

Filed on behalf of Jina Pharmaceuticals Ltd.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ATOSSA THERAPEUTICS, INC.,
Petitioner

v.

JINA PHARMACEUTICALS LTD.,
Patent Owner

Case PGR2026-00015
Patent No. 12,245,997

**PATENT OWNER'S PRELIMINARY RESPONSE
UNDER 37 C.F.R. §42.107**

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Wyeth & Cordis Corp. v. Abbott Labs.,
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35 U.S.C. § 102 1, 41

35 U.S.C. § 112 1, 16, 28, 32

PATENT OWNER'S EXHIBIT LIST

EX.	DESCRIPTION
2001	Information Disclosure Statement filed in U.S. Patent Application No.17/226,671
2002	Shoukath M. Ali <i>et al.</i> , <i>Endoxifen is a new potent inhibitor of PKC: A potential therapeutic agent for bipolar disorder</i> , BIOORGANIC & MEDICINAL CHEM. LETTERS 20 (2665-2667) (February 2010)
2003	WIPO Patent Publication No. WO 2008/048194 to Yesiloglu.
2004	Nilesh Shah <i>et al.</i> , <i>Clinical Practice Guidelines for Management of Bipolar Disorder</i> , INDIAN J. PSYCHIATRY 59 (Supplement 1) (S52-S66) (January 2017)
2005	Shiv Gautam <i>et al.</i> , <i>Clinical Practice Guidelines for Bipolar Affective Disorder (BPAD) in Children and Adolescents</i> , INDIAN J. PSYCHIATRY 61 (Supplement 2) (S294-S305) (January 2019)

I. INTRODUCTION

Atossa Therapeutics, Inc. (“Petitioner”) petitioned for post grant review of claims 1-10 (the “Challenged Claims”) of U.S. Patent No. 12,245,997 (EX1001, the “997 patent”). Petitioner’s grounds are related to written description, enablement, indefiniteness, and anticipation. For the reasons outlined below, Petitioner has failed to establish that it is more likely than not that at least one of the Challenged Claims is unpatentable under 35 U.S.C. §§ 102 or 112.

Regarding the Section 112 grounds, Grounds 1-3, Petitioner asks the Board to ignore specific disclosure in the specification and then fails to cite case support for its approach. Regarding the Section 102 ground, Ground 4, there can be no dispute that the prior art reference on which Petitioner relies (Ex. 1004, Ahmad 2016) was repeatedly discussed during prosecution for precisely the same disclosures as cited in the Petition. Given that the Petition ignores the relevant specification disclosure and prosecution history details and fails to cite supporting case law for its positions, Patent Owner submits that the Petition should be denied.

II. THE 997 PATENT

A. Subject Matter of the 997 Patent

The Petition argues that there is no Section 112 support for the following claim terms:

- “[T]he Method Does Not Include a Rescue Medication”

- “Up to 21 days”
- “Monitoring The Dose Administered To The Patient No Sooner Than 21 Days After Commencement Of The Administering To The Patient”
- “Additional Conditions Described in the Dependent Claims”
- “Maintaining a Therapeutically Effective Concentration of Endoxifen”
By Administering a “Dose In a Range From 2 mg to 16 mg... For Up to 21 Days” With No “Rescue Medication”

A detailed analysis of the 997 patent demonstrates otherwise.

1. The 997 Patent Provides Disclosure related to Improved Treatment of Bipolar I Disorder and Additional Conditions with Endoxifen

The 997 patent is titled “Methods for Making and Using Endoxifen.” EX1001, Cover. The 997 patent is directed at methods of using a protein kinase C (PKC) inhibitor, namely endoxifen, for the treatment of a patient with bipolar I disorder. EX1001, Abstract. Bipolar I disorder was commonly treated with prescription medications, and several drugs were approved for treatment, including lithium, valproate (divalproex sodium), carbamazepine, and atypical antipsychotics. *Id.* at 1:25-27. The 997 patent explains that while these drugs show signs of relief for patients, many individuals had issues with tolerability and efficacy. *Id.* at 28-31. The 997 patent further explains that such prior drugs required continued dose monitoring:

There is also a continuous need to observe the therapeutic dose monitoring in patients during the treatment. The clinicians, for example, may find themselves in situations in which better tolerated agents are less effective, and vice versa. Also, the adherence to the treatment is affected by adverse effects such as sedation, weight gain, thrombocytopenia, and thyroid disorders.

EX1001 at 1:33-39. The 997 patent acknowledges that “[a]vailable treatments help a substantial proportion of patients, but are not beneficial for estimated 40-50% of the population.” *Id.* at 1:40-43.

As a solution to these problems, the 997 patent explains that endoxifen is a “non-steroidal selective estrogen receptor modulator (SERM) of the triphenylethylene group.” EX1001, 1:64-65. Endoxifen is a metabolite of tamoxifen and has been found to be effective in patients that have failed previous hormonal therapies. *See id.* at 1:65-2:1. The present invention relates to the use of endoxifen citrate, which has the chemical structure shown in Figure 1.

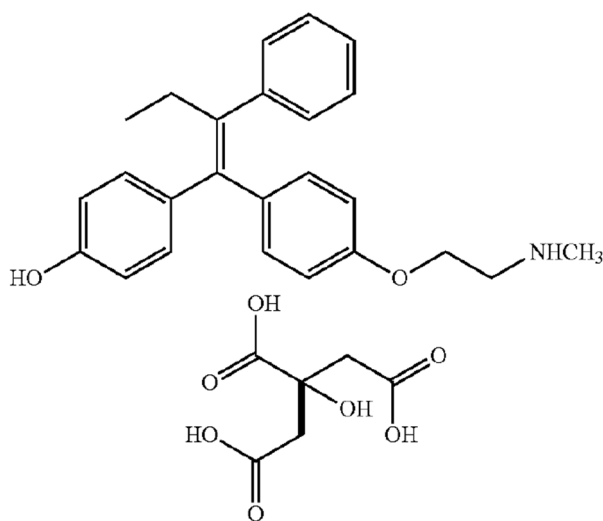


Figure 1. Chemical Structure of Endoxifen Citrate ($C_{25}H_{27}NO_2 - C_6H_8O_7$)

While the 997 patent acknowledges that the *mechanism* that endoxifen exerts its therapeutic effects has not been established in bipolar disorder, the 997 patent specifies that the *efficacy* of endoxifen is well understood and can be mediated through PKC. EX1001, 2:29-32. Namely, the specification notes that PKC “represents a family of enzymes highly enriched in the brain, where it plays a role in regulating both pre- and post-synaptic aspects of neurotransmission.” *Id.* at 2:32-35. Further, the specification explains that “[e]xcessive activation of PKC results in symptoms related to bipolar disorder.” *Id.* at 2:35-36. The specification explains that endoxifen has become an effective treatment for bipolar disorders, as compared to previous treatments, because, for example, it has exhibited “four-fold higher potency than tamoxifen in inhibiting the PKC activity,” and has a “broad therapeutic index, as compared to divalproex sodium.” *Id.* at 2: 40-46. Further, the 997 Patent explains

that “[t]argeting the PKC signaling pathway for bipolar disorder can improve the patient compliance, when therapeutic dose monitoring is not required in patient, and such treatment can provide significant improvement in mania and depression.” *Id.* at 1:60-63.

