

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ACERTA PHARMA B.V.,
Patent Owner.

Case IPR 2023-00478
Patent No. 10,272,083

PATENT OWNER'S PRELIMINARY RESPONSE

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MPEP § 7.17.02	45

PATENT OWNER'S EXHIBIT LIST

Exhibit	Description
2001	Defendants' Invalidity Contentions (Excerpt)
2002	<i>Reserved</i>
2003	<i>Reserved</i>
2004	Merck-Covalution Agreement
2005	Claim Construction Stipulation, <i>Acerta Pharma, et al. v. Alembic Pharmaceuticals Ltd, et al.</i> , No. 22-154-GBW-SRF, Dkt. No. 1083 (D. Del. Mar. 13, 2023)
2006	108th Congress, House Report H.R. 2391
2007	S7520, Senate Report, June 25, 2004
2008	Acerta Company Report
2009	Acerta History Report

INTRODUCTION

The Board should exercise its discretion to deny institution of Sandoz Inc.’s (“Sandoz”) Petition for *inter partes* review of U.S. Patent No. 10,272,083 (“the ’083 patent”). During prosecution, Patent Owner Acerta Pharma B.V. (“Acerta”) overcame two rejections raising the same arguments Sandoz rehashes in its two Grounds, based on the same or cumulative art. Acerta overcame the Examiner’s rejections for good reason: the ’083 patent discloses novel methods of treating mantle cell lymphoma (“MCL”) using acalabrutinib (a compound about which the prior art disclosed next to nothing) using a different, substantially lower dose (100 mg) and different dosing schedule (twice daily) than the 560 mg, once-daily dose taught by the breakthrough treatment ibrutinib (a more potent compound and at the time the only marketed compound in acalabrutinib’s class). On this record, there is no reasonable basis to conclude that the claims are not patentable.

1. Sandoz’s IPR is a prototypical candidate for discretionary denial under 35 U.S.C. § 325(d). Sandoz admits that Acerta overcame rejections based on its primary reference in Ground 2, WO 2013/010868 (“Barf-PCT”), and admits that its primary reference in Ground 1, U.S. Patent No. 9,758,524 (“Barf”) is a related U.S. patent with a specification identical to Barf-PCT. While Barf includes specific

claims to methods of using the compound now known as acalabrutinib¹ to treat MCL, those claims add nothing beyond the disclosure in Barf-PCT—relied upon by the Examiner in the rejections overcome by Acerta—that acalabrutinib is useful in treating lymphomas which include MCL. In addition, Barf does not qualify as prior art under 35 U.S.C. § 102(a)(2) because it arose out of the subject matter of a joint research agreement under § 102(b)(2)(C) and § 102(c). The only other reference in both Grounds 1 and 2 that Sandoz relies on is a series of publications that Sandoz labels “Cheson,” a single sentence of which disclosed that an early-stage compound (CC-292) was being evaluated for twice-daily dosing. But other references the Examiner relied upon in the rejections overcome by Acerta likewise mentioned the possibility of twice-daily dosing, rendering Cheson cumulative, at best. In short, Sandoz’s IPR presents the same arguments made by the Examiner and overcome by Acerta during prosecution, relying on references that are the same or substantially the same as those previously considered.

Sandoz’s two rote and conclusory paragraphs related to the Examiner’s purported errors do not begin to approach Sandoz’s burden of demonstrating that the Examiner erred in a way material to patentability. Sandoz implicitly admits as much

¹ Acalabrutinib was not yet named in the prior art, but was instead only referred to as a numbered figure or by its chemical formula.

by preemptively requesting a reply to Acerta's POPR. Far from "not consider[ing]" that acalabrutinib was exemplified in Barf-PCT, the Examiner and Acerta repeatedly discussed that fact during prosecution. And, in contrast to Sandoz's unfounded allegation that the Examiner "failed to consider Barf-PCT's dosing range," Acerta directly quoted Barf-PCT's dosing range in overcoming the Examiner's rejections.

In allowing the claims, the Examiner correctly determined that the prior art did not teach or suggest the use of a twice-daily, 100 mg dose of acalabrutinib to treat MCL. Barf-PCT's only disclosure related to the dosing of its compounds is the huge range of between 0.0001-25 mg/kg. In overcoming the Examiner's rejections, Acerta persuasively argued that disclosure did not teach or suggest the use of a specific, 100 mg, twice-daily dose of acalabrutinib to treat MCL with a reasonable expectation of success. Similarly, Acerta correctly argued that the prior art disclosure of the FDA-approved, 560 mg once-daily use of ibrutinib to treat MCL taught away from a lower dose, twice-daily regimen for acalabrutinib.

2. Relatedly, institution is not warranted because Sandoz has not demonstrated a reasonable likelihood of success on the merits. The prior art disclosed the FDA-approved use of a once-daily, 560 mg dose of the first-in-class compound ibrutinib to treat MCL. Barf and Barf-PCT disclose acalabrutinib among dozens of other exemplified compounds, and reveal only general data about those compounds' potency against a handful of enzymes, including BTK. Those limited,

prior-art data show that the dozens of disclosed compounds were less potent than ibrutinib, and therefore the POSA would have had no motivation to pursue the counterintuitive approach of using a lower dose than ibrutinib's 560 mg daily dose to treat MCL, much less have a reasonable expectation of success. Cheson, on the whole, emphasizes the prominence of the breakthrough treatment ibrutinib administered once per day at a high dose, even while discussing other compounds in development. The disclosure that another compound *more* potent than Barf-PCT's disclosed compounds was being evaluated for twice-daily dosing would not have provided a reasonable expectation of success even when combined with Barf or Barf-PCT: Cheson does not teach or suggest that a daily dose lower than 560 mg (let alone a dose as low as 100 mg twice-daily) would be safe and effective to treat MCL, even if dosed more than once-daily.

3. Discretionary denial is also appropriate under 35 U.S.C. § 314(a) for efficiency reasons. Instituting trial here would only result in redundant litigation of issues between these proceedings and related, ongoing proceedings in the U.S. District Court for the District of Delaware. Sandoz here challenges the validity of a small but overlapping subset of the claims asserted, and the art identified, in the district court proceedings, which also involve five additional patents. Thus, all of the claims that Sandoz challenges here already face validity challenges based on the same art in the district court proceeding. What is more, the district court proceeding

involves four additional generic manufacturer defendants whose invalidity contentions demonstrate that they will pursue the same arguments raised here, regardless of the outcome of this proceeding. Finally, an unchallenged Orange Book-listed patent does not expire until 2026, so institution will not accelerate generic entry. Consistent with that timeline, the district court trial is scheduled for March 3, 2025. Simply put, Sandoz’s challenge here to seven claims of the ’083 patent is a non-dispositive and duplicative offshoot of much larger proceedings in the district court. Discretionary denial here is the more efficient outcome.

In light of the substantial reasons for discretionary denial and Sandoz’s failure to show a likelihood of success on the merits, the Board should deny institution.

BACKGROUND

I. The ’083 Patent

Ibrutinib, marketed under the trade name Imbruvica®, was the first-in-class, small-molecule inhibitor of Bruton’s tyrosine kinase (“BTK”). EX1001, 56:18-22, 69:20-25, 72:3-6. BTK is a protein in the B-cell receptor signaling pathway that contributes to malignant B-cell survival and proliferation. *Id.*, 1:14-33, 69:18-20. Ibrutinib forms a covalent bond with an amino acid residue on BTK and thereby blocks its activity. *Id.*, 56:56-57, 74:36-37; EX1002 ¶¶ 82-83; EX1019, 4.

As of the priority date, ibrutinib was the first and only BTK inhibitor to be FDA-approved to treat B-cell malignancies, with an approved dosing regimen of 560

mg once-daily for MCL and 420 mg once-daily for chronic lymphocytic leukemia (“CLL”). EX1004, 998-99. Ibrutinib was “highly potent in inhibiting BTK,” EX1001, 56:53-54, and demonstrated “substantial antitumor activity” in patients with various relapsed or refractory cancers. *Id.*, 56:22-50. In addition to BTK, ibrutinib was known to bind to and inhibit kinases other than BTK, rather than selectively inhibiting BTK. *Id.*, 56:51-64. Despite its off-target activity, numerous medical journals reported that ibrutinib was safe at high doses: in clinical trials of ibrutinib as a single agent against B-cell malignancies, no maximum tolerated dose was found, and ibrutinib was considered “well tolerated at dose levels through 840 mg.” *Id.*, 56:22-36.

Departing from the path paved by ibrutinib, the inventors of the ’083 patent conceived of a method of treating MCL, CLL, and small lymphocytic lymphoma (“SLL”) using a *less* potent compound at a much *lower* total daily dose. EX1001, 57:5-18, 57:19-23, 66:34-68:67, 99:2-32 (claim 1), 100:39-65 (claim 8). The inventors of the ’083 patent also departed from ibrutinib’s dosing regimen by dosing acalabrutinib more frequently, twice per day. *Id.*, 65:20-21, 66:34-68:67, Figs. 3, 9–12.

There were no data in the prior art suggesting that the 100 mg, twice-daily administration of acalabrutinib would be safe or effective in treating humans suffering from MCL or the other types of cancers discussed in the ’083 patent. For

instance, Sandoz’s expert, Dr. John P. Fruehauf, does not suggest that the prior art provided data on acalabrutinib’s pharmacologic properties, including its terminal elimination half-life, in any model, let alone in actual human patients. Rather, the only data available on acalabrutinib—which Sandoz highlights in its brief and expert declaration—was on potency in preliminary biochemical assays that were not conducted in cells or in an animal model, let alone in human patients. Pet., 19, 25, 32-33; EX1002 ¶¶ 83, 95, 122-23. However, those data showed that acalabrutinib was less potent in those biochemical assays than ibrutinib. This data would have taught away from attempting to use a lower dose of acalabrutinib (as compared to the approved dosing regimen for ibrutinib) to treat MCL.

