

Filed on behalf of: Agios Pharmaceuticals, Inc.

Entered: July 27, 2026

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

AGIOS PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2026-00351
Patent 11,878,049

PATENT OWNER'S BRIEF ON DISCRETIONARY DENIAL

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EXHIBIT LIST

Exhibit	Description
2001	File History of U.S. Patent 11,878,049 (“’049 patent FH”)
2002	U.S. Patent Application Publication No. US 2020/0277279 A1
2003	Comparison of Apotex’s Petition to Apotex’s Expert Declaration (Ex. 1003)
2004	Email from Omar Jabri, Head, IP Strategy, Apotex, Inc., to Jim Burns, Chief Legal Officer, Agios (Apr. 8, 2026, 9:30 a.m.)
2005	FDA, <i>Orange Book: Approved Drug Products With Therapeutic Equivalence Evaluations – Product 001: Mitapivat Sulfate (PYRUKYND) Tablet EQ 5mg Base</i> , https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=216196&Appl_type=N (last visited July 22, 2026)
2006	FDA, <i>Orange Book: Approved Drug Products With Therapeutic Equivalence Evaluations – Product 004: Mitapivat Sulfate (AQVESME) Tablet EQ 100mg Base</i> , https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=004&Appl_No=216196&Appl_type=N (last visited July 22, 2026)
2007	Complaint, <i>Agios Pharms., Inc. v. Annora Pharma Private Ltd.</i> , No. 1:26-cv-00603 (D. Del. May 26, 2026), Dkt. No. 1
2008	Declaration of Theodore James Washburn, Jr.
2009	APOTEX, https://www.apotex.com/global (last visited July 22, 2026)
2010	Default Protective Order

I. INTRODUCTION

Patent Owner Agios Pharmaceuticals, Inc. (“Agios”) is a small U.S. company that spent over a decade developing mitapivat—now the first and only approved pyruvate kinase activator—and securing FDA approval of PYRUKYND[®] for pyruvate kinase deficiency (“PKD”) and AQVESME[™] for anemia in adults with alpha- or beta-thalassemia. But, for patients taking mitapivat, drug-drug interactions with concomitant medications that are moderate inducers of cytochrome P450 3A4/5 enzymes (“CYP3A4/5”), which accelerate the breakdown of mitapivat in the body, can force patients to discontinue or avoid therapy altogether. The ’049 patent teaches Agios’s solution to that clinical problem: dosing regimens that allow physicians to prescribe mitapivat at safe and effective doses even when patients must also take a moderate CYP3A4/5 inducer. In stark contrast to Agios’s years of innovative research and investment, Petitioner Apotex Inc. (“Apotex”) is a large, foreign company specializing in generic drugs, with no investment in the pioneering science behind mitapivat. Through this Petition, Apotex seeks to strip away the hard-won patent rights that incentivized Agios’s investment.

Apotex’s Petition should be discretionarily denied. First, Apotex’s Petition second-guesses the Examiner’s allowance over substantially the same prior art and arguments already disclosed to and considered by the Examiner during prosecution. Four of Apotex’s five references—Sizemore, Agresta, Grace Presentation, and

Grace Abstract—were before the Examiner during prosecution, and Agios overcame the Examiner's rejections over Sizemore and Agresta. The fifth reference, Dana-Farber, is cumulative of the art the Examiner squarely considered: it discloses the same Phase 2 clinical trial already described in Agresta and Grace Presentation (identified by the same NCT number, NCT02476916), and the same exclusion of strong CYP inducers already described in Sizemore. In allowing the claims, the Examiner correctly explained, "there are no teaching[s] or suggestions within the prior art to combine a moderate inducer of ... CYP3A4/5 ... with the claimed doses of mitapivat." Ex. 2001 ('049 patent FH), 1607. That finding is a considered judgment, rendered after a full review of the references Apotex now recycles. The Board should not waste its resources reassessing substantially the same art and arguments the Office already considered and properly rejected.

Second, discretionary denial is also warranted because the Petition's merits are particularly weak, as Agios's forthcoming Preliminary Response ("POPR") will demonstrate. Rather than identifying express disclosure of the claim limitations in the prior art, Apotex impermissibly relies on expert testimony to fill critical gaps. Most notably, the prior art does not disclose co-administration of mitapivat with a moderate CYP3A4/5 inducer, as the Examiner properly recognized in allowing the claims. Apotex attempts to fill this gap through expert testimony, but the PTAB's rules prohibit that approach. Apotex did not, and cannot, "specify where each

element of the claim is found in the prior art patents or printed publications relied upon.” 37 C.F.R. § 42.104(b)(4); Mem. from the Acting Under Sec’y of Com. for Intell. Prop. & Dir. of the USPTO to Members of the P.T.A.B. at 1 (P.T.A.B. July 31, 2025) (“7/31/2025 Acting Dir. Mem.”). Petitioner’s challenge does not merit institution.

Third, institution would invite the wasteful, duplicative litigation the AIA was designed to prevent. Apotex conspicuously refused to file a *Sotera* stipulation, preserving its ability to pursue the same art and arguments in district court. And district court litigation is coming—the Petition itself telegraphs Apotex’s intent to drag Agios into district court imminently—and litigation involving the ’049 patent is already underway, albeit with a different generic challenger. Indeed, even after Agios establishes the validity of the ’049 patent before the Board, it will be forced to defend its patent again—against the same or overlapping arguments—risking inconsistent outcomes and wasting the Board’s resources.