Given the effectiveness of endoxifen discussed above, the present invention of the 997 patent discloses methods for maintaining a therapeutically effective concentration of endoxifen citrate to the treatment of bipolar disorder. EX1001 at 2:47-49. Further, the 997 patent discloses methods to treat patients with manic episodes (*id.* at 2:50-54), and patients with depression or depressive episodes (*id.* at 2:55-59).

2. The 997 Patent Provides Disclosure for Administering 2-16 mg of Endoxifen Citrate for 21 Days to Maintain a Therapeutically Effective Concentration of Endoxifen

The invention of the 997 patent provides a method of maintaining a therapeutically effective concentration of endoxifen for treatment of bipolar I disorder in a patient, namely an amount of endoxifen citrate in plasma that “is sufficient to decrease or prevent or cure the symptoms associated with a medical condition or infirmity or to normalize body functions in disease or disorders that result in impairment of specific bodily functions.” EX1001, 3:36-41. The specification provides a variety of methods under the invention, including

administering a dose of 2-16 mg of endoxifen citrate in an enteric coated tablet (*see, e.g.,* EX1001, 2:60-65) for at least 21 days (*see, e.g.,* EX1001, 3:2-4).

3. The 997 Patent Provides Disclosure for Methods of Maintaining a Therapeutically Effective Concentration of Endoxifen without Rescue Medication

The 997 patent further addresses the need for the use of “rescue medications,” which refer to additional medications that may be needed to treat “breakthrough or recurring symptoms,” including, for example, lithium, valproate, lamotrigine, benzodiazepines, or anticholinergics. *See* EX1001 at 3:42-46. The inventors of the 997 patent recognized that the prior art treatment regimens for bipolar disorder frequently relied on the use of additional rescue medication to effectively control breakthrough or recurring symptom. *See id.* at 1:28-31. As explained during the prosecution history of the 997 patent, the inventors found that there is no need to administer other rescue medications during the treatment of the bipolar I disorder by maintaining the therapeutically effective concentration of endoxifen in the patient, which is achieved by administering endoxifen citrate to the patient as recited in claim 1. *See* EX1002, 4:57-59.

B. Prosecution History

1. The 997 Patent Was Extensively Prosecuted for Four Years.

Patent Owner filed U.S. Patent Application No. 17/226,671 (the “671 application”) on April 9, 2021, titled ENDOXIFEN FOR THE TREATMENT OF

BIPOLAR I DISORDER. The 671 application claims priority to a provisional application No. 63/008,162, filed April 10, 2020.

The 671 application was thoroughly examined by the Patent Office. Indeed, the 671 application was pending before the Office for nearly four years, and the claims of the application were rejected no fewer than seven times (three non-final office action (“NFOA”) rejections, two final office action (“FOA”) rejections, and two advisory action rejections). *See, generally*, EX1002. During prosecution, the applicant submitted several references in its information disclosure statement (*see* EX2001), which included the Ahmad 2016 reference supporting Petitioner’s current anticipation ground (EX1004); the Examiner extensively considered Ahmad 2016 (EX1004) en route to allowing the claims of the 997 patent. *See* EX1001, Cover; EX1002 at 41.

2. The Examiner Considered, Cited, and Rejected the Pending Claims over Ahmad 2016 in its First Office Action.

The 671 application initially claimed methods of maintaining a therapeutically effective concentration of endoxifen for treatment of a patient with bipolar I disorder, where the method comprised

administering to the patient, a dose of 2 mg to 16 mg of endoxifen citrate in an enteric coated tablet once per day for at least 21 days; wherein the patient is not administered rescue medication during the said treatment.

EX1002 at 14.

The Examiner initially rejected the pending claims of the 671 application as anticipated by Ahmad 2016, which was previously cited in an IDS.¹ *See* EX1002 at 167-168. Among other things, the examiner stated that “Ahmad teaches concomitant medications such as lorazepam have been discontinued before treatment and thus meet the instant claim limitation.” *Id.* at 169. The Patent Owner amended the pending claims to recite that “no rescue medication is administered to the patient during the treatment of the bipolar I disorder” *Id.* at 200. Patent Owner explained that “Ahmad (2016) allows to administer benzodiazepines to the patient to whom endoxifen is administered, up to 10 days from starting administering of endoxifen, and Ahmad (2016) does not disclose that no rescue medication is administered to the patient during the treatment of the bipolar I disorder” *Id.* at 202. Conversely, the inventors of the 671 application found that there was no need to administer other

¹ In fact, Patent Owner submitted multiple information disclosure statements (IDS) throughout the course of prosecution and prior to any substantive examination. *See* EX1002 at 41; *see also*, EX2001. Patent Owner cited and provided the Patent Office with a copy of Ahmad 2016 as early as July 13, 2021.

medications (for example lorazepam) during the claimed treatment for the bipolar I disorder and thus distinguished from Ahmad 2016. *Id.*

3. The Examiner Maintained the Anticipation and Obviousness Rejections of the Pending Claims over Ahmad 2016

The Examiner maintained her anticipation rejection in view of Ahmad 2016 and further rejected the pending claims as obvious over Ahmad 2016. Again, the Examiner maintained that “Ahmad teaches [that] concomitant medications such as lorazepam have been discontinued before treatment and thus meet the instant limitations.” EX1002 at 218. Alternatively, the Examiner argued that “Ahmad suggests one can include benzodiazepines only as needed and therefore it is not necessary to administer benzodiazepines during the administration of endoxifen.” *Id.* at 219. The Examiner concludes, from this suggestion, that it would have been obvious for a POSITA to “choose to administer only endoxifen without any other medication such as benzodiazepines ...” *Id.*

In response, Patent Owner emphasized that Ahmad’s study focuses “on the valuation of the efficacy and safety of endoxifen in BPD I patients with current manic or mixed episode” *Id.* at 240. Patent Owner further explained that because monotherapy was often not sufficiently effective, a wide variety of combination therapies were commonly used to treat bipolar I disorder. *Id.* at 240-41. The study of Ahmad 2016 provided for such combination therapies by allowing

benzodiazepines as adjunctive medication as needed, therefore taking it outside the scope of claim 1, which teaches that there is no need to administer other rescue medications, such as benzodiazepines and lorazepam. *Id.* at 241-42.