Nonetheless, clinical data reported for the first time in the ’083 patent shows that patients receiving acalabrutinib 100 mg, twice-daily substantially outperformed patients receiving acalabrutinib once-daily (as well as patients previously reported to have received ibrutinib) in a number of different ways. EX1001, 66:34-53 (Table 5), Figs. 9–12, 7:62-8:6, 68:14-56. The amount of BTK occupied, and the length of that occupancy, was greater and longer in the acalabrutinib twice-daily group, as compared to ibrutinib and acalabrutinib once-daily groups. *Id.*, 67:53-63 (reporting “94%-99%” BTK occupancy for 200 mg total dose of acalabrutinib versus “80%-90%” BTK occupancy for 420 mg and 840 mg doses of ibrutinib); EX1004, 1078-79 (discussing Byrd’s report of higher sustained BTK occupancy for 100 mg twice-

daily than for various once-daily doses of acalabrutinib at drug trough of 24 hours post-dose). The clinical data ultimately proved that acalabrutinib dosed twice per day at the lower dose was as effective as ibrutinib at a much higher once-daily dose, with fewer side effects. EX1004, 1078, 1382. As a result, when the FDA approved acalabrutinib to treat MCL under the trade name Calquence®, the approved dosing regimen was 100 mg, twice-daily (“BID”). *Id.*, 994-95.

II. The Challenged Claims

The '083 patent claims methods of treating CLL, SLL, and MCL through a specified oral dosing regimen of a BTK inhibitor of Formula (II), namely acalabrutinib. EX1001, Claims 1, 8.

Claim 8, the sole independent claim that Sandoz challenges, recites “[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 [acalabrutinib] . . . or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.” EX1001, 100:39-65.

The remaining dependent claims that Sandoz seeks to cancel further recite using a pharmaceutically acceptable salt of acalabrutinib (claim 9); yielding an increase in “monocytes and NK cells in peripheral blood” of the human subject after treatment for a period of “about 14 days, about 28 days, [or] about 56 days” (claim 10); treating certain subtypes of MCL (claim 11); co-administering “a

therapeutically effective dose” of an anti-CD20 antibody (claim 12); administering the free form of acalabrutinib (claim 19); or administering a salt of acalabrutinib (claim 20). *Id.*, 100:66-101:36, 102:34-39.

For purposes of this preliminary response only, Patent Owner does not challenge Sandoz’s proposed priority date of January 21, 2015, which is the filing date of International Application PCT/IB2015/000645, from which the ’083 patent issued. *See* Pet. 12, citing EX1001, 1(22). Patent Owner reserves the right to assert any other priority date for the ’083 patent in any subsequent proceeding.²

III. The Grounds References

Sandoz alleges two grounds of unpatentability, each based on obviousness over Barf (EX1005) or Barf-PCT (EX1006), in view of Cheson (EX1008). Pet., 5. Sandoz concedes that its reasoning in Grounds 1 and 2 are “substantially the same.” *Id.*, 49.

² Petitioner’s assertion that “[a]lthough the ’083 patent claims priority to three provisional applications filed in 2014, none describes treating MCL by administering 100 mg of acalabrutinib twice daily,” Pet., 12, is irrelevant since Petitioner acknowledges that its “grounds references predate the earliest provisional filing of January 21, 2014.” *Id.*, 13 n. 2.

A. Barf-PCT (EX1006)

Barf-PCT is a 2013 international patent publication that discloses a genus of BTK inhibitor compounds and exemplifies 133 compounds in that genus, one of which—Example 6—is the compound now known as acalabrutinib. EX1006, 1(43), 10:19-16:27, 35:16-36:2. Barf-PCT discloses that its compounds “can be used in therapies to treat or prevent Bruton’s Tyrosine Kinase (Btk) mediated disorders,” *id.*, 21:19-20, which include, among others, “non-Hodgkin lymphoma (in particular the subtypes diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL)). *Id.*, 22:15-17.

Barf-PCT provides tables containing data related to the exemplified compounds’ potency against several enzymes, including BTK. Those data are the results of biochemical assays used to determine the concentration of the test compound that is required for 50% inhibition of its maximum effect in vitro (“EC₅₀”). EX1006, 17:4-5. Of the 133 compounds, 79 (including acalabrutinib) are described in those tables as having a BTK EC₅₀ of less than 10 nM. *Id.*, 94.

Dosing information in Barf-PCT is general to all the compounds in the specification, and broadly discloses “a dosage for humans preferably contains 0.0001-25 mg per kg body weight,” *id.*, 20:16, 20:24-25, which “may be presented as one dose or as multiple subdoses administered at appropriate intervals throughout

the day, or, in case of female recipients, as doses to be administered at appropriate daily intervals throughout the menstrual cycle.” *Id.*, 20:25-27.

B. Barf (EX1005)

Sandoz contends that Barf is prior art solely under § 102(a)(2). Pet., 21. Barf is U.S. patent No. 9,758,524, issued on September 12, 2017. EX1005, 1. Barf claims priority to the same application chain as Barf-PCT, dating back to 2011. *Id.*, 1(60). Barf on its face is assigned to Merck Sharp & Dohme B.V., *id.*, 1(73), and is licensed to Acerta pursuant to a 2012 development agreement between Merck Sharp & Dohme B.V. and Acerta’s predecessor-in-interest, Covalution Pharma B.V. EX2004; EX2008; EX2009.

Barf has the same specification as Barf-PCT, including the same disclosed genus, the same broad and general dosing information related to that genus, the same disclosure that compounds in the genus are useful in treating BTK-mediated disorders including MCL, the same example compounds, and the same tables containing EC₅₀ potency data. *Id.*, 9:9-14:26, 145:1-24, 19:39-41, 17:62-18:1, 27:36-74:49. The only difference between Barf and Barf-PCT are their claims. Barf’s claim 1 recites a method of treating MCL with the compound now known as acalabrutinib. Claim 12, which depends from claim 1, further recites the method of claim 1, wherein the “amount administered to the human subject is 0.0001-25 mg per kg body weight.” *Id.*, 150:3-32, 151:14-15.

C. Cheson (EX1008)

“Cheson” is a compilation of four articles from different authors, who were presenters at a conference chaired by Bruce D. Cheson. EX1008 at 1-15. Cheson was published in September 2013 as a supplement in the journal *Clinical Advances in Hematology & Oncology*. EX1008, 1.

Cheson states its “Educational Objectives,” are to “compare current and emerging treatment strategies for patients with B-cell malignancies,” and to “[d]iscuss evidence produced by recent studies on investigational therapies or regimens for treatment of some prevalent B-cell malignancies.” *Id.*, 2. As a whole, Cheson shows that ibrutinib was the most clinically advanced BTK inhibitor, with data showing that a high once-daily dose was safe and effective. Cheson’s first article, authored by Gribben, states that while “[s]everal BTK inhibitors are being evaluated in clinical trials; the furthest in development is ibrutinib,” which is “administered orally once daily.” *Id.*, 4. The second article, authored by Cheson himself, mentions various therapies of which ibrutinib is the only BTK inhibitor discussed alongside its positive phase I clinical data. *Id.*, 7. The third article, authored by O’Brien, prominently discusses ibrutinib as a single agent and in combination therapies, noting clinical data of a phase 1b/2 trial where patients received “fixed doses of 420 mg or 840 mg daily,” which were “well tolerated” and demonstrated the “substantial efficacy of ibrutinib in CLL patients.” *Id.*, 9. The

final article, authored by Goy, discusses several therapies of which ibrutinib is again the only BTK inhibitor discussed. *Id.*, 13-14. Goy favorably reports on a phase 2 clinical trial with MCL patients who received ibrutinib “560 mg daily” and showed an overall response rate of 68% with mild or moderate adverse events. *Id.*

IV. The Relevant Prosecution History

As discussed further below with respect to discretionary denial under 35 U.S.C. § 325(d), the arguments and references in Sandoz’s Grounds are either identical to, or substantively the same as, those considered during prosecution.

In the first of two office actions, the Examiner rejected all the claims as obvious over the combined disclosures of Smyth (US 2013/0338172), which the Examiner referred to as “the 172,” and Barf-PCT, which the Examiner referred to as “the 868” or “Johannes.” EX1004, 906-10. Smyth, the Examiner asserted, disclosed methods of treating various lymphomas including MCL using formulations of BTK inhibitor compounds, including ibrutinib, that were structurally similar to the claimed compound of Formula II (acalabrutinib), and were delivered orally “at a concentration from 300 to 1000 mg per day as much as 2 to 4 times a day.” *Id.*, 908-09. The Examiner further noted that Barf-PCT disclosed BTK inhibitor compounds useful in treating lymphomas, including the “identical” compound of “claimed

formula II,” *i.e.*, acalabrutinib.³ *Id.*, 909. In the Examiner’s initial view, it would have been obvious to combine “the specific compound of the 868 [acalabrutinib] into the method of treatment of the 172 [“2 to 4 times a day”] in order to treat a variety of cancer conditions with an oral multiple day formulation.” *Id.*, 909.

To overcome the Examiner’s rejections, Acerta argued that the prior art taught away from the claimed dose and dosing regimen, and submitted clinical data of unexpected results of the claimed dosing regimen. Specifically, Acerta argued that the Examiner had failed to consider the “entirety of the relevant art,” principally the FDA-approved 2013 and 2014 labels of Imbruvica® (ibrutinib) for treatment of MCL and CLL, which “reflect[ed] the understanding in the medical community that relatively large, once daily dosing of IMBRUVICA® is required for treatment of both mantle cell lymphoma (560 mg once daily) and chronic lymphocytic leukemia (420 mg once daily).” EX1004, 998-99. In other words, the ibrutinib labels taught

³ The Examiner misidentified acalabrutinib as appearing in Example 1 rather than Example 6 of Barf-PCT. EX1004, 909. But it is beyond doubt that he was comparing “formula (II)” in the pending application to the identical compound in Barf-PCT, which is acalabrutinib. In any event, Acerta removed any doubt in responding to the Examiner’s rejection, where Acerta wrote “the compound of Formula (II) is disclosed as Example 6 on page 30 of the ’868 application.” *Id.*, 997.

the use of a large, once-daily dose of a BTK inhibitor, not the lower, twice-daily dose claimed in the pending application. Moreover, Acerta argued, Smyth did not teach or suggest the lower dose, twice-daily dosing regimen for acalabrutinib. *Id.*, 1000. Barf-PCT, Acerta argued, similarly did not teach the lower, twice-daily dose, because it only disclosed the broad range of 0.0001-25 mg/kg for dosing its disclosed compounds. *Id.* (quoting EX1006, 22).

