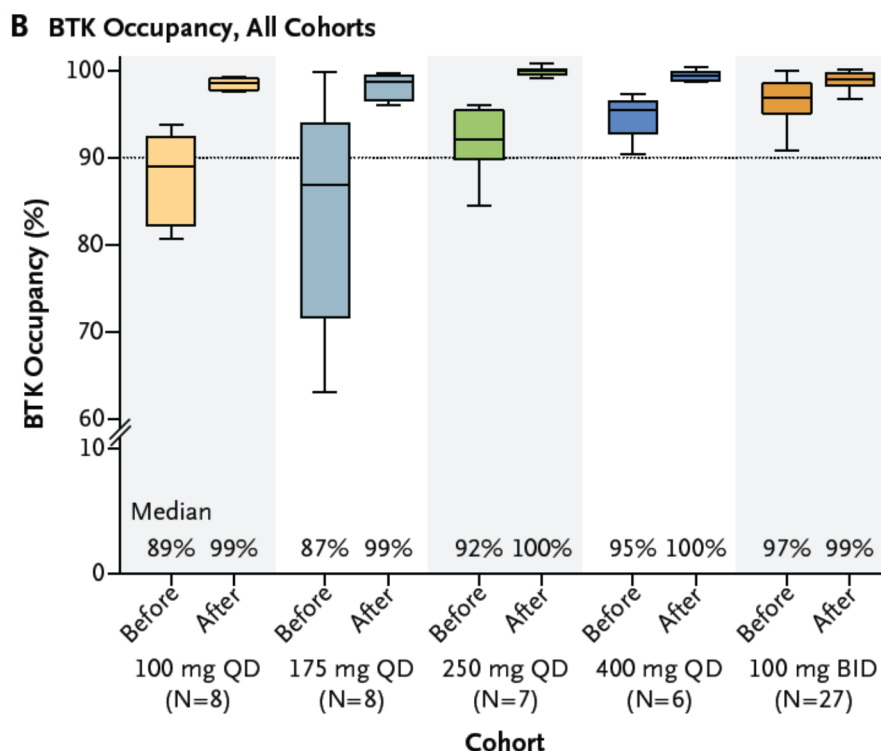
(Emphases added.)

Regardless, lower doses were expressly contemplated in ibrutinib's labeling. EX1002 ¶234. As of 2014, the label recommended up to two reductions by 140 mg (for a total 280 mg reduction) for toxicity-related adverse events and instructed physicians to “[r]educe IMBRUVICA dose to 140 mg if a moderate CYP3A inhibitor must be used.” EX1016, 2-3. Thus, notwithstanding the 560 mg default, doses as low as 140 mg were also FDA-approved. *Id.*

In short, given that the claims do not require FDA-approved doses, lower and equally effective doses of ibrutinib should have been used in any assertion of unexpected results as a more relevant comparator. And when those lower ibrutinib doses—which achieved maximum BTK occupancy—are used as the comparator, it becomes clear that the BTK occupancy obtained with the claimed daily dose of acalabrutinib is not a probative unexpected result. EX1002 ¶235.

b. Acalabrutinib's twice-daily dosing does not produce probative unexpected results.

The applicants also argued that twice-daily dosing produces unexpected results. As discussed above (§IV.C), the applicants cited Byrd, which compared four *once-daily* cohorts (ranging 100-400 mg) to a single *twice-daily* cohort (100 mg) in CLL patients. EX1004, 1078-79. The applicants cited the following box plot in Byrd showing the BTK occupancy in each cohort:



EX1010, 6; EX1004, 1079. The applicants acknowledged “BTK target occupancy was complete (99 to 100%) four hours after dosing for all cohorts” (labeled “After” above), reflecting no difference between once- and twice-daily dosing. EX1004, 1079; EX1002 ¶237. The applicants nevertheless highlighted two points from Byrd in support of alleged unexpected results.