4. Ahmad 2016 was Cited in Several Subsequent Office Actions

The Examiner once again maintained her anticipation rejection over Ahmad 2016, noting that Ahmad teaches that “all concomitant psychotropic medications except benzodiazepines (such as lorazepam) have been discontinued” and therefore Ahmad excludes any one of the medications cited in the claim. EX1002 at 271. The Examiner further rejected the pending claims of the 671 application as obvious over Ahmad in view of Ali (EX2002), which was also cited in Patent Owner’s IDS. *Id.* The Examiner found that “it would have been obvious for one of an ordinary skill in the art before the effective filing date of the instant invention to choose to administer only endoxifen without any other medication such as benzodiazepines in the teachings of Ahmad because while Ahmad suggests administering benzodiazepines only as needed during endoxifen treatment ... Ali also demonstrates endoxifen alone for effectively inhibiting PKC and therefore effective bipolar disorder. *Id.* at 272.

Patent Owner then amended the claims to clarify that “no rescue medication is required for the treatment of the bipolar I disorder.” EX1002 at 304. And again, Patent Owner argued that the Ahmad 2016 study allowed the administration of benzodiazepines as concomitant medicines. *Id.* at 306-307. With respect to the

obviousness rejection, Patent Owner argued that Ali's study failed to provide a sufficient indication as to adverse events or side effects of synthesized endoxifen in human patients, and therefore failed to teach or suggest the no rescue medication is require for the treatment of the bipolar I disorder, as recited in the claims. *Id.* at 308-09; *see* EX2002 at 1-2.

The Examiner issued a fourth office action, maintaining her obviousness rejection of the pending claims of the 671 application based on Ahmad 2016. EX1002 at 317-326. Again, the Examiner asserted that Ahmad 2016 teaches that benzodiazepines are allowed as adjunctive medication as needed at the discretion of the investigator. *Id.* at 320. The Examiner also reiterated that Ali demonstrated the use of endoxifen alone for effectively inhibiting PKC and therefore effective bipolar disorder treatment. *Id.* at 327-28.

Patent Owner then amended the claims to recite that "the method does not include a rescue medication for treatment of the bipolar I disorder" to clarify that the present invention involves the complete removal of a rescue medication. EX1002 at 342. Therefore, the teachings of Ahmad 2016 did not disclose the claimed methods of claim 1 because Ahmad 2016 allowed for benzodiazepines as adjunctive medicine, as needed. *Id.* Further, Patent Owner argued that Ali does not remedy the deficiency of Ahmad because it related to the "in vitro" effects of endoxifen as opposed to showing the efficacy in human patients. *Id.* at 343-44; EX2002 at 1-2.

Thus, the combination of Ahmad and Ali did not disclose every limitation of claim 1 of the 671 applications.

The Examiner then withdrew her obviousness rejection and instead asserted that the claims were obvious over Ahmad 2016 in view of Yesilogluz, which was also cited in the IDS. EX1002 at 387. Yesilogluz taught the use of tamoxifen for the treatment of bipolar disorder. EX1002 at 390; EX2003 at 1:6-23. The Examiner maintained that Yesilogluz described methods of administering tamoxifen alone to patients and achieving a positive response. *Id.* The Examiner also noted that Yesilogluz did not require the use of any additional “antimanic or antidepressant compounds,” such as lithium or valproate. *Id.* Therefore, the Examiner concluded that it would have been obvious to choose to administer only endoxifen without any other medications. *Id.* at 391.

In response to the rejection, Patent Owner maintained its arguments that Ahmad 2016 does not provide motivation to use endoxifen alone. EX1002 at 412. Namely, Ahmad 2016 notes that “[a]ll psychotropic medications except benzodiazepines (lorazepam/diazepam only) were discontinued at least 2 days before randomization.” *Id.* at 412; EX1003 at 254. Further, Patent Owner noted that Yesilogluz does not teach the use of endoxifen and further taught that “[a]ll psychotropic medication therapy (*except benzodiazepines*) are tapered during the screening period and 15 discontinued at least 1 day before randomization.” EX1002

at 413; EX2003 at 6:13-15. Therefore, Patent Owner argued, the combination of Ahmad 2016 and Yesiloglu does not teach the claimed limitation of a method that does not include rescue medication. EX1002 at 413.

5. The Examiner Allowed the Claims of the 997 Patent After Extensively Citing Ahmad 2016.

The Examiner then issued a notice of allowance on November 27, 2024, noting that the closest prior art (Ahmad 2016) does not teach the claimed invention. EX1002 at 434. Namely, the Examiner acknowledged that Ahmad 2016 “requires administering up to 5 mg/day benzodiazepines as adjunct medication, thus teaching away from the limitation ‘wherein the method does not include a rescue medication for the treatment of the bipolar I disorder.’” *Id.*

C. Person of Ordinary Skill in the Art

A POSITA for purposes of the 997 patent is someone with a graduate degree, namely a Ph.D. (in organic chemistry, medicinal chemistry, pharmaceutical chemistry, or a related field) or a M.D., and four to six years of experience in diagnosing, treating, or researching bipolar disorder and other psychiatric conditions.

D. Claim Construction

For the purposes of this response, Patent Owner does not contest Petitioner’s assertion that the preamble is limiting as a statement of the intentional purpose for which the method is performed - maintaining a therapeutically effective

concentration of endoxifen citrate. However, Patent Owner contests Petitioner's attempts to rewrite the claim without basis in the claims, specification, or prosecution history.

Further, Patent Owner contends the term "the method does not include a rescue medication" is clear on its face, should be given its plain and ordinary meaning, and that the Board does not need to construe the claim to deny institution of the Petition. However, if construction is required, Patent Owner disagrees with Petitioner's attempt to rewrite the meaning of the claim to require that method "prospectively prohibit the use of any rescue medication for the treatment of bipolar I disorder at any time during the claimed endoxifen course (2-16mg once daily for up to 21 days)." Paper 1, at 30. There is nothing in the intrinsic record that requires the method to "*prospectively prohibit*" the use of rescue medication, to the extent that the Petitioner's construction can be understood.