In addition to the prior art teaching away from a low, twice-daily dose, Acerta provided the Examiner with clinical data demonstrating the unexpectedly superior extent and duration of BTK occupancy with acalabrutinib's 100 mg, twice-daily dosing, along with less toxicity relative to the high, once-daily dosing of ibrutinib. *Id.*, 1000-01. For instance, Acerta argued that Example 2 demonstrated that acalabrutinib provides "greater BTK occupancy, superior 24-hour coverage and less inter-patient variability at a significantly lower dose (200 mg QD [once daily]) than ibrutinib (420 mg and 840 mg QD) in patients being treated for chronic lymphocytic leukemia." *Id.*, 1000-01. Additionally, Acerta cited a 2016 clinical study article by Byrd in *The New England Journal of Medicine*, which showed that "the short half-life and selective properties of acalabrutinib allow twice-daily dosing with virtually complete and continuous BTK inhibition without increased toxic effects." *Id.* By contrast, "twice-daily dosing of ibrutinib has not been pursued and may not be

possible owing to the potential for drug accumulation given the ibrutinib half-life of 4 to 13 hours.” *Id.*

In sum, Acerta argued to the Examiner in responding to the first office action that Smyth and Barf-PCT—alone or in combination—did not suggest departing from the large, once-daily dose of ibrutinib that the “medical community recognize[d]” for effective treatment of MCL. And moreover, that it was unexpected that the lower, twice-daily dose of acalabrutinib provided “continuous and improved BTK occupancy (greater than 95% over a period of 24 hours) relative to ibrutinib, particularly since acalabrutinib has limited or no plasma accumulation at lower doses.” EX1004, 1002.

The Examiner’s second and final office action, dated May 3, 2018, again rejected all of the pending claims as obvious over Smyth in view of Barf-PCT and a third reference, Evarts (US 2014/0179673). *Id.*, 1034-35. As to Smyth and Barf-PCT, the Examiner restated his prior reasoning. *Id.* Evarts, the Examiner found, taught the “use of specific dosage amounts for the treatment of various cancers.” *Id.*, 1035. The Examiner asserted that Evarts discussed treating MCL with BTK inhibitor compounds, and noted that the “dosage form comprises from 100-150 mg of the active agents,” and “can be administered twice daily,” in oral form. *Id.* Therefore, he concluded, that “[i]t would have been obvious to follow the treatment regimen of the Evarts patent in order to optimize the treatment of leukemia.” *Id.*

Acerta met with the Examiner on October 9, 2018, and submitted a written response on November 5, 2018, seeking reconsideration. *Id.*, 1069-80. Again Acerta emphasized the unexpected results of the claimed dosing regimen, highlighting additional clinical data from the Byrd publication. *Id.*, 1077-79. The data reported in Byrd demonstrated that the “once-daily cohorts had a lower median BTK target occupancy and more variance compared to the 100 mg twice-daily cohort immediately prior to administration of the next dose” of acalabrutinib. *Id.*, 1079.

The Examiner issued a Notice of Allowance on December 10, 2018, crediting Acerta’s arguments. *Id.*, 1382. Specifically, the Examiner noted that “[w]hile other BTK inhibitor compounds, are known in the prior art,” they differ chemically from acalabrutinib, such that the claimed dosing regimen was unexpectedly “superior for BTK inhibition without increase[d] toxicity.” *Id.* The Examiner further noted that the closest chemical compound in the prior art is ibrutinib, but its half-life suggested that a twice daily dosage would not have been effective. *Id.*

ARGUMENT

Three independent bases support the discretionary denial of institution of Sandoz’s Petition. First, Sandoz’s arguments are the same as those the Examiner considered during prosecution, and Sandoz’s three Grounds references (Barf (EX1005), Barf-PCT (EX1006), and Cheson (EX1008)), are either the same or

substantially the same as those the Examiner considered during prosecution, and the Examiner did not materially err in evaluating the art and arguments. As a result, the Board should exercise its discretion to deny institution under § 325(d). Furthermore, Barf (EX1005), one of two allegedly new references, is not prior art because it arose out of the subject matter of a joint research agreement.

Second, there is no reasonable basis to conclude that Sandoz would prevail on either of its two Grounds: the art taught that a more potent prior art compound—ibrutinib—was FDA-approved as a breakthrough cancer treatment at a dose of 560 mg once-daily for the treatment of MCL. The only potency data available from Barf and Barf-PCT on the compound now known as acalabrutinib is that it was a weaker inhibitor of the target kinase, BTK, than ibrutinib (and other prior art BTK inhibitors in early development). There was no reason why the POSA would have been motivated to treat MCL patients with acalabrutinib at a much lower dose of 100 mg twice-daily, let alone have had a reasonable expectation of success—indeed, the POSA would have been taught away from such a dosing regimen.

Third, on this record, the Board should exercise its discretion to decline institution under § 314(a). The Petition addresses only one of the patents (and just a subset of its asserted claims) at issue in the parallel district court litigation. And there is an unchallenged patent that prevents FDA approval of any generic version of acalabrutinib until at least 2026, after the trial scheduled for March 3, 2025. There

is no efficiency to be gained in litigating these issues on a separate track before the Board.

V. The Board Should Exercise Its Discretion Pursuant to § 325(d) to Deny Institution

The Board should deny institution under § 325(d) because Petitioner's references and arguments are the same as, or cumulative to, what the Examiner considered, and Petitioner has failed to demonstrate that the Examiner erred in any material way.

Under § 325(d), the Board applies a two-part test:

(1) [a] whether the same or substantially the same art previously was presented to the Office or [b] 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 Electromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential) ("*Advanced Bionics*").

Both parts of the test are satisfied here.

A. The Same or Substantially the Same Art Previously Was Presented to the Office

All three of Sandoz's Grounds references—Barf-PCT (EX1006), Barf (EX1005) and Cheson (EX1008)—are identical to or substantially the same as the

prior art references presented to the Office during the prosecution of the '083 patent. Additionally, as discussed below, Barf is not prior art because it is exempt as joint research subject matter under 35 U.S.C. § 102(b)(2)(C) and § 102(c). *See infra* §V.D.

With respect to Barf-PCT, Sandoz concedes that “the Examiner considered Barf-PCT” during prosecution, as the reference formed the basis of his two obviousness rejections. Pet., 8-10, 68; EX1004, 909, 1034-35. Therefore, it is undisputed that Barf-PCT is the “same art previously presented to the Office,” and the first element of the *Advanced Bionics* test is met with respect to this reference. *Advanced Bionics* at 13.

As to Barf, Sandoz concedes that “Barf-PCT is the international application counterpart to Barf,” and “provides the same disclosures as Barf, including acalabrutinib, treating MCL, and the overlapping dosing range,” which Sandoz claims support its obviousness arguments under both Grounds. Pet., 1-2. Accordingly, based on Sandoz’s own admissions, Barf is “substantially the same art previously presented to the Office,” meaning that like Barf-PCT, Barf satisfies the first element of the *Advanced Bionics* test. *Advanced Bionics* at 7.

Nevertheless, Sandoz argues that Barf is not substantially the same as Barf-PCT because the “Examiner did not consider Barf’s claims.” Pet., 68. But Barf’s claims at most disclose the use of the compound now known as acalabrutinib to treat

MCL. EX1005, 150:1-32, Claim 1. And Sandoz does not suggest the Examiner failed to consider Barf-PCT's disclosure of acalabrutinib and its use as a treatment for lymphomas. Nor could it. The Examiner's rejections reflect that he understood and found that Barf-PCT itself disclosed acalabrutinib in an example, and disclosed its use in treating "cancers including lymphomas," even if it did not include a specific claim to that subject matter. *See, e.g.*, EX1004, 909, 1034-35; EX1006, 22:15-16, 35:15-36:2. Barf's claims, therefore, do not add to the disclosures in Barf-PCT that were considered by the Examiner and eventually overcome by Acerta.

Moreover, Barf and Barf-PCT have identical specifications, including the same dosing language of "0.0001-25 mg per kg body weight" which Sandoz cites from Barf's specification and claim 12. *See* EX1005, 17:62-63, 151:14-16; EX1006, 20:24-25; Pet., 2, 24, 26. In similar cases, the Board has found references to be substantially the same under § 325(d) where both references share the same specification but have different claims. *See, e.g., Alarm.com, Inc., v. Vivint, Inc.*, IPR2022-00728, Paper 6 at 19-20 (P.T.A.B. Nov. 1, 2022); *Ivantis, Inc. et al v. Sight Sciences, Inc.* IPR2022-01530, Paper 14 at 13-14 (P.T.A.B. Mar. 27, 2023); *Johnson & Johnson Surgical Vision, Inc., v. Alcon Inc.* IPR2021-01069, Paper 16 at 14-15 (P.T.A.B. Dec. 10, 2021); *cf. Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1574-75 (Fed. Cir. 1997).

For example, in *Alarm*, the Board found two different patents, with different claims, to be the same for purposes of § 325(d) because the two patents “share[] the same written description and drawings in all relevant parts.” IPR2022-00728, Paper 6 at 20. Likewise, in *Ivantis*, the Board found that a patent application cited in the petition was the same as a patent that was before the Examiner, despite not having identical claims, because the two references “contain[] identical text and figures.” IPR2022-01530, Paper 14 at 12. The same is true in this case: the disclosures of Barf and Barf-PCT are the same notwithstanding the difference in claims.

Sandoz’s remaining reference, Cheson, is a combination reference for both Grounds, used solely to argue that the “twice-daily” limitation is obvious. Pet., 40-43, 52. According to Sandoz, the POSA would have been motivated to administer the claimed dose twice daily because Cheson reported that CC-292, a second-generation BTK inhibitor, was being evaluated for twice-daily dosing in early clinical trials in CLL patients. *Id.*, 40-41 (quoting EX1008, 10). In its § 325(d) argument, Sandoz contends, without further explanation, that “Cheson was not even disclosed during prosecution.” Pet., 68. That ignores the relevant legal test which considers whether a reference is the “same *or substantially the same*” as the art presented to the Office. *Advanced Bionics* at 7 (emphasis added).