First, the applicants contended that the degree of BTK occupancy “immediately before administration of the next dose (at trough)” (labeled “Before” above) differed between once-daily and twice-daily groups because (i) the median BTK occupancy ranged from 87-95% for once-daily cohorts, whereas (ii) the median BTK occupancy was 97% for the twice-daily cohort. EX1004, 1079. Second, given the Examiner’s focus on ibrutinib, the applicants quoted Byrd’s

statement that “twice-daily dosing of ibrutinib ... may not be possible owing to the potential for drug accumulation.” *Id.*, 1078. The Examiner relied on both arguments in the notice of allowance (*id.*, 1382), but they fail to show probative unexpected results for multiple reasons.

First, it was not unexpected that twice-daily dosing would provide more continuous BTK occupancy than once-daily dosing. EX1002 ¶239. As discussed, that is one reason a POSA would have been motivated to use twice-daily dosing. *Supra* §X.A.1.c.ii. Again, a POSA would have known CC-292 and ONO-4059 were administered twice daily for this reason, so a similar improvement in BTK occupancy with acalabrutinib was not unexpected. *Id.*; EX1002 ¶239; EX1032 (Brumskill), 3 (“The half-life of CC-292 is 2 h and BTK resynthesis occurs after 12 h, therefore b.i.d. dosing maintains BTK inhibition.”); EX1033 (Yoshizawa), 1-2 (“We hypothesized that the efficacy of ONO-4059 could be further enhanced by increasing the drug trough concentration,” suggesting “a more frequent dosing regimen such as BD may be a more effective treatment”); EX1008 (Cheson), 4 (“Other BTK inhibitors are being evaluated in a twice-daily schedule in an attempt to overcome the synthesis of new BTK molecules....”).

Second, “[u]nexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art.” *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013)

(quotation omitted). At most, the difference in BTK occupancy between Byrd's once- and twice-daily cohorts is a difference in degree, not kind. EX1002 ¶240. BTK occupancy at trough for once-daily dosing ranged 87-95% compared to 97% for twice-daily. EX1004, 1079; EX1010, 6. That is a difference in degree, especially since the disparity between the highest-occupancy once-daily cohort (95%) and the twice-daily cohort (97%) was only 2%. EX1002 ¶240.

Third, the applicants failed to show "what properties were expected," which is necessary "to properly evaluate whether a superior property was unexpected." *Pfizer*, 480 F.3d at 1371. Because they were focused on rebutting the Examiner's obviousness theory based on ibrutinib, the applicants highlighted Byrd's statement that "twice-daily dosing of ibrutinib ... may not be possible owing to the potential for drug accumulation given the ibrutinib half-life of 4 to 13 hours." EX1004, 1078. But the applicants never showed that a POSA would expect acalabrutinib's half-life or accumulation to be the same as ibrutinib's. EX1002 ¶241. Instead, they denied a POSA would expect acalabrutinib to share ibrutinib's properties. EX1004, 997-98, 1077. Nor did they cite any evidence suggesting a POSA would believe acalabrutinib could *not* be dosed twice daily, or that such dosing would not improve BTK occupancy. EX1002 ¶241. With no evidence of a contrary expectation, there is no basis to find the results unexpected.

Fourth, the applicants cited no evidence that a POSA would have expected ibrutinib's half-life to preclude twice-daily dosing. *Id.* ¶242. While Byrd speculated that twice-daily dosing for ibrutinib “may not be possible owing to the potential for drug accumulation” (EX1010, 9), Byrd was published no earlier than December 2015 (*id.*, 1) and is not prior art. Contrary to Byrd's statement, Advani (which *is* prior art) reports that ibrutinib has a “[m]ean apparent terminal half-life [that] ranged from 4 to 8 hours,” with “no evidence of accumulation of ibrutinib exposure after repeated daily oral dosing.” EX1009, 9.

Byrd cites another paper by de Jong that reports a broader range for terminal mean half-life of 4-13 hours (EX1010, 9, 10 n.32), but this paper was received in May 2015 and is not prior art (EX1036, 1). Moreover, Byrd fails to mention de Jong's acknowledgment of “minimum drug accumulation after repeated dosing.” EX1036, 2. Thus, a POSA in January 2015 would have had no expectation that ibrutinib could not be dosed twice daily, and the Examiner's statement that ibrutinib's half-life “is such that a twice daily dosage would not be effective” (EX1004, 1382) is neither relevant nor supported. EX1002 ¶243.