Petitioner seems to suggest that Patent Owner disclaimed the plain meaning of the claim with respect to the use of rescue medication during prosecution. Paper 1 at 29-30. Petitioner, however, fails to show the "existence of a clear and unmistakable disclaimer that would have been *evident to one skilled in the art.*" *Genuine Enabling Tech., LLC v. Nintendo Co.*, 29 F.4th 1365, 1374 (Fed. Cir. 2022) (emphasis added). For example, despite such a burden, Petitioner provides no expert testimony opining on whether a POSITA would have found the alleged statements

as clear and unmistakable disclaimer, but rather only expert testimony parroting what was told to him by Petitioner. *See, e.g.*, EX1003 at ¶55 (“I have also been asked to assume that ‘the method does not include a rescue medication for the treatment of the bipolar I disorder’ as used in each of the Challenged Claims means the claims ‘positively exclude[] a rescue medication from the claimed method’ such that the claims prospectively prohibit the use of any rescue medication for the treatment of bipolar I disorder at any time during the claimed endoxifen course (2-16 mg once daily for up to 21 days).”) Further, Petitioner fails to point to any statement made by Patent Owner narrowing the scope of the claims, but rather relies only on the statements of the examiner. *See* Paper 1 at 30 (“The Examiner ... explain[ed] that the final amendment ‘positively excludes a rescue medication’”).

Given the lack of expert testimony and failure to show that Patent Owner made statements of disclaimer, Petitioner’s proposed claim construction should be rejected. If needed, Patent Owner proposes that the claim be construed as in accordance with how it was construed during the prosecution of the 997 patent, i.e., that the method involves the complete removal of a rescue medication.

Regardless, a precise construction of the term “the method does not include a rescue medication” is not necessary to deny institution here. *See, e.g., Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (only terms that are necessary to resolve the dispute need be construed). Even with

the Petitioner's rewritten construction of "method does not include a rescue medication," Petitioner fails to meet its burden to warrant institution.

III. CLAIMS 1-10 ARE SUPPORTED BY A WRITTEN DESCRIPTION

While spending much of its brief arguing that the 997 patent lacks sufficient disclosure, the real complaint by Petitioner appears to be that the specification lacks actual reduction to practice. Instead of focusing on the specification as a whole, the Petitioner repeatedly complains the clinical study identified in the specification is insufficient to provide written description support for a wide variety of limitations. However, the Petitioner provides no law supporting its proposition and fails to properly credit the specification. Further, when read as a whole from the perspective of a POSITA, the specification clearly conveys that the inventors of the 997 patent possessed methods of maintaining a therapeutically effective concentration of endoxifen by administering endoxifen within a 2-16 mg dosage range for 21 days without the need for rescue medication or dose monitoring. As such, the Board should reject the Petitioner's written description challenges.

A. Legal Standard

The written description requirement of 35 U.S.C. §112 provides that the specification shall contain a written description of the invention. 35 U.S.C. §112(a). "The essence of the written description requirement is that a patent applicant ... must describe his or her invention so that the public will know what it is and that he or

she has truly made the claimed invention.” *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298 (Fed. Cir. 2014). “Written description is a question of fact, judged from the perspective of one of ordinary skill in the art as of the relevant filing date.” *Falkner v. Inglis*, 448 F.3d 1357, 1363 (Fed. Cir. 2006). However, the “written description requirement does not demand either examples or an actual reduction to practice, a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010). Indeed, the “level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Id.* at 1351.

B. The 997 Patent Provides Adequate Support for the Limitation Requiring That the “The Method Does Not Include Rescue Medication”

Petitioner argues that independent claims 1-10 lack written description because “[t]here is simply no disclosure in the specification supporting the interpretation of the ‘does not include a rescue medication’ language that PO argued for and obtained during prosecution.” Paper 1 at 39.

Claim 1 of the 997 patent requires that the “method does not include rescue medication for the treatment of bipolar disorder.” EX1001, Claim 1. Claim 6

provides the same limitation. *See id.* at Claim 6. As explained above, the 997 patent provides the following definition of rescue medication:

The term "rescue medication" refers to an additional medication necessary to treat breakthrough or recurring symptoms. For present disclosure, the rescue medications are selected from the group of lithium, valproate, lamotrigine, benzodiazepines, anticholinergics and like thereof.

EX1001, 3:42-46.

As an initial matter, to the extent that Petitioner relies on its proposed claim construction of “[t]he method does not include rescue medication,” Petitioner’s challenge under §112 should be rejected as it relies on a claim construction and prosecution history disclaimer arguments that are not supported by expert testimony. *See supra* § II.D. Further and contrary to Petitioner’s argument, Petitioner admits that the specification describes a clinical study where “no rescue medications were administered to any of the patients.” EX1001 at 4:57-59. But Petitioner complains that this express patent disclosure does not meet the written description requirement because a “POSITA reading the specification would not have understood the description of this *trial* to be conveying that it positively excluded (prospectively prohibited) all rescue medication as the claims require,” in accordance with its unsupported claim construction. *See* Paper 1 at 41. However, even if Petitioner’s construction of “method does not include rescue medication” is correct, Petitioner

has failed to point to any legal support for its proposition that written description support is found only if the specification discloses a clinical study where the negative limitation is “prospectively forbidden” “during treatment.” Paper 1 at 40-41. Conversely, the clinical study outlined in the specification notes that “at the [end of treatment], *none* of the patient[s] required rescue medications, [and] *no* rescue medications were administered to any of the patients” EX1001, 4:57-59. Based at least on this disclosure, a POSITA would have understood that Patent Owner was in possession of a method for maintaining a therapeutically effective concentration of endoxifen citrate wherein the method does not include rescue medication.

Further, Petitioner appears to argue that there is no written description support because the specification does not explicitly disclaim a method where a rescue is included. *See* Paper 1 at 40 (arguing that statement in the specification “is not a statement that rescue medication were positively (prospectively) prohibited.”); *see also id.* at 39 (asserting that “passage . . . does not convey to POSITA that PO possessed the claimed method in which rescue medication is completely positively excluded.”) (*citing* EX1001 at 3 (3:42-46)). The specification is not required to expressly state that rescue medication is “prospectively prohibited;” rather it must only reasonably convey that the inventors possessed a method in which rescue medication is not included. “Negative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation.”

Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1351 (Fed. Cir. 2012). However, “[s]uch written description support need not rise to the level of disclaimer,” as Petitioner argues. *Id.* Accordingly, Petitioner’s sole argument that the absence of “a statement that rescue medication were positively (prospectively) prohibited” leaves this limitation without written description support cannot carry the day.

And contrary to Petitioner’s contention, as to this limitation, “[t]he written description requirement is satisfied . . . [because] the specification conveys with reasonable clarity to those skilled in the art that the inventor was in possession of the claimed invention.” *Pharmacyclics LLC v. Alvogen, Inc.*, 2022 WL 16943006, at *7 (Fed. Cir. Nov. 15, 2022).

Given the above, the Petitioner has failed to meet its burden of establishing that it is more likely than not that Claims 1-10 are unpatentable under 35 U.S.C. §112 for lack of written description.

C. The 997 Patent Provides Adequate Support for Dosage Range of 2 mg to 16 mg

The specification repeatedly discloses various methods of maintaining a therapeutically effective concentration of endoxifen by administering a dose of 2 to 16 mg of endoxifen citrate. *See, e.g.*, EX1001, 1:8-11; 2:60-65; 3:7-10; 4:44-48. Despite the repeated disclosures regarding the dosage range, Petitioner nevertheless asserts that the specification does not demonstrate possession of the claimed dosage

range. And while Petitioner concedes “that the inventor need not disclose a particular type of information, such as experimental data” to establish that the inventor was in possession of the claimed invention, Petitioner complains that a “POSITA would not have understood the named inventors to have been in possession of the claimed invention based on the specification and would instead have needed to conduct their own scientific research to confirm that the full range of claimed doses[.]” Paper 1 at 45. In essence, Petitioner argues that “the absence of . . . testing data” for the entire range means that the range lacks written description support. This argument is legally flawed.

As explained above, “[w]ritten description requires that the specification reasonably convey to those skilled in the art that the inventor had possession of the claimed invention as of the filing date.” *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1371 (Fed. Cir. 2023). Assuming arguendo that actual reduction to practice requires test data for the entire range, the law does not require “an actual reduction to practice” to comply with the written description requirements. *Univ. Of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 926 (Fed. Cir. 2004) (“We of course do not mean to suggest that the written description requirement can be satisfied only by providing a description of an actual reduction to practice.”). “Constructive reduction to practice is an established method of disclosure.” *Id.* “[A] constructive reduction to practice that in a definite way

identifies the claimed invention can satisfy the written description requirement.” *Ariad Pharm.*, 598 F.3d at 1352. Petitioner does not dispute that the specification “identifies the claimed invention,” and more specifically, “2 mg to 16 mg.” For example, in *Endo Pharms.*, the Federal Circuit found that the specification contained adequate written description although the patent owner did not test every dosage amount before claiming such in the patent. *Endo Pharms. Inc. v. Teva Pharms. USA, Inc.*, 731 Fed. App’x 962, 973 (Fed. Cir. 2018). Accordingly, at minimum the specification “in a definite way identifies the claimed invention.”

Further, the absence of actual “scientific research to confirm that the full range of claimed doses would be suitable to maintain a therapeutically effective concentration of endoxifen for treatment of patients with bipolar I disorders,” (Paper 1 at 45), does not mean that the limitation lacks written description support, as Petitioner argues. “The decision [concerning therapeutic effectiveness] would be informed by FDA guidance, not the written description in the specification.” *United Therapeutics*, 74 F.4th at 1370.

Finally, “the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Regents of the Univ. of California v. Broad Inst., Inc.*, 136 F.4th 1367, 1383 (Fed. Cir. 2025) (citations omitted). “When the technology at issue is ‘complex’ and ‘highly unpredictable’ ...

the level of detail required to satisfy the written description requirement may be greater.” *Id.* (citations omitted). To determine the level of disclosure necessary, several factors are considered, including the “predictability of the aspect at issue.” *Ariad Pharms.*, 598 F.3d at 1351 (citing *Capon v. Eshhar*, 418 F.3d 1349, 1357-58 (Fed. Cir. 2005)). Neither Petitioner nor its expert contend that repeating clinical trials with a different dosage strength is complex and/or highly unpredictable task.

Federal Circuit precedent is clear that testing at each dosing level is not required for written description support, if the specification clearly explains the effective dosage range of the present invention. *See Endo Pharms.*, 731 Fed. App’x at 972-73 (“Nothing in our controlling precedent requires patent owners to test release rates for each dosage level before claiming such rates in the patents.”). Here, the 997 patent expressly points to a dosage range of 2-16 mg of endoxifen citrate throughout the specification.

Given the above, the Petitioner has failed to meet its burden of establishing that it is more likely than not that Claims 1-10 are unpatentable under 35 U.S.C. §112 for lack of written description.

D. The 997 Patent Provides Adequate Support for A Method of Maintaining A Therapeutically Effective Concentration for “Up to 21 days”

Petitioner asserts that claims 1 and 6 of the 997 patent are invalid for lack of written description to the extent that they claim a method of maintaining a

therapeutically effective concentration of endoxifen “for up to 21 days.” Paper 1 at 48. Petitioner’s complaint is the claim recites “up to 21 days,” rather than “for at least 21 days,” as recited in the specification. As an initial matter, “the description requirement does not demand any particular form of disclosure, or that the specification recite the claimed invention in *haec verba*,” as Petitioner suggests. *See Ariad Pharm.*, 598 F.3d at 1352 (citation omitted).

Separately, “claim construction is inherent in any written description analysis.” *In re Katz Interactive Call Processing Patent Litig.*, 639 F.3d 1303, 1319 (Fed. Cir. 2011). Yet Petitioner myopically focuses its attention on the phrase “up to 21 days” without considering the effect of the claim as a whole and, specifically, the “wherein” clause that recites the negative limitation “wherein the method does not include a rescue medication.” The specification explains that in the clinical study, endoxifen was administered for “at least 21 days” and “at EOT . . . no rescue medications were administered to any of the patients.” EX1001 at 4:57-58. Therefore, the clinical study data necessarily discloses a method of maintaining a therapeutically effective concentration of endoxifen for up to 21 days. The claimed method recites “administering to the patient . . . endoxifen citrate . . . for up to 21 days, wherein the method does not include a rescue medication.” EX1001 at 4:65-5:1.

The entire claim limitation in view of the specification exposes the weakness in Petitioner’s argument, as the specification clearly conveys treating a patient for up to 21 days without the use of a rescue medication. By disclosing treating a patient for at least 21 days without providing rescue medication, the specification reasonably conveys to a POSITA treating the patient for up to 21 days without providing rescue medication. A POSITA would understand that a disclosed 21-days treatment period necessarily discloses a treatment duration of up to 21 days.