Cheson is substantially the same as, and cumulative of, other references the Examiner cited during prosecution as teaching twice-daily administration. Cheson

is a compilation of articles cumulative of the art before the Office. Cheson, on the whole, features ibrutinib prominently and the Examiner clearly considered ibrutinib the closest prior art. EX1008, 4, 7, 9, 13-14; EX1004, 1382. As to Cheson's discussion of a twice-daily regimen, in both office actions, the Examiner relied on Smyth which he noted taught "BTK inhibitors similar to those recited in the instant claims" administered orally "as much as 2 to 4 times a day." EX1004, 908-09, 1034. Moreover, in the second office action, the Examiner relied on Evarts as teaching "specific dosage amounts" to treat MCL, including an express teaching that "[t]he dosage form can be administered twice daily," to "provide an optimal treatment regimen." *Id.*, 1035. Because the Petition relies on Cheson in the same manner as the Examiner relied on both Smyth and Evarts, Cheson is cumulative. *Advanced Bionics* at 15-17 (analyzing whether petitioner relied on ground reference in substantially same manner as the Examiner cited reference of record); *see also Panduit Corp. v. Corning Optical Communications LLC*, IPR2021-01562, Paper 20 at 15-16 (P.T.A.B. April 6, 2022) (finding first prong of *Advanced Bionics* met where grounds reference "is relied upon for the same proposition as previously presented prior art").

That all three of Sandoz's Grounds references are the same or substantially the same as the art presented to the Office is itself sufficient to satisfy the first

element of the *Advanced Bionics* test. *Id.* at 16, 19; *Ziegmann v. Stephens*, IPR2015-01860, Paper 13 at 19-20 (P.T.A.B. Sept. 6, 2017) (same).

B. The Same or Substantially the Same Arguments Previously Were Presented to the Office

In addition to asserting the same or substantially the same references the Examiner considered during prosecution, Sandoz also re-raises the same substantive obviousness arguments considered by the Examiner. Sandoz argues that claim 8 of the '083 patent is obvious because (1) Barf and Barf-PCT disclose that acalabrutinib is useful to treat MCL; that (2) the POSA would have arrived at the 100 mg, twice-daily dose either (a) because it falls within a range disclosed in the specification of both Barf and Barf-PCT, or (b) through routine experimentation; and that (3) Cheson purportedly teaches twice-daily administration. Pet., 1-2, 29-32, 50-52. The Examiner considered and ultimately rejected each of these arguments in allowing the claims.

1. With respect to Sandoz's argument that claim 8 is obvious because Barf and Barf-PCT disclose acalabrutinib and that it is useful to treat MCL, the Examiner made this identical argument in rejecting the claims as obvious. The Examiner asserted in both rejections that Barf-PCT disclosed BTK inhibitor compounds useful in treating lymphomas, which include MCL, and the Examiner further noted that

Barf-PCT disclosed the “identical” compound of “claimed formula (II),” *i.e.* acalabrutinib. EX1004, 909, 1034-35; EX1006, 35:15-36:2, 22:15-16.

2a. Similarly, the Examiner considered Sandoz’s argument that the 100 mg, twice-daily dose in claim 8 of the ’083 patent is obvious because Barf and Barf-PCT disclosed a dosing range—“0.0001-25 mg per kg body weight”—that encompasses the claimed dose. Pet., 29, 51. Acerta put this exact argument before the Examiner in response to the Examiner’s first rejection, EX1004, 1000, which found the claims to be obvious in part because of Smyth’s disclosure of ibrutinib dosed at “300 to 1000 mg per day.” *Id.*, 909. Acerta argued in response that given “the recognized dosing regimen required for IMBRUVICA®,” Smyth did not teach that a dose lower than this range could be used to treat MCL. *Id.*, 999-1000. And, critically for purposes of the § 325(d) analysis, Acerta further argued that Barf-PCT “simply reports the following information on dosing the compounds of that application[:]. . . a dosage for humans preferably contains 0.0001-25 mg per kg body weight”; “[a]ccordingly, the specific 100 mg acalabrutinib [twice daily] dosing regimen for the treatment of chronic lymphocytic leukemia, small lymphocytic leukemia, or mantle cell lymphoma as provided in the pending claims is neither taught nor suggested by” Smyth or Barf-PCT. *Id.*, 1000. The Examiner clearly appreciated (and accepted) this argument, because in rejecting the claims a second time, he stated that the combination of Smyth and Barf-PCT “is silent to the specific

dosage form and amount.” *Id.*, 1034-35. The Examiner therefore considered and rejected the precise overlapping range argument pressed here by Sandoz.

Additionally, the Examiner asserted in the second rejection, that Evarts disclosed methods of treating cancers using BTK inhibitor compounds at a dose of 100-150 mg twice daily. EX1004, 1035. The Examiner, therefore, considered an overlapping-range argument based not only on Barf-PCT, but also based on Evarts. Acerta overcame the Examiner’s overlapping-range argument based on Evarts by pointing out the unexpected clinical study finding that acalabrutinib could be administered twice daily at a significantly lower dose than ibrutinib, and provide continuous and improved BTK occupancy relative to ibrutinib. EX1004, 1077. The Examiner thus evaluated multiple overlapping range arguments during prosecution—one the same and one substantially the same as the overlapping range argument pressed by Sandoz.

2b. Also presented to the Examiner was Sandoz’s argument that an “independent basis for obviousness” of the 100 mg limitation is that the “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.” Pet., 34, 52. The Examiner considered the same point when he wrote in the second rejection that the POSA would take the teachings of Evarts, including the “specific dosage amounts” disclosed therein to “optimize the treatment of leukemia.”

EX1004, 1035. Acerta overcame this rejection based on the ibrutinib art's teaching away from the lower daily dose and the unexpected clinical data related to acalabrutinib's BTK occupancy as compared to ibrutinib. *Id.*, 1077, 1382.

3. Cheson's disclosure that twice-daily administration of CC-292, another BTK inhibitor, was being evaluated in early clinical trials, is also substantially similar to arguments presented during prosecution. Pet., 40-41, 52. The Examiner considered the dosing regimen of other BTK inhibitor compounds during prosecution. For example, the Examiner noted Smyth's disclosure of dosing "2 to 4 times a day" and Evarts' disclosure of a compound that "can be administered twice daily" to "optimize the treatment of leukemia." EX1004, 908-09, 1034-35. Sandoz's Cheson argument is thus the same or substantially the same as the arguments considered by the Examiner.

As such, Sandoz's arguments were considered carefully during examination, and the first element of the *Advanced Bionics* test is met. Notwithstanding the ability to anticipate these straightforward § 325(d) arguments, Sandoz offers two conclusory paragraphs on § 325(d) that, as reflected below, misstate the record,

ignore key aspects of the legal framework, and are inconsistent with other parts of its Petition. Pet., 68-69.⁴

C. Petitioner Has Not Demonstrated that the Office Erred in a Manner Material to the Patentability of the Challenged Claims

Sandoz has not come close to demonstrating that the Examiner’s treatment of the art or arguments was unreasonable, much less incorrect. Under *Advanced Bionics*, “[i]f a condition in the first part of the framework is satisfied and the petitioner fails to make a showing of material error, the Director generally will exercise discretion not to institute *inter partes* review.” *Id.* at 8-9. The Board has

⁴ Rather than substantively engage with the § 325(d) analysis, Sandoz instead preemptively requests a reply. Pet., 66. The Board should deny Sandoz’s request for a reply because absent a “showing of good cause,” Petitioners are not allowed a reply to a patent owner’s preliminary response. 37 C.F.R. § 42.108(c) (2021). Sandoz’s desire to circumvent the word limit does not rise to good cause because under Board precedent, a petitioner “may not neglect to address an issue with the expectation that additional briefing will be permitted in reply.” *See Edwards Lifesciences Corp. v. Boston Scientific Scimed Inc.*, IPR2017-00444, Paper 8 at 3 (P.T.A.B. May 22, 2017) (denying petitioner authorization to file a reply to address § 325(d) arguments).

explained, that “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.* at 9. This legal standard “reflects a commitment to defer to [the] previous Office evaluations of the evidence of record unless material error is shown.” *Id.*

Sandoz lists four errors the Examiner allegedly made: 1) the Examiner did not consider that acalabrutinib was disclosed in Barf-PCT because he erroneously cited Example 1, rather than Example 6; 2) the “Examiner [] failed to consider Barf-PCT’s dosing range or apply the presumption of obviousness for the claimed dose”; 3) the Examiner did not “apply the law of routine experimentation or a POSA’s knowledge of clinical testing for other BTK inhibitors”; and finally that 4) the Examiner mistakenly allowed the claims “based on alleged unexpected results.” Pet., 68-69. As explained below, the Examiner’s treatment of these issues was correct and certainly not unreasonable.

1. The Examiner Did Not Materially Err by Citing Example 1, Rather Than Example 6 in Barf-PCT

Sandoz suggests the Examiner did not consider Barf-PCT’s disclosure of acalabrutinib because he mistakenly cited to “Example 1,” rather than “Example 6 that actually discloses it.” Pet., 68. This tenuous argument misconstrues the record and is contrary to Sandoz’s position in the parallel district court litigation.

In both office actions, the Examiner found the claims obvious based on Barf-PCT which he noted disclosed the “identical” compound of “claimed formula (II),” meaning acalabrutinib. EX1004, 909, 1034. It is thus clear the Examiner’s reasoning reflects that he was aware that acalabrutinib was disclosed in Barf-PCT even if he cited to the wrong example. Moreover, Acerta ensured that any oversight on the Examiner’s part was corrected by pointing out in its January 25, 2018 response, that “Example 6,” rather than “Example 1” disclosed acalabrutinib. EX1004, 997. Acerta further noted that “the compound of Example 6 disclosed in [Barf-PCT]” was “the compound of Formula (II) of the pending claims.” *Id.*, 997-98. Therefore, Sandoz’s suggestion that the Examiner did not consider that Barf-PCT disclosed acalabrutinib is untenable given the prosecution record.

Indeed, Sandoz conceded this very point in the parallel district court litigation. Defendants there (including Sandoz) served invalidity contentions for the ’083 patent stating that the Examiner “noted that [Barf-PCT] discloses the use of BTK inhibitor compounds for treating lymphomas, including *specifically with the compound acalabrutinib*,” and that “[a]ccording to the Examiner, a skilled artisan would have included *acalabrutinib as disclosed in [Barf-PCT]* into the formulation disclosed in Smyth” EX2001, 4 (emphasis added). Moreover, Sandoz’s argument entirely overlooks the relevant legal standard which requires a showing that the Examiner’s error was “material.” *Advanced Bionics*, at 8-9. Here, the fact

that the Examiner wrote “Example 1,” rather than “Example 6” to identify acalabrutinib, is immaterial given the overwhelming evidence in the record that demonstrates that the Examiner based his reasoning on the disclosure of Example 6 (acalabrutinib) and not Example 1 in Barf-PCT.