Accordingly, the claimed twice-daily dosing does not produce probative unexpected results. *Id.* ¶244.

2. The results in the specification fail to demonstrate probative unexpected results.

The specification also includes alleged results comparing acalabrutinib to ibrutinib. EX1001, Figs. 1-25. As discussed below, the specification characterizes certain findings as “unexpected” or “surprising,” yet the applicants did not rely on such findings during prosecution, which fail to show probative unexpected results. Most of the alleged results that are deemed “unexpected” or “surprising” are preclinical tests using cell cultures and animal models with small drug concentrations. EX1002 ¶245; EX1001, 71:1-5, 70:17-21 (“surprising” lack of platelet-aggregation inhibition in mouse model using human platelets pretreated with 0.1-1.0 μ M drug concentrations); *id.*, 71:22-42 (“unexpected” cytotoxicity benefit in NK cells of CLL patients treated with 0.1-1.0 μ M drug concentrations); *id.*, 75:7-76:8 (“surprising” lack of inhibition in cells).

These preclinical results are irrelevant to the claims. “Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention.” *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). None of these preclinical tests involved treating MCL in a human with 100 mg acalabrutinib twice daily, as required by all challenged claims. EX1002 ¶247. At most, these tests relate to alleged unexpected results of acalabrutinib itself, which is not novel because it was disclosed in Barf and Barf-PCT. *Id.*; *see also* EX1001,

74:39-42 (admitting “[c]linical investigation is needed to determine the impact of this finding on patients ... for the unexpected property”).

The only *clinical* evidence deemed unexpected or surprising compares a CLL study on acalabrutinib with previously reported results from a different trial on ibrutinib. EX1002 ¶248; EX1001, 67:1-15, 67:48-49, 68:25-26. This evidence also lacks a nexus to the claims because it does not relate to MCL; the results were “observed in CLL patients.” EX1001, 67:10; EX1002 ¶248.

Moreover, “when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.” *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). Here, treating MCL with ibrutinib is not the closest prior art. EX1002 ¶249. Rather, Barf’s treatment of MCL with *acalabrutinib* is the closest prior art, and thus any alleged unexpected result would need to compare the claimed therapy with the therapy previously disclosed in Barf. *Id.*

Even if ibrutinib were the relevant comparator, the alleged unexpected results would be “properly discounted” as based on a flawed study. *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003). The specification cites no head-to-head trial comparing acalabrutinib and ibrutinib; the applicants simply compared results from different trials. EX1002 ¶250. That is not a proper

comparison since the trials' different conditions were not controlled or accounted for. *Id.* Thus, a POSA would have disregarded this comparison. *Id.*

Regardless, the specification “is devoid of any evidence of what the skilled artisan would have expected,” let alone evidence the results were unexpected. *Pfizer*, 480 F.3d at 1371; EX1002 ¶251. At most, the specification states that some results are “attributable to the high BTK selectivity” of acalabrutinib. EX1001, 67:52. Yet acalabrutinib’s selectivity for BTK was known: Barf and Barf-PCT show acalabrutinib (Example 6) is highly selective for BTK and not other kinases. EX1002 ¶251; EX1005, col. 145-49 (Tbls. 1-5) (EX1007, 97-101); EX1006, 94-98. Moreover, Barf and Barf-PCT express a preference for BTK selectivity, warning that “an inhibitor that inhibits multiple or all kinases of the Src-family kinases simultaneously may cause serious adverse effects.” EX1005, 2:50-52 (EX1007, 2:38-39); EX1006, 2:32-33. Thus, the '083 patent does not show the benefits of acalabrutinib’s selectivity were unexpected. EX1002 ¶251.

XI. DISCRETIONARY FACTORS

Although this Petition does not implicate any factors under 35 U.S.C. §§314(a) or 325(d), Petitioner addresses these provisions below. To the extent the Preliminary Response requests discretionary denial, Petitioner requests a reply.

A. The Board should not deny review under §314(a).

Under the Director’s interim procedure, regardless of any factors that otherwise apply, “the PTAB will not discretionarily deny institution of an IPR or PGR in view of parallel district court litigation where a petitioner stipulates not to pursue in a parallel district court proceeding the same grounds as in the petition or any grounds that could have reasonably been raised in the petition.” *Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation*, 7 (USPTO Dir. June 21, 2022).