Given the above, the Petitioner has failed to meet its burden of establishing that it is more likely than not that Claims 1-10 are unpatentable under 35 U.S.C. §112 for lack of written description.

E. The 997 Patent Provides Adequate Support for the Limitation Requiring “Monitoring the Dose Administered to the Patient No Sooner than 21 Days After Commencement”

Petitioner asserts that Claim 6 of the 997 patent is invalid for lack of written description due to its limitation requiring “monitoring the dose administered to the patient no sooner than 21 days after commencement.”

The limitation is properly understood as a negative limitation. “Negative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation.” *Santarus*, 694 F.3d at 1351. However, “[s]uch written description support need not rise to the level of disclaimer,” as Petitioner argues. *Id.* “Rather, as with positive limitations, the disclosure must only reasonably

convey to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Novartis Pharm. Corp. v. Accord Healthcare, Inc.*, 38 F.4th 1013, 1020 (Fed. Cir. 2022) (cleaned up).

Here, the patent specification recognizes that one of the disadvantages of prior art methods of treating bipolar disorders included “a continuous need to observe the therapeutic dose monitoring in patients during the treatment.” EX1001 at 1:33-35. The inventors recognized that “[t]argeting the PKC signaling pathway for bipolar disorder can improve the patient compliance, when therapeutic dose monitoring is not required in patient.” *Id.* at 1:60-63 (emphasis added). This disclosure provides an affirmative reason to exclude continuous therapeutic monitoring prior to 21 days. Further, clinical study data disclosed in the specification was carried out for 21 day and “[a]t the EOT, none of the patient required rescue medications, no rescue medications were administered to any of the patients,” and none of the patients discontinued from the study. *Id.* at 2:57-59. Petitioner does not analyze these portions of the specification in view of the law relating to written description in the context of negative limitations.

Given the above, the Petitioner has failed to meet its burden of establishing that it is more likely than not that Claims 6-10 are unpatentable under 35 U.S.C. §112 for lack of written description.

F. The 997 Patent Provides Adequate Support for Dependent Claims

As a last ditch effort, Petitioner claims that the dependent claims of the 997 patent are not supported by the written description because “[t]he single example in the specification does not mention any of these additional symptoms” Paper 1 at 58. By focusing on only the clinical study data, Petitioner ignores the broader disclosures of the specification describing treatment of bipolar disorder symptoms.

The patent specification explicitly provides:

the present application provides a method for maintaining a therapeutically effective concentration of endoxifen for treatment of bipolar I disorder in a patient, wherein the patient *has manic episodes with or without mixed features*. In another embodiment the present application provides a method for maintaining a therapeutically effective concentration of endoxifen for treatment of bipolar I disorder in a patient, wherein the patient *has depression or associated with depressive episodes*.

EX1001 at 3:66-4:8 (emphasis added). A POSITA would know that “[t]he bipolar I disorder criteria represent the modern understanding of the classic *manic-depressive disorder*[.]” EX1009 at 7 (emphasis added). These clinical features are inherent components of bipolar I diagnostic criteria. The specification provides that “[t]he clinical study was a multicenter, randomized, double-blind, double-dummy, active controlled, parallel study to assess the efficacy and safety of endoxifen enteric coated

tablet 8 mg and divalproex sodium extended release tablet 1000 mg in patients of bipolar I disorders.” EX1001 at 4:50-54.

Further, it was well understood in the field that mania and depression are common symptoms of individuals with bipolar I disorder², and thus a POSITA would not require the extensive disclosure sought by the Petitioner to understand that the inventors of the 997 patent were in possession of the claimed invention.

Given the above, the Petitioner has failed to meet its burden of establishing that it is more likely than not that Claims 2-5 and 7-10 are unpatentable under 35 U.S.C. §112 for lack of written description.

IV. CLAIMS 1-10 ARE ENABLED

A. Legal Standard

The Patent Act requires that the “specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains ... to make and use the same” 35 U.S.C. §112(a). A patent’s

² *See, e.g.*, EX1004 at S295 (noting that “[b]aseline symptoms of mania or depression can be recorded using appropriate scales to be more objective (Young Mania Rating Scale/Children’s Depression Rating Scale and global impression of the clinician.”); *see id.* at S298; EX1005 at S53-S54.

specification must “enable the full scope of the invention as defined by its claims.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610-12 (2023). However, the patent laws allow for “a reasonable amount of experimentation.” *Id.* at 612. “What is reasonable in any case will depend on the nature of the invention and the underlying art.” *Id.* at 612.

It is not required that a specification describe with particularity how to make and use every single embodiment within a claimed class. *Id.* at 610. “Nor is a specification necessarily inadequate just because it leaves the skilled artist to engage in some measure of adaptation or testing.” *Id.* at 611; *Mowry v. Whitney*, 81 U.S. 620, 644 (1872) (“[T]he definiteness of a specification must vary with the nature of its subject. Addressed as it is to those skilled in the art, it may leave something to their skill in applying the invention.”) Rather, “[e]ven ‘a considerable amount of experimentation is permissible,’ if it is ‘merely routine’ or the specification ‘provides a reasonable amount of guidance’ regarding the direction of experimentation.” *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1386 (Fed. Cir. 2013) (citing *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360–61 (Fed.Cir.1998)); *see also, Cephalon Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1338 (Fed. Cir. 2013) (“extensive experimentation does not necessarily render the experiments unduly extensive where the experiments involve repetition of known or commonly used techniques.”).

B. The Specification Fully Enables a POSITA to Make and Use Claims 1-10 of the 997 Patent

Petitioner argues that the claims 1-10 of the 997 patent are non-enabled because “there is simply nothing in the specification telling POSITA how to determine, without undue experimentation, whether a therapeutically effective concentration of Endoxifen has been reached ...” Paper 1 at 63.

Although citing the definition, the Petitioner chooses to ignore that the definition itself teaches a POSITA how to determine whether a therapeutically effective concentration has been met. Namely, the 997 patent describes that the therapeutically effective concentration has been reached when the “concentration of Endoxifen in plasma [] is sufficient to decrease or prevent or cure the symptoms associated with a medical condition or infirmity or to the normal body functions in disease or disorders that result in impairment of specific body functions.” EX1001 at 3:36-41. Therefore, the specification of the 997 patent fully enables a POSITA to make and use methods of maintaining a therapeutically effective concentration of endoxifen.