2. The Examiner Correctly Considered Barf-PCT’s Dosing Range and the Presumption of Obviousness

Sandoz’s contention that the Examiner erred because he “failed to consider Barf-PCT’s dosing range or apply the presumption of obviousness,” Pet., 68, is again contrary to the record and the law. As discussed above, *supra* §V.B, the Examiner considered Barf-PCT’s dosing range because Patent Owner expressly argued that Barf-PCT’s dosing information, including the “0.0001-25 mg per kg body weight” range, did not render the claims obvious either alone or in combination with Smyth. EX1004, 1000.

Second, the Examiner *did* apply the “presumption of obviousness” for the claimed dose based on what he viewed as overlapping dosing range disclosures. In the first office action, the Examiner relied on Smyth to find the claims obvious, noting that Smyth taught “BTK inhibitors similar to those recited in the instant claims” administered orally “at a concentration from 300 to 1000 mg per day as much as 2 to 4 times a day.” EX1004, 908-09. In the second office action, the Examiner relied on Evarts as teaching “specific dosage amounts” to treat MCL,

including dosage amounts “from 100-150 mg of the active agents” which “can be administered twice daily,” which he viewed as obvious to rely on to “optimize the treatment of leukemia.” *Id.*, 1034-35.

The Examiner, however, correctly concluded that Acerta had rebutted the obviousness rejection by presenting evidence of unexpected results. *See In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). Specifically, in allowing the claims, the Examiner first credited Acerta’s clinical data demonstrating unexpected results. EX1004, 1382. The Examiner wrote, “the 100 mg, twice daily oral dosage is unexpectedly superior for BTK inhibition without increased toxicity.” *Id.* (cleaned up). That finding by the Examiner was based on Acerta’s arguments in its response to the second rejection that it was unexpected that acalabrutinib could be orally administered twice daily at a significantly lower dose than ibrutinib and yet provide continuous and improved BTK target occupancy relative to ibrutinib, with less toxicity. *Id.*, 1077-1078; EX1010, 9 (reporting “no cases of atrial fibrillation” to date for acalabrutinib at 14 months of follow-up, in contrast to such events noted for ibrutinib during the same interval). In addition, Acerta had argued that ibrutinib’s FDA-approved label taught away from the claimed dosing regimen since it reflected the understanding in the medical community that a relatively large, once-daily dose of that drug was required to treat MCL. EX1004, 998-99, 1077. Based on this evidence, which neither Sandoz nor its expert contends is inaccurate, the Examiner

concluded the claims were novel, noting that “[w]hile other BTK inhibitor[s]” were known in the prior art of which ibrutinib was the closest chemically, it was unexpected that the claimed method of treatment with acalabrutinib was “superior for BTK inhibition without increase[d] toxicity.” *Id.*, 1382.

3. The Examiner Evaluated Clinical Dosing References Regarding Other BTK Inhibitors and Correctly Applied the Law of Routine Experimentation

Sandoz is wrong that the Examiner failed to “apply the law of routine experimentation or a POSA’s knowledge of clinical testing for other BTK inhibitors.” Pet., 68.

a. “Clinical testing for other BTK inhibitors”

The file history demonstrates that the Examiner considered clinical testing of other BTK inhibitors. Acerta disclosed a reference discussing two other BTK inhibitors in clinical development—CC-292 and ONO-4059—on an Information Disclosure Statement (“IDS”) dated August 3, 2017, and the reference was considered by the Examiner. EX1004, 1048 (disclosing WO 2014159745 which discusses “AVL-292 [Avila Therapeutics/Celgene Corporation]”⁵ and “ONO-4059” as among a class of BTK inhibitor compounds to be used to treat MCL). Moreover, CC-292 is discussed extensively in the ’083 patent’s specification. EX1001, 69:23-

⁵ “CC-292” was previously called “AVL-292.” EX1008, 10.

29, 70:11-46. The Examiner typed “ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH,” along with his initials “/M.Y./” on the April 30, 2018 IDS, and did not line through that reference, indicating that he had considered the reference, including its discussion of the use of CC-292 and ONO-4059 in MCL therapy. EX1004, 1048, 1052. Based on this evidence, which Sandoz does not mention, the Examiner considered this reference. *See Microsoft Corp., v. Koninklijke Philips N.V.*, IPR2018-00279, Paper 11 at 12 (P.T.A.B. June 8, 2018) (reference previously presented to, and considered by, Office where examiner did not line through reference on IDS).

Sandoz’s argument that the Examiner did not consider the dosing of other BTK inhibitors is also wholly undermined by the extensive searches the Examiner conducted for BTK inhibitors and their dosing regimens. EX1004, 912-15, 1389. For instance, the Examiner searched the terms “‘btk’ with inhibitor,” “oral orally,” “lymphocytic,” “tablet capsule,” “day week month,” “twice same (daily day).” *Id.* Moreover, the Notice of Allowance acknowledged that “[w]hile other BTK inhibitor compounds are known in the prior art, they differ[] chemically from [acalabrutinib],” with ibrutinib being the closest chemical compound in the prior art to acalabrutinib. *Id.*, 1382. Neither Sandoz nor its expert addresses the Examiner’s conclusion, much less challenges it. Nor does Sandoz or its expert contend the Examiner erred by weighing more heavily the extensive prior-art clinical data associated with

ibrutinib—which also dominates Cheson—over the early-phase data of the more chemically distinct BTK inhibitors like CC-292 and ONO-4095.

It was not unreasonable for the Examiner to conclude that the most pertinent art was that discussing the most clinically advanced compound which also is the closest structurally to the compound in question. *See Daiichi Sankyo Co. v. Matrix Laboratories., Ltd.*, 619 F.3d 1346, 1353-54 (Fed. Cir. 2010) (promising data, not just structural similarity, relevant to identifying closest prior art).

b. “Routine Experimentation”

Contrary to Sandoz’s contention, Pet., 68, the Examiner correctly “appl[ied] the law of routine experimentation.” According to Sandoz, the POSA 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.” Pet., 34-40; EX1002 ¶¶ 127-42. However, the “FDA guidance” Sandoz and its expert cite, proves otherwise. Pet., 35; EX1002 ¶ 141. For example, the FDA’s 2010 S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (EX1027) states that the starting dose in humans “should be scientifically justified using all available nonclinical data (*e.g.*, pharmacokinetics, pharmacodynamics, toxicity).” *Id.*, 9. But neither Sandoz nor its expert points to any of that data for acalabrutinib in the prior art, much less contend that the Examiner overlooked it.

Indeed, the Examiner initially applied a routine experimentation rationale in rejecting the claims as obvious when he found the POSA could have used the “specific dosage amounts” in the Evarts reference to “optimize the treatment of leukemia.” EX1004, 1034-35. But he correctly rescinded his rejection—and with it, his optimization theory—after he was presented with Patent Owner’s evidence and arguments regarding ibrutinib’s FDA-approved once-daily, 560 mg dosing regimen for MCL, *id.*, 999, and Byrd’s study of unexpectedly superior BTK inhibition levels for twice-daily dosing of acalabrutinib relative to once-daily dosing of ibrutinib. *Id.*, 1078-79. Specifically, Patent Owner quoted Byrd’s observation that “the short half-life and selective properties of acalabrutinib allow twice daily dosing with virtually complete and continuous BTK inhibition without increased toxic effects,” *id.*, 1078, and in view of those data Patent Owner argued that “[t]he unexpected benefit of the claimed 100 mg [twice-daily] dosing regimen relative to the other dosing regimens evaluated could not have been predicted in view of the cited references and are a result of the pharmacokinetic and pharmacodynamic properties of acalabrutinib.” *Id.*, 1079.

Therefore, based on (i) the absence of pharmacokinetics, pharmacodynamics, and toxicity data on acalabrutinib in the prior art and (ii) the prominence of ibrutinib, the BTK inhibitor deemed most structurally similar, with its FDA-approved higher daily dose, the Examiner reasonably concluded that the lower claimed dose of

acalabrutinib was not a matter of routine experimentation. The POSA would have had to experiment to uncover substantial unknown data on acalabrutinib, and experiment on dosing in ways inconsistent with how ibrutinib was dosed, to arrive at the claimed invention. It was not unreasonable for the Examiner to conclude the claimed dose and regimen were non-obvious. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (claim not obvious “[b]ecause the problem was not known”); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) (claims not obvious based on lack of pharmacokinetic data and pharmacodynamic data in prior art); *Cambrios Film Solutions Corp. V. C3Nano Inc.*, IPR2019-00709, Paper 15 at 34 (P.T.A.B. Aug. 26, 2019) (denying institution because “broad range” in petitioner’s ground references gave “insufficient guidance” and thus failed “to invite routine experimentation”).

Sandoz cites *Merck & Co. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989), in support of its routine optimization argument, Pet., 39, but that case has no bearing here since it “involved little more than following clearly delineated steps outlined by the prior art.” *Horizon Pharma Ir. Ltd. v. Actavis Laboratories, UT, Inc.*, 2017 WL 27037f85, at *13 (D.N.J. May 12, 2017), *aff’d sub nom. HZNP Meds. LLC v. Actavis Laboratories UT, Inc.*, 940 F.3d 680 (Fed. Cir. 2019). When “only broad ranges were disclosed” in the prior art without “clearly delineated steps” for adjusting the dosage to reach the end goal (here, safety and

efficacy), courts have rejected obviousness challenges premised on “routine optimization.” *Id.*

In this case, not only are there broad ranges, but the little data available on acalabrutinib in the prior art taught away from the claimed dose. Table 1 of Barf-PCT and Barf indicates that the potency (EC_{50}) of acalabrutinib against BTK was less than 10 nM. EX1005, 145:5-23. The Petition itself notes that the prior art showed ibrutinib, CC-292, ONO-4059 each had a higher potency against BTK. Pet., 32; EX1002 ¶¶ 122-23; EX1019, 4. Ibrutinib was approved by the FDA and CC-292 selected for advancement to phase II clinical trials at much higher doses than 100 mg twice per day (200 mg daily). EX1016, 1 (560 mg once per day for ibrutinib in MCL); EX1020, 2 (“preliminary recommended phase 2 dose expansion cohort at 500 mg BID” (twice per day) for CC-292).