Petitioner stipulates that, should the Board institute review, Petitioner will not pursue in parallel district court proceedings the same grounds as in the Petition or any grounds that could have reasonably been raised in the Petition. Thus, the Board should not exercise discretion to deny institution under §314(a).

B. The Board should not deny review under §325(d).

The Board may consider whether “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. §325(d). Two issues are relevant: “(1) 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 first part of the framework is satisfied, 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 at 8 (PTAB Feb. 13, 2020) (precedential). An examiner “err[s] in the prosecution leading to the issuance of the [challenged] patent” if key prior art “was not considered.” *Oticon Med. AB v. Cochlear Ltd.*, IPR2019-00975, Paper 15 at 19 (PTAB Oct. 16, 2019) (precedential).

Neither prong of *Advanced Bionics* is met. Neither the same art nor the same arguments were considered. The Examiner did not consider Barf’s claims, which are the primary art for Ground 1. Nor did the Examiner consider Cheson, a combination reference for both grounds. Cheson was not even disclosed during prosecution. Although the Examiner considered Barf-PCT, at issue in Ground 2, it was only as a secondary reference in combination with Smyth ’172 and Evarts, which Petitioner does not rely on. *Supra* §IV.C.

Regardless, the Examiner erred in considering Barf-PCT. The Examiner repeatedly found acalabrutinib disclosed in Example 1, which is incorrect, and did not consider Example 6 that actually discloses it. EX1004, 909, 997, 1034. The Examiner also failed to consider Barf-PCT’s dosing range or apply the presumption of obviousness for the claimed dose. *Supra* §X.A.1.c.i. Nor did the Examiner apply the law of routine experimentation or a POSA’s knowledge of clinical testing for other BTK inhibitors. *Supra* §X.A.1.c.ii.

Moreover, the Examiner allowed the claims based on alleged unexpected results. EX1004, 1382. As discussed, however, the applicants' allegations were incorrect. *Supra* §X.C.1. Thus, the Examiner materially erred, and the Board should not exercise discretion to deny institution under §325(d).

XII. CONCLUSION

The Board should institute IPR and cancel claims 8-12 and 19-20.

Dated: February 3, 2023

WINSTON & STRAWN LLP
1901 L Street NW
Washington, DC 20036
Telephone: 202-282-5000
Fax: 202-282-5100
Email: acalabrutinibIPR@winston.com

Respectfully submitted,

/Jovial Wong/
Jovial Wong
Reg. No. 60,115

Lead Counsel for Petitioner

Charles B. Klein
(to seek *pro hac vice* admission)
Eimeric Reig-Plessis
(to seek *pro hac vice* admission)
Sharon Lin
(to seek *pro hac vice* admission)

Back-Up Counsel for Petitioner

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24, I certify that the foregoing PETITION FOR *INTER PARTES* REVIEW contains 13,995 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: February 3, 2023

Respectfully submitted,

WINSTON & STRAWN LLP

1901 L Street NW

Washington, DC 20036

Telephone: 202-282-5000

Fax: 202-282-5100

Email: acalabrutinibIPR@winston.com

/Jovial Wong/

Jovial Wong

Reg. No. 60,115

Lead Counsel for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: PETITION FOR *INTER PARTES* REVIEW and Exhibits 1001-1043 by next-business day delivery on February 3, 2023, on Patent Owner's correspondence address of record for the subject patent, as well as another address likely to effect service on Patent Owner, as follows:

169588 - Morgan, Lewis & Bockius LLP - Acerta (PH)
1701 Market Street
Philadelphia, PA 19103
UNITED STATES

Daniel M. Silver
McCarter & English, LLP
Renaissance Centre
405 N. King Street, 8th Floor
Wilmington, DE 19801

Dated: February 3, 2023

Respectfully submitted,

WINSTON & STRAWN LLP
1901 L Street NW
Washington, DC 20036
Telephone: 202-282-5000
Fax: 202-282-5100
Email: acalabrutinibIPR@winston.com

/Jovial Wong/
Jovial Wong
Reg. No. 60,115
Lead Counsel for Petitioner