The Petitioner’s main complaint appears to be that the specification does not provide an example or test data for *every single* dosage amount of endoxifen claimed by claim 1 of the 997 patent. Paper 1 at 63. However, Petitioner has cited no law requiring such a disclosure. In fact, the Federal Circuit has declined to find claims

not enabled when the claims are broader than a specific example. *See Pharmacyclics*, 2022 WL 16943006, at *8 (rejecting non-enablement argument that “Example 13 discloses a dose of exactly 560 mg per day, rather than the full claimed scope”). It is clear from the specification that a POSITA would be able to use the disclosure of the 997 patent, including the clinical study data, to practice the method described in Claims 1-10.

Petitioner also claims that a “POSITA would have needed to test administration of various doses and resulting concentrations and evaluate patients’ need for rescue medications across those doses to arrive at the full scope of the claimed invention.” Paper 1 at 67. However, Petitioner’s argument that the claims are not enabled is again inconsistent with the Federal Circuit precedent. Even if it were true that a POSITA would need to test administration of various doses and resulting concentrations, that does not, by itself, mean that the claims are not fully enabled.

For example, the Federal Circuit has made clear that the question of undue experimentation is a “matter of degree.” *Cephalon Inc.*, 707 F.3d at 1338. Namely, the Federal Circuit has clarified that what is required is that the experimentation “not be unduly extensive.” *Id.* “[T]he fact that a clinician’s involvement may be necessary to determine effective amounts of the single compound . . . does not itself constitute undue experimentation.” *Id.* In fact, “[e]ven ‘a considerable amount of

experimentation is permissible,’ if it is ‘merely routine’ or the specification ‘provides a reasonable amount of guidance’ regarding the direction of experimentation.” *Wyeth & Cordis Corp.*, 720 F.3d at 1386 (citing *Johns Hopkins Univ.*, 152 F.3d at 1360–61); *see also*, *Cephalon Inc.*, 707 F.3d at 1338 (“extensive experimentation does not necessarily render the experiments unduly extensive where the experiments involve repetition of known or commonly used techniques.”).

Neither Petitioner nor its expert claims that the experimentation required to practice the full scope of the claim requires something more than “merely routine,” “known or commonly used techniques.” That being the case, Petitioner cannot carry its burden of showing that the full scope of the claims is not enabled. Under the *Wands* factors, the claimed methods involve predictable dose optimization, routine pharmacokinetic measurement, and established clinical assessment tools, and neither Petitioner nor its expert establish otherwise. These considerations weigh strongly against any finding of undue experimentation.

Given the above, the Petitioner has failed to meet its burden of establishing that it is more likely than not that Claims 1-10 are unpatentable under 35 U.S.C. §112 for lack of enablement.

V. CLAIMS 6-10 ARE NOT INDEFINITE

A. Legal Standard

A claim is rendered indefinite only when the patent claim, specification and prosecution history fail to inform a POSITA, with reasonable certainty, of the scope for the invention. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). The Supreme Court made clear that “definition is to be evaluated from the perspective of someone skilled in the relevant art” reading the claims “in light of the patent’s specification *and prosecution history*.” *Id.* at 908 (emphasis added); *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015) (“[W]e look to the patent record—the claims, specification, and prosecution history—to ascertain if they convey to one of skill in the art with reasonable certainty the scope of the invention claimed.”). Because ascertaining whether a claim is not indefinite, implicates claim construction principles, the Federal Circuit has held that “[w]hether a claim complies with the definiteness requirement of 35 U.S.C. § 112 ¶ 2 is a matter of claim construction[.]” *Noah Sys., Inc. v. Intuit Inc.*, 675 F.3d 1302, 1311 (Fed. Cir. 2012).

B. Petitioner Has Failed to Show that Claim 6 of the 997 Patent is Indefinite In view of the Claims, Specification, and Prosecution History

Petitioner argues that claim 6 of the 997 patents is not definite because “the [997] patent never explains what ‘monitoring the dose administered to the patent’

means, and it also not clear from the plain language of the claim. However, Petitioner fails to appreciate that the definiteness of a claim is not measured solely from the view of the claim language itself, but also in view of the specification and the prosecution history. Further, Petitioner fails to appreciate that the question of definiteness is viewed as from a POSITA.

As an initial matter, the scope of “monitoring the dose administered to the patient” is clear from the claim itself. Specifically, claim 6 recites a method that requires “maintaining a therapeutically effective concentration of endoxifen” by administering the claimed dose and “monitoring the dose administered . . . no sooner than 21 days.” Petitioner argues that the preamble is limiting. Taking that as true, the meaning of “therapeutically effective concentration” informs the meaning of “monitoring the dose administered . . . no sooner than 21 days.” *See Brookhill-Wilk I, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1299 (Fed. Cir. 2003) (“While certain terms may be at the center of the claim construction debate, the context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those terms.”); *see also Pause Tech., LLC v. TiVo, Inc.*, 419 F.3d 1326, 1331 (Fed. Cir. 2005) (“Proper claim construction demands interpretation of the entire claim in context, not a single element in isolation.”) (cleaned up). The specification defines “therapeutically effective concentration” as “a concentration of endoxifen in plasma which is sufficient to

decrease or prevent or cure the symptoms associated with a medical condition or infirmity or to normalize body functions in disease or disorders that result in impairment of specific bodily functions.” Ex. 1001 at 3 (3:36-41). In view of this definition, the conduct that falls inside the scope of “monitoring the dose administered . . . no sooner than 21 days” is readily ascertainable, i.e., monitoring is measuring the concentration of endoxifen in plasma in view of the symptoms of bipolar disorder.

The scope of this limitation is further confirmed by the prosecution history. For example, during prosecution Patent Owner distinguished Ahmad 2016 (EX1004), making clear “the monitoring of the patients necessary in Ahmad 2016” – for example continuously monitoring patients to investigate whether the rescue medication was needed – “is not necessary in the method of claim 1.” EX1002 at 243. Ahmad 2016 teaches “[e]fficacy and safety assessments were done based on *evaluation parameters on Days 4, 7, 14, and 21* (end of treatment).” EX1004 at 3 (describing testing of blood plasma and YMRS symptom scales). A POSITA would thus understand the negative limitation on monitoring to clearly exclude all such monitoring. *See, e.g., Grace Instrument Indus., LLC v. Chandler Instruments Co., LLC*, 57 F.4th 1001, 1009 (Fed. Cir. 2023) (finding claims sufficiently definite where “prosecution history supports this understanding”); *Ironburg Inventions Ltd. v. Valve Corp.*, 64 F.4th 1274, 1287 (Fed. Cir. 2023) (finding claims definite and

noting prosecution history “provides some additional data to a person of ordinary skill, at minimum confirming that an ‘elongate member’ in the context of the ‘525 patent cannot be circular”).