Under Sandoz’s theory of the case, “a POSA would have assumed that the highest end of [a dose] range was intended for less potent compounds with higher EC_{50} s.” Pet., 33. In other words, the lower the potency, the higher the dose. Therefore, the POSA reading Barf-PCT and Barf’s BTK EC_{50} data for acalabrutinib, as well as the broad potential dose range, in concert with prior-art disclosures of ibrutinib’s and CC-292’s higher potency and high dosage, would have moved toward the higher end of the dose range for acalabrutinib to at least a daily dose of 1000 mg, *i.e.*, higher than ibrutinib/CC-292. *See* Pet., 32 (arguing that clinically evaluated

doses for ibrutinib, CC-292, and ONO-4059 ranged from 20 to 1000 mg). In view of this art teaching away from a lower dose, the Examiner's conclusion that the claimed 100 mg, twice-daily dose was non-obvious was correct, and certainly reasonable.

4. The Examiner Properly Allowed the Claims Based on Unexpected Results

Sandoz argues that the Examiner also erred because he “allowed the claims based on alleged unexpected results.” Pet., 69. The Examiner made no such error. Sandoz's scattershot arguments as to why the alleged results are “neither probative nor unexpected,” suffer from the fundamental flaw that neither Sandoz nor its expert contend that the Examiner was wrong in relying on ibrutinib's approved FDA dosing schedule as the “starting point.” *Id.*, 56. Rather, Sandoz and its expert merely contend that *this* Petition “starts from a dosing range from *acalabrutinib* disclosed in Barf and Barf-PCT, which does not depend on any structural similarity with ibrutinib.” *Id.*, 56-57; EX1002 ¶ 231. In other words, Sandoz is merely offering an alternative view, and in doing so ignores the § 325(d) legal standard which states that “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Advanced Bionics* at 9.

During prosecution, following rejections, Acerta explained that the FDA-approved label of for Imbruvica® (ibrutinib) “reflect[ed] the understanding in the medical community that a relatively large, once daily dosing of IMBRUVICA® is required for treatment of both mantle cell lymphoma (560 mg once daily) and chronic lymphocytic leukemia (420 mg once daily).” EX1004, 999. It was thus unexpected that acalabrutinib’s much lower dose of 100 mg, twice daily would achieve safe and effective treatment.

In support of its position, Acerta cited data from a clinical study of acalabrutinib. The data from Byrd, as related to the Examiner, showed that the 100 mg BID dose achieved a high initial BTK occupancy of 99% 4 hours post-dose and maintained occupancy at 97% at a drug concentration “trough” of 24 hours post-dose, whereas the once-daily cohorts showed greater declines in initial BTK occupancy levels over the same time period. EX1004, 1001 (discussing Figure 1(C) from EX1010, 327-28). Byrd expressed surprise that acalabrutinib’s more “complete and continuous BTK inhibition” was “without increased toxic effects.” EX1004, 1078 (quoting EX1010); *see* EX1010, 331 (reporting that continuous acalabrutinib administration had generated only grade 1 or 2 adverse events, and no case of atrial fibrillation, where there had been atrial fibrillation events reported during the same treatment timeframe for ibrutinib).

Furthermore, Acerta attributed the superior BTK occupancy and safety results for the 100 mg twice-daily dose of acalabrutinib to “[t]he short half-life and selective properties of acalabrutinib.” EX1004, 1078 (quoting EX1010, 331); EX1010, 331 (discussing acalabrutinib’s lack of inhibitory activity against EGFR, ITK, and TEC, as distinguished from ibrutinib’s less selective profile); EX1010, 326-27, 331 (reporting on acalabrutinib “mean half-life [of] approximately 1 hour across all cohorts” relative to previously reported ibrutinib half-life of “4 to 13 hours”).

Based on these data, the Examiner correctly concluded that Acerta had established unexpected properties. It was not unreasonable for the Examiner to conclude, based on Byrd, that the claimed dosing regimen was unexpectedly “superior for BTK inhibition without increase[d] toxicity.” EX1004, 1382. This case is similar to *Apotex Inc. v. Auspex Pharms., Inc.*, in which the Board rejected petitioner’s argument that the Examiner materially erred in crediting patent owner’s evidence of unexpected results in the “absence of any showing that the Examiner relied upon materially false or incomplete statements during prosecution, or otherwise failed to properly apply the standard for assessing unexpected results.” IPR2021-01507, Paper 9 at 34-35 (P.T.A.B. Mar. 9, 2022) (lower dose unexpectedly yielded similar metabolic AUC to higher dose, with smaller QTcF prolongations and fewer side effects). Nor was it error for the Examiner to conclude that the most relevant compound in the prior art was ibrutinib, *see Daiichi Sankyo Co.*, 619 F.3d

at 1353-54, and that the ibrutinib art suggested that a lower twice-daily dosage of acalabrutinib would not be effective. While Sandoz may disagree, that does not warrant institution. *See Apotex Inc. v. Celgene Corp.*, IPR2018-00685, Paper 8 at 25-26 (P.T.A.B. Sept. 27, 2018) (denying institution where Examiner correctly credited unexpected results for claimed MCL method of treatment, and petitioner “has neither sufficiently pointed out how the Examiner erred, nor provided additional evidence or facts that warrant reconsideration of the Examiner’s decision”).

D. Barf Is Not Prior Art

An independent reason why the Board should deny institution under § 325(d) is that Barf is not only cumulative with Barf-PCT, it is also not prior art. Barf falls under the joint research exception under 35 U.S.C. § 102(b)(2)(C) and § 102(c), which provides that a disclosure shall not be prior art to a claimed invention under § 102(a)(2) if the following three conditions are met:

- (1) the subject matter disclosed was developed and the claimed invention was made by, or on behalf of, 1 or more parties to a joint research agreement that was in effect on or before the effective filing date of the claimed invention;
- (2) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and
- (3) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

35 U.S.C. § 102(c).

The statute defines a joint research agreement as “a written contract, grant, or cooperative agreement entered into by 2 or more persons or entities for the performance of experimental, developmental, or research work in the field of the claimed invention.” 35 U.S.C. § 100(h); *see also* MPEP § 7.17.02. No particular form of agreement is required, so long as this definition and the other requirements are met.⁶ Here, all three requirements under 35 U.S.C. § 102(c) are met with respect to the claims of the ’083 patent and Barf.

First, the disclosure in Barf and the claimed invention in the ’083 patent were made by parties to a joint research agreement that was in effect before the effective filing date of the ’083 patent. On August 20, 2012, before the January 21, 2015 effective filing date assumed for purposes of this Petition (or even the 2014 filing

⁶ When Congress enacted the joint research agreement exception as part of the 2003 CREATE Act, it specifically noted that it did “not intend to prescribe the specific form of the agreement parties must use to benefit from [the] Act nor to require the writing to be contained in a single instrument.” EX2006, 9. The intent was to allow parties to “structure their relationships” in a “more flexible manner.” EX2007, 1.

dates of the earliest provisional applications on the patent's face), Merck and the predecessor-in-interest to Patent Owner,⁷ entered into an agreement for the development and commercialization of BTK inhibitor compounds. EX2004. Merck provided know-how (§ 4.01) and a license (§ 2.01) to intellectual property, including Barf and related patents (§§ 2.01, 1.25) for the purpose of allowing Patent Owner to research and develop such compounds as a treatment of cancer. The agreement required Patent Owner to use reasonable efforts to develop acalabrutinib, (§ 1.08) provide reports to Merck on progress, (§ 3.03), and contemplated that any new patent applications from that work would be filed and owned by Patent Owner (§§ 8.01, 8.02). Accordingly, the agreement qualifies as a joint research agreement under § 102(c). *See* 35 U.S.C. § 100(h).

Second, the claimed invention of the '083 patent, which covers the 100 mg, twice-daily dosing regimen for CLL, MCL, and SLL for Calquence® that was approved by the FDA, was made by Patent Owner's employees as a result of activities undertaken within the scope of the joint research agreement to develop and commercialize acalabrutinib. Patent Owner performed the clinical trials work leading to the filing and ultimate issuance of the '083 patent in the course of

⁷ EX2008; EX2009 (Acerta company and history reports showing that Covalution is Acerta's predecessor-in-interest)

developing and obtaining regulatory approval for acalabrutinib. *See* EX1004, 513; EX1001, 58-68.

Third, the Board has granted Patent Owner leave to file a motion for leave to request a certificate of correction to identify these parties to a joint research agreement as required by § 102(c)(3). With that certificate, the Barf patent would not qualify as prior art to the '083 patent under § 102(a) because the requirements for the exception in § 102(c) will have been met. *See Global Tel*Link Corp. v. Securus Technologies, Inc.*, IPR2014-00824, Paper 36 at 16 (P.T.A.B. Dec. 2, 2015).

VI. Petitioner Has Not Established a Reasonable Likelihood of Prevailing on Any Ground

Sandoz has failed to raise a reasonable likelihood of prevailing on any of the obviousness theories in its Grounds. The “100 mg twice daily” dose limitation and the “treating mantle cell lymphoma” limitation, which are present in every challenged claim, are not obvious for two independently sufficient reasons: (1) the POSA would have had no motivation to combine Barf or Barf-PCT’s disclosure of the Example 6 compound and a broad mg/kg dose range with Cheson’s disclosure of the twice-daily dosing evaluation for CC-292; and (2) the POSA would have had no reasonable expectation of success that a 100 mg, twice-daily dosing regimen of acalabrutinib would be effective in treating MCL.

A. Sandoz Proposes and Relies on an Erroneous Construction of Claim 8

Sandoz interprets the preamble language of claim 8, which recites “[a] method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of,” EX1001, 100:39-40, as merely requiring an “intent to treat MCL” regardless of whether there is any therapeutic effect. Pet., 16. This strained and incorrect construction appears to be designed to eliminate Sandoz’s burden to demonstrate that the POSA would have a reasonable expectation of success in treating MCL with the claimed dosing regimen. The Board should reject that construction because it is contrary to the plain language of the claim which requires *some* amount of efficacy in order to “treat[]” MCL, although not a particular level. This construction is supported by the intrinsic record, Federal Circuit precedent, and Sandoz’s own agreed-upon construction of that term in the parallel district court proceeding.⁸

As an initial matter, Sandoz’s proposed construction is contrary to the definition it agreed to in the parallel district court proceeding. There, Patent Owner and defendants (including Sandoz), entered into a stipulation construing the same

⁸ In the event the Board institutes trial, Patent Owner reserves the right to challenge Petitioner’s proposed construction of claim 10. Pet., 17-18.

claim 8 preamble language at issue here as “limiting as to the intentional purpose for which the method must be performed, *i.e.*, treating Mantle Cell Lymphoma (MCL) in a human subject, which requires *treating MCL in a human subject*, but does not require a particular level of efficacy.” EX2005, 5 (emphasis added). Simply put, Sandoz agreed that the claim language necessarily required *some* amount of efficacy in order to actually “treat[] MCL in a human subject,” although not a particular level. There is no basis for Sandoz to reverse course here and seek a construction that entirely erases any efficacy requirement from the quoted language of claim 8.