Further, Petitioner provides only conclusory arguments as to why a POSITA would not understand the term by itself. As has been explained above, monitoring and optimization for bipolar I disorders was well known and understood within the field. *See, e.g.*, EX2004 at 2, 4-5; EX2005 at 1-5.

Given the Petitioner’s incomplete analysis of the claims, specification, and prosecution history in view of a POSITA, the Petitioner has failed to meet its burden of establishing that it is more likely than not that Claims 6-10 are unpatentable under 35 U.S.C. §112 for indefiniteness.

VI. CLAIMS 1-10 ARE NOT ANTICIPATED BY AHMAD 2016

A. Legal Standard.

“A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention” *Galderma Labs., L.P. v. Teva Pharmaceuticals USA, Inc.*, 799 Fed. App’x 838, 842-43 (Fed. Cir. 2020). Anticipation cannot be found unless a single prior art reference discloses “every element of the claimed invention arranged as in the claim.” *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1069 (Fed. Cir. 2017). Further, anticipation requires that the anticipatory reference also “enables one with ordinary skill in the art to

practice the invention.” *Galderma Labs.*, 799 Fed. App’x at 842-43 (quoting *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009)).

B. Independent Claim 1

Despite the Examiner’s repeated consideration of Ahmad 2016 during prosecution, Petitioner again asserts that Claims 1-4 of the 997 patent are anticipated by Ahmad 2016 (EX1004). The Petitioner’s anticipation argument rests on a misguided claim construction position regarding the limitation “the method does not include a rescue medication for treatment of the bipolar I disorder.”

Namely, Petitioner avers that “to the extent [Patent Owner] now contends this limitation does not require this positive exclusion it relied on to obtain allowance, the claims 1-4 are anticipated by Ahmad 2016.” Paper 1 at 76. As explained above, there is nothing in the intrinsic record that requires the method to “*prospectively prohibit*” the use of rescue medication, to the extent that the Petitioner’s construction can be understood. In any event, a precise construction of the term “the method does not include a rescue medication” is not necessary to deny institution here.

First, under Petitioner’s “prospectively prohibit” construction, there is no suggestion or teaching that the study of Ahmad 2016 prospectively prohibited the use of rescue medication. As explained during prosecution, Ahmad explicitly allowed “concomitant medications” (i.e., the concomitant administration of benzodiazepines as adjunctive medication), noting that during the study “[a]ll

psychotropic medications except benzodiazepines (lorazepam/diazepam only) were discontinued at least 2 days before randomization.” EX1004 at 254. Instead of teaching that rescue medication was ‘prospectively prohibited,” Ahmad 2016 explicitly teaches that benzodiazepines (i.e., rescue medication) were *not* ‘prospectively prohibited.’ Further, Ahmad 2016 continues:

Benzodiazepines (lorazepam/diazepam only) (up to 5 mg/day, preferably in divided doses) were allowed as adjunctive medication *as needed at the discretion* of the investigator from 2 days prior to randomization but not beyond the first 10 days of investigational medicinal product dosing. Benzodiazepines were avoided within 12 h of scheduled mania ratings. The usage of two benzodiazepines was *permitted to reduce undue excitement by using these adjuvants* in an appropriate manner while avoiding efficacy or safety overlap with the endoxifen or divalproex.

EX1004 at 254 (emphasis added). The use of benzodiazepines during Ahmad 2016 study falls squarely within the very definition of rescue medication provided in the 997 patent (which is used to treat breakthrough or recurring symptoms as needed). As such, Ahmad 2016 fails to teach or suggest at least this limitation under Petitioner’s proposed definition and, therefore, does not anticipate Claim 1 of the 997 patent.

Second, under Patent Owner’s proposed construction (i.e., the method involves the complete removal of a rescue medication), Ahmad is still devoid of any

teaching or suggesting that rescue medication was removed from the study. As explained previously, Ahmad 2016 allowed “[a]ll psychotropic medications except benzodiazepines ...” EX1004 at 254. The 997 patent lists benzodiazepines as an exemplary rescue medication. EX1001 at 1:42-46 (The term “rescue medication” refers to an *additional medication necessary to treat breakthrough or recurring symptoms*. For present disclosure, the rescue medications [included] ... benzodiazepines....). Again, the design of Ahmad 2016 specifically allowed benzodiazepines as adjunctive medication *when necessary*, meaning the study did not involve the complete removal of rescue medication. EX1004 at 254; *see also, id.* (acknowledging “[s]everal reports have been published about evaluation of mood-stabilizing drugs where concomitant intake of benzodiazepines was permitted during the study.”) And even further, there is no indication in Ahmad 2016 whether any patients were or were not administered adjunctive medication during the study. As such, Ahmad 2016 fails to anticipate Claim 1 of the 997 patent.

Given such, the Petitioner has failed to meet its burden of showing that it is more likely than not that claim 1 is anticipated under 35 U.S.C. §102.

C. Dependent Claims 2-4.

Petitioner also argues that claims 2-4 are anticipated by Ahmad 2016. Paper 1 at 82-86. To anticipate, the Petitioner has the burden of showing that each and every limitation is disclosed in the prior art. *In re Crish*, 393 F.3d at 1256. Claim 2-

4 depend from claim 1 and are therefore not anticipated for at least the reasons set forth above with respect to claim 1.

Given such, the Petitioner has failed to meet its burden of establishing that it is more likely than not that claims 2-4 are anticipated under 35 U.S.C. §102.

VII. CONCLUSION

For the reasons stated above, Petitioner has failed to establish that it is more likely than not that at least of the challenged claims are unpatentable. The Petition should be denied under 37 C.F.R. §42.208(c).

Respectfully submitted,

McAndrews, Held & Malloy, Ltd.

Dated: March 26, 2026

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PGR2026-00015
U.S. Patent No. 12,245,997

CERTIFICATE OF WORD COUNT

I certify under 37 CFR § 42.24(d) that this **PATENT OWNER'S PRELIMINARY RESPONSE** contains 8,794 words, as determined by Microsoft Word.

Dated: March 26, 2026

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CERTIFICATE OF SERVICE

I certify that Patent Owner's Preliminary Response was served on March 26,
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