The agreed-upon construction in the district court makes sense. The Petition’s proposed construction, by contrast, would render the word “administering” entirely redundant to the word “treating” which are both found in the claim. This violates a cardinal rule of construction that “claims are interpreted with an eye toward giving effect to all terms in the claim.” *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006); *see also Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005). The intrinsic record as a whole makes clear that the word “treating” means more than merely administering a dose to a patient. The specification describes the central object of the invention as providing an efficacious treatment for CLL/SLL and MCL. For instance, the specification expressly discusses a clinical study that had the purpose of “evaluat[ing] the safety and efficacy of the second generation BTK inhibitor of Formula (II) in *treating* subjects with

chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).” EX1001, 58:39-43. The study repeatedly defines treatment as positive biological responses inside a subject to the administration of the drug. *See, e.g., id.*, 60:17-63:20, 64:50-67.

Accordingly, the Federal Circuit law is clear that the intended purpose of treating MCL patients is taken into account in assessing whether the POSA would have had a reasonable expectation of success in achieving a successful treatment for MCL. *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1344-45 (Fed. Cir. 2021) (Board correctly construed claim’s preamble language directed to a method for “treating at least one vasomotor symptom,” as limiting and appropriately ruled that patent challenger was required to show reasonable expectation of success in treating vasomotor symptoms). Therefore, Sandoz’s attempt to eliminate the requirement that it show that the POSA had a reasonable expectation of success in actually treating MCL, rather than merely an “intent,” is impermissible. As discussed below, *infra* §VI.C, Sandoz’s implausible construction is driven by the fact that neither it nor its expert can point to any pharmacologic data in the prior art that would have given the POSA any reasonable expectation that MCL could be treated with a low 100 mg, twice-daily dose.

B. No Motivation to Combine the Grounds References

Sandoz cannot prevail as to any of the challenged claims because it has failed to articulate a motivation for the POSA to use a 100 mg, twice-daily dosing regimen of acalabrutinib to treat MCL.

1. No presumption of obviousness of the claimed dose

Sandoz argues that Barf and Barf-PCT's disclosure of a generic dose range for its class of compounds encompassed, and thus rendered obvious, the claimed total daily dose of 200 mg for acalabrutinib. Pet., 29-31, 51-52. Sandoz further argues that the dose range of "0.0001-25 mg per kg body weight" disclosed and claimed in Barf, *id.*, 150:31-31, 151:14-16, converts to a fixed dose range of "0.007-1750 mg" assuming an average human weight of 70 kg. Pet., 29-30. Finally, Sandoz argues that this converted dose range includes the claimed total dose of 200 mg and thus establishes a presumption of obviousness under *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003) and its progeny. *Id.* However, there is no overlap because the disclosed numerical range (0.0001-25 mg per kg body weight) does not explicitly encompass the claimed numerical limitation (100 mg twice daily). The "Federal Circuit has only applied the [*Peterson*] presumption where the overlapping range is expressly disclosed, not where an overlap might be assumed based on other motivating factors." *Moderna Therapeutics, Inc. v. Arbutus Biopharma Corp.*, IPR2019-00554, Paper 40 at 24 (P.T.A.B. Jul. 23, 2020); *see also Twi Pharms., Inc.*

v. Merck Serono SA, IPR2023-00050, Paper 8 at 16, 19-26 (P.T.A.B. Mar. 28, 2023) (denying institution and rejecting contention that the “1.75 mg/kg” dose limitation in challenged method-of-treatment claims was rendered obvious by Ground reference’s disclosure of fixed 100-140 mg dose range, despite petitioner’s contention that the fixed dose range “amounts to about 1.75 mg/kg for . . . a large section of the patient population”).

But even assuming that the conversion to a fixed dose is proper, the *Peterson* presumption of obviousness does not arise here because this case is far from the “typical[]” case that *Peterson* referenced in holding that a “*prima facie* case of obviousness typically exists when the [claimed] ranges . . . overlap the ranges disclosed in the prior art.” 315 F.3d at 1329. Rather, Barf and Barf-PCT’s dose range “is so broad as to encompass a very large number of possible distinct [doses],” and thus cannot trigger a presumption of obviousness. *Id.*, 1330 n.1; *Genetics Institute, LLC v. Novartis Vaccines &Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011). The ’083 patent’s claimed total daily dose of 200 mg is one point within a range covering multiple orders of magnitude (assuming conversion to a fixed dose range). Such a broad prior-art range cannot benefit from a *Peterson* presumption. *See Genetics Inst.*, 655 F.3d at 1306 (declining to apply *Peterson* presumption because there were thousands of protein variants encompassed in the prior art range).

Perhaps aware of the fact that its converted fixed dose range of “0.007-1750 mg” from Barf-PCT and Barf is too large to benefit from the presumption of obviousness, Pet., 29, Sandoz attempts to “narrow[] the range of possibilities” by relying on the dosing ranges of other BTK inhibitors (ibrutinib, CC-292, and ONO-4059). *Id.*, 31. But even then, the dosing range is still remarkably large—“20-1000 mg”—and thus does not trigger a presumption of obviousness. *Id.*, 32.

2. No motivation to select claimed daily dose of 200 mg

None of Petitioner’s prior-art BTK inhibitor dosing references cure Barf-PCT and Barf’s failure to teach or suggest a 200 mg daily dose for acalabrutinib because the prior art as whole taught away from such a low dose for B-cell malignancies.

Petitioner’s own reference, Cheson, demonstrates the prior art’s preference for a relatively high dose for treating MCL and CLL/SLL. The doses reported in Cheson for prior-art BTK inhibitor compounds are *at least* twice the daily 200 mg dose claimed in the ’083 patent. Cheson highlights ibrutinib as “the furthest in [clinical] development,” EX1008, 4, and reports that a phase 1b/2 trial of ibrutinib in CLL/SLL patients administered the compound at the “fixed doses of 420 mg or 840 mg” once-daily. *Id.*, 9. Cheson further discloses that a phase 2 trial of ibrutinib in MCL used a dose of “560 mg daily” and attained favorable overall response rates and progression-free survival at that dose. *Id.*, 14.

Moreover, all of the CC-292 background references cited by Petitioner disclose clinically evaluated doses surpassing the claimed daily dose of 200 mg, and even ibrutinib's highest clinically evaluated dose of 840 mg. For example, Brown (EX1020) discloses that as of the priority date, CC-292 had undergone a phase 1 study with doses up to 1000 mg once-daily and twice-daily dose levels of 375 mg and 500 mg. *Id.*, 2. CC-292 was found to be "well tolerated," and the test doses did not reveal a "maximum tolerated dose." *Id.*, 2-3. Based on this toxicity profile, the investigators had enrolled patients in a "preliminary recommended phase 2 dose expansion cohort at 500 mg BID." *Id.*, 2. The "recommended phase 2 dose" of 500 mg twice-daily amounts to a total daily dose of 1,000 mg, a five-fold increase from acalabrutinib's claimed daily dose of 200 mg, and appreciably greater than even ibrutinib's highest evaluated dose of 840 mg. Each of Petitioner's remaining CC-292 references, Pet., 32, 40-43, simply refer back to the phase I data first reported in Brown. EX1020, 2-3; EX1018, 6, 9 n. 78; EX1019, 15; EX1021, 2; EX1032, 3. Petitioner's CC-292 dosing references amplify the prior-art teachings about ibrutinib that a therapy for MCL and CLL/SLL required a high total daily dose to attain satisfactory efficacy without sacrificing safety.

Petitioner's ONO-4059 references do not change the landscape. Petitioner relies on Hutchinson (EX1019) to argue that clinical trials of ONO-4059 as of the priority date had been associated with "Responses seen at 20-320 mg." Pet., 32.

The referenced portion of Hutchinson reports emerging data for “10 evaluable patients” in a phase I study of ONO-4059. EX1019, 7. Hutchinson’s tentative findings for this limited sample of ten patients were that “[a]lthough early in development, responses have been seen at all dose levels (20-320 mg).” *Id.*

But the Petition improperly cherry picks this early data for ONO-4059 while ignoring the teachings of Hutchinson as a whole, which focus on the much higher doses used for ibrutinib. Hutchinson is a review article on BTK inhibitors, and predominantly deals with “the first-in-class BTKi” ibrutinib with its “spectacular” efficacy and “clinical success.” EX1019, 1, 4. Consistent with its focus on ibrutinib, Hutchinson opens the discussion on clinical BTK inhibitors by reporting the results of ibrutinib’s phase Ib-II trial with CLL patients at doses of “420 mg” and “840 mg.” *Id.*, 5. The discussion of ONO-4059 is a sliver of Hutchinson’s later discussion of “[c]linical experience with the other BTKi,” which Hutchinson appropriately qualifies as “more limited.” *Id.*, 7. A holistic reading of Petitioner’s ONO-4059 references does not teach or suggest the adoption of ONO-4059’s phase I range of “20-320 mg” for acalabrutinib; rather, the reference discourages it. Only by disregarding the overall tenor of the prior-art as a whole regarding ibrutinib, CC-292, and ONO-4059 can Petitioner advance its strained reading that the POSA would have been “funneled” toward an “effective range of 20-1000 mg for other BTK inhibitors.” Pet., 33.

As if an afterthought, Petitioner adds at the end of its argument for the alleged obviousness of the dose limitation: “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.” Pet., 40. But that assumes, without basis, that 100 mg would be included and ignores the requirement of some amount of efficacy. The question here is whether the POSA reading Barf and Barf-PCT with Cheson, equipped with the background knowledge of Petitioner’s prior-art BTK inhibitor references, would have had a motivation to combine Barf and Barf-PCT’s dose range disclosure with Cheson’s dosing frequency disclosure to arrive at the claimed method of *treating* a human subject suffering from MCL. Regardless of the quantum of clinical response, as discussed *supra* §VI.A, under the correct claim construction, the POSA must have had a motivation to dose acalabrutinib at the daily total of 200 mg to treat a patient suffering from MCL and must have reasonably expected *some* level of efficacy. None of Petitioner’s cited references furnished a motivation for the POSA to elevate early-phase clinical data regarding CC-292 and ONO-4059 over the more extensive and advanced clinical data for ibrutinib. Properly considered as a whole, the prior art taught the POSA that a relatively high dose of acalabrutinib was needed for an efficacious method of treating MCL.

3. No motivation to practice claimed dosing schedule of twice daily

Petitioner argues that “[a] POSA practicing Barf would have been motivated to administer acalabrutinib twice daily based on Cheson.” Pet., 40, 50-52 (equivalent arguments for Barf-PCT and Cheson). By separating the twice-daily dosing limitation from the 100-mg dose limitation this way, Petitioner improperly attempts to narrow the lens through which Cheson should be assessed. Cheson does not provide any motivation to dose acalabrutinib twice daily *at the 100 mg divided dose*.

Petitioner’s arguments rest on a cherry-picked reading of Cheson that disregards that Cheson as a whole teaches away from a twice-daily dose of 100 mg and toward once daily doses of much larger amounts.

First, Gribben’s article within Cheson discloses that among the “[s]everal BTK inhibitors” in clinical trials, “the furthest in development is ibrutinib” and that “[i]brutinib is administered orally once daily.” EX1008, 4. Second, the only BTK inhibitor Bruce D. Cheson mentions in his article in the compilation is ibrutinib alongside its positive phase I clinical data. *Id.*, 7. Third, the O’Brien article within Cheson, too, touts ibrutinib as having attained “substantial efficacy” against CLL in a recent phase 1b/2 trial at the “fixed doses of 420 mg or 840 mg daily.” *Id.*, 9. Fourth, the Goy article within Cheson—the only article with a title exclusively

referencing “Mantle Cell Lymphoma”—reports the results of a phase 2 trial of ibrutinib in MCL where a 560 mg once-daily dose achieved high and durable remission rates. *Id.*, 11-14. In view of these disclosures in Cheson about the first-in-class ibrutinib compound, the POSA would not have focused on the limited data available for CC-292.

Moreover, Petitioner’s own “background” references confirm that the POSA would have looked to ibrutinib’s once-daily dosing as the model for obtaining good efficacy and toxicity profiles. Evans (EX1029), Barf 2012 (EX1030), and Advani (EX1009) each disclosed to the POSA that the irreversible mechanism of action enables BTK inhibitors like ibrutinib and CC-292 to sustain the level of BTK occupancy needed for BTK inhibition for a prolonged duration, in spite of rapid clearance of the drug from plasma, and that irreversible BTK inhibitors are “suitable for less frequent dosing regimens.” EX1029, 7; EX1030, 16; EX1009, 12. Others of Petitioner’s background references, in turn, highlighted the once-daily 560 mg dose of ibrutinib used to treat patients with MCL. EX1032, 2; EX1018, 4.

The weight of the prior art, therefore, favored once-daily dosing of BTK inhibitors with an irreversible mode of action such as ibrutinib and acalabrutinib. The portions of Cheson relating to ongoing phase I clinical evaluation of twice-daily dosing of CC-292 were drowned out by the teachings of the prior art as a whole, and Sandoz’s argument thus fails.

C. No Reasonable Expectation of Success in Treating MCL with 100 mg Twice-Daily Dose of Acalabrutinib

As recounted above, the prior art had shown that a higher dose once-daily regimen of ibrutinib worked in treating MCL. However, there was no data in Barf or Barf-PCT (or any other prior art for that matter) that could reasonably suggest that the lower 100 mg twice-daily dosing of acalabrutinib could treat human subjects with MCL with any level of safety or efficacy, especially in view of its lower potency against BTK. The POSA was missing critical information. There is no suggestion by Sandoz or its expert that any of the pertinent information on acalabrutinib was available, including its pharmacokinetic profile, toxicological properties, or half-life; nor was there available information about BTK's *de novo* resynthesis rate in malignant B cells from MCL patients or the relative rates of non-covalent off-target inhibition and covalent BTK inhibition needed to have an expectation of success.

Without the benefit of drug pharmacokinetic and target pharmacodynamic data in the prior art, the POSA would not have had a reasonable expectation of success in treating MCL patients by dosing acalabrutinib at 100 mg twice-daily. *See Miltenyi Biomedicine GmbH v. Trs. of the Univ. of Pa*, IPR2022-00853, Paper 11 at 41 (P.T.A.B. Oct. 11, 2022) (denying institution where insufficient data to support reasonable expectation of success); *Alkermes Pharma Ir. Ltd. v. Otsuka Pharm. Co.*, IPR2017-00287, Paper 13 at 27-29 (P.T.A.B. May 4, 2017) (same). Rather, based

on the Petition’s potency comparisons, *supra* §V.C.3.b, the POSA would have expected that acalabrutinib would need to be dosed in an amount higher than ibrutinib and the other BTK inhibitors to have any chance of success in treating MCL patients.

D. Twice Daily Dosing of Acalabrutinib Proved Unexpectedly Superior

As discussed *supra* §§ V.C.2, V.C.4, Patent Owner showed unexpectedly that acalabrutinib lower, twice-daily dose was as effective as ibrutinib with fewer cardiovascular side effects. These data help confirm the non-obviousness of the challenged claims. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015); *In re Applied Materials*, 692 F.3d 1289, 1297 (Fed. Cir. 2012).

VII. The Board Should Exercise Its Discretion Pursuant to § 314(a) to Deny Institution

Denying institution is consistent with the policies underlying discretionary denials under 35 U.S.C. § 314(a). Under § 314(a), the Board takes a “holistic view of whether efficiency and integrity of the system are best served by denying or instituting review.” *Samsung Elecs. Co., v. Cal. Inst. of Tech.*, IPR2023-00133, Paper 10 at 15 (P.T.A.B. May 4, 2023). Here, numerous factors identified in *Apple, Inc. v. Fintiv* support discretionary denial. IPR2020-00019, Paper 11 at 6 (P.T.A.B. Mar. 20, 2020) (precedential). In particular, denial is warranted because these proceedings would neither hasten generic entry into the market as Sandoz claims,

nor be an efficient use of the Board's resources in view of parallel district court litigation – Sandoz and four other generic drug manufacturers have challenged the validity of the '083 patent in the District Court of Delaware.

First, Sandoz's argument that institution is justified because it will "promote the Office's objective to ensure that the patent system, as a whole, does not unnecessarily delay generic and biosimilar competition," is inapplicable here. Pet., 2. There is a blocking patent, U.S. Patent No. 7,459,554, that is Orange Book listed for Calquence®, which expires November 24, 2026, and is not challenged by any defendant group in the district court litigation. So even if the Board were to institute trial, and find favorably for Sandoz within a year of institution, the '554 patent would still block entry. Further, Patent Owner has asserted several additional patents against Sandoz and the other defendants concerning their generic versions of Calquence® in the ongoing district court litigation. Trial is scheduled for March 3, 2025. None of these other patents are challenged in the Petition and will need to be addressed by the district court irrespective of whether institution is granted. For instance, the district court litigation involves a compound patent (U.S. Patent No. 9,290,504) that expires in 2032. So, Sandoz's IPR challenge to some of the '083 patent claims does not clear a path to market. Moreover, the district court defendants include major generic pharmaceutical companies with an incentive to identify and raise before the district court the strongest invalidity arguments possible. The

district court invalidity contentions already include substantially more references and invalidity arguments than the Petition. The district court cases against these generic companies, including a separate trial against only Sandoz, amply fulfill the public interest in making sure that economically significant patents receive scrutiny.

Second, institution would be a waste of the Board's limited resources in view of the ongoing district court litigation. All of the prior art and arguments in the Petition have been asserted by the district court defendants. *See* EX2001. In particular, the district court defendants' invalidity contentions include allegations that claims 8–12 and 19 of the '083 patent are invalid under 35 U.S.C. § 103 in view of Barf, Barf-PCT, and Cheson, thereby duplicating both grounds raised in the Petition. Put simply, all the issues raised in this IPR are already being litigated in Delaware by the same parties and more, and there is no evidence of a stay of those proceedings.

Sandoz purports to circumvent the need for any consideration of the *Fintiv* factors by offering a stipulation that it will not pursue duplicate grounds in the district court litigation. But Sandoz ignores that such stipulations are only given weight when they actually work to “*avoid[] inconsistent outcomes between the PTAB and the district court and allow[] the PTAB to review grounds that the parallel district court litigation will not resolve.*” *Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court*

Litigation, at 7 (USPTO Dir. June 21, 2022) (emphasis added). Sandoz's stipulation does not avoid inconsistent outcomes or ensure that the Board will not review grounds that the district court will necessarily resolve.

Regardless of the Board's decision concerning patentability of the challenged claims of the '083 patent, the district court would still decide the same issues raised in the Petition because no other district court defendant has filed an IPR or moved to join Sandoz's Petition. As third parties to the IPR, they presumably are not bound by the outcome in this IPR. *See* 35 U.S.C. § 315(e)(2). Even as to Sandoz, litigation would continue as it has challenged additional claims of the '083 patent not at issue here based on the same art. The Board has previously exercised its discretion to deny institution when a petitioner's stipulation fails to properly mitigate the inefficiency concerns of parallel litigation. *See Nokia of America Corp. v. Godo Kaisha IP Bridge 1*, IPR2022-00755, Paper 9 at 13 (P.T.A.B. Nov. 2, 2022). Likewise, Sandoz's stipulation does nothing to guard against inconsistent outcomes since it does not prevent the Court from ruling differently than the Board on the same art and arguments raised in the Petition. In fact, as discussed above, Sandoz has already asked this Board to adopt claim constructions that are contradictory to those that Sandoz itself accepted in the district court.

CONCLUSION

For the foregoing reasons, the Board should deny institution of Sandoz's Petition for IPR of the '083 patent.

Date: May 15, 2023

Respectfully submitted,

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CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

I hereby certify that the foregoing complies with the type-volume limitations of 37 C.F.R. § 42.24 and contains 13,933 words, excluding those portions exempted under 37 C.F.R. § 42.24(a).

/Stanley E. Fisher/

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CERTIFICATION UNDER 37 C.F.R. § 42.6(e)

Pursuant to 37 C.F.R. § 42.6(e), the undersigned hereby certifies that a true and correct copy of the foregoing was served on May 15, 2023, by delivering a copy via electronic mail on the following attorneys of record:

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