Finally, denial is warranted in light of the public interest. Agios employs roughly 500 employees, all but three in the United States. One drug—mitapivat—is central to Agios’s mission of bringing innovative treatments to patients with rare diseases, in which Agios has invested over \$688 million to date. That singular focus allowed Agios to pioneer PYRUKYND[®] and AQVESME[™], both orphan drug treatments for blood disorders afflicting extremely small patient populations. Agios

further invested in costly human clinical trials (reported in the '049 patent) to investigate the effect of co-administration of mitapivat with a CYP3A4/5 inducer in order to maximize access to this life-changing treatment. The patent system exists to incentivize precisely this kind of high-risk investment in therapies for underserved patient populations. Allowing a foreign-based manufacturer to weaponize the Board against a U.S. innovator and strip away its intellectual property will chill future pharmaceutical investment in rare diseases, where the patient populations are too small to justify research and development costs absent robust patent protection.

II. BACKGROUND

Mitapivat is the first and only pyruvate kinase activator ever approved. *See* Ex. 1011, 2. It is a life-altering drug for patients with certain rare types of inherited hemolytic anemia – a devastating condition caused by the premature destruction of red blood cells as a result of particular rare blood disorders. *See id.* 23. Mitapivat drastically improves quality of life for patients with few alternative treatment options (or, in the case of PKD, no alternative medications). *See id.* 44-45.

Patients suffering from hemolytic anemia are often treated with multiple drugs simultaneously. Because mitapivat is broken down in the body primarily by CYP3A4/5, drugs that modulate CYP3A4/5 activity can significantly alter mitapivat exposure, raising serious safety and efficacy concerns that could force patients to discontinue or avoid treatment. *See* Ex. 1001, 2:3-14. CYP3A4/5 modulators are

classified by whether they induce or inhibit the enzyme and by the strength of that effect—strong, moderate, or mild. *Id.* 5:44-60.

The '049 patent addresses this problem for one critical class of modulators: moderate CYP3A4/5 inducers. *Id.* 45:25-30. Drugs that are co-administered with mitapivat can induce CYP3A4/5, leading to increased breakdown of mitapivat in the body. *Id.* 2:3-8. Further complicating matters, it was also known that mitapivat itself induces CYP3A4/5 – i.e., mitapivat induces its own breakdown. Ex. 1005, 42. The invention described by the '049 patent—and the clinical trials underlying it—allow physicians to confidently prescribe mitapivat at safe and effective doses even when patients are taking a moderate CYP3A4/5 inducer.

III. DENIAL IS WARRANTED UNDER 35 U.S.C. § 325(d)

Denial of institution is warranted because Apotex's challenge is based on “substantially the same prior art or arguments” previously presented to the Office. 35 U.S.C. § 325(d); *see also* 37 C.F.R. § 42.4(a). Under § 325(d), the Board follows the *Advanced Bionics* two-part test, first assessing whether the art and arguments are substantially the same as those already presented to the Office and, if so, determining if the Office erred in a manner material to patentability. *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7-9 (P.T.A.B. Feb. 13, 2020) (precedential); *see also Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15,

2017) (precedential as to section III.C.5, first paragraph) (setting forth non-exclusive factors (a)-(f) to consider in § 325(d) analysis).

A. *Advanced Bionics* Step 1 (*Becton* Factors (a), (b), and (d)): Substantially The Same Art And Arguments Were Previously Presented During Examination

The Director should deny institution because all five references in Apotex's Grounds were considered by the Examiner or are cumulative of the art the Examiner considered during prosecution. "Challenging the claims using the same prior art that was previously presented on an IDS is sufficient to satisfy the first part of the *Advanced Bionics* framework." *Ecto World, LLC v. Rai Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 4 (P.T.A.B. May 19, 2025) (precedential as to section A) (citing *Advanced Bionics*, IPR2019-01469, Paper 6 at 7-8).

Four of Apotex's five references—Sizemore, Agresta, Grace Presentation, and Grace Abstract—were previously presented during examination and satisfy *Advanced Bionics* step 1. An IDS submitted during examination provided each reference to the Office. Ex. 2001, 1249-1258.¹ The Examiner also expressly stated

¹ Apotex describes "Sizemore" as WO 2019/104134 A1, which is the international publication of U.S. Patent No. 11,254,652 B2 (the "'652 patent"). The IDS discloses US 2020/0277279 A1, which is the U.S. patent application publication of the '652

that he “considered” each reference. Ex. 2001, 1249-1258.²

The fifth reference Apotex relies on, Dana-Farber, also meets *Advanced Bionics* step 1 because it is cumulative of the art the Examiner evaluated—namely, Sizemore. A reference is cumulative if it does not “differ[] in any material respect from” art that was before the Examiner. *Nespresso USA, Inc. v. K-Fee Sys. GmbH*, IPR2021-01222, Paper 9 at 13-14 (P.T.A.B. Jan. 18, 2022). That is the case here. Apotex relies on Dana-Farber because it “restricted products known to ... *strongly* induce [CYP3A4] metabolism” from co-administration with mitapivat; based on that disclosure, Apotex mistakenly contends that Dana-Farber supports treating patients taking *moderate* CYP3A4 inducers with mitapivat.³ See Ex. 1007, 6 (emphasis

patent. Ex. 2001, 1251. WO 2019/104134 A1 and US 2020/0277279 A1 are substantively identical. Compare Ex. 1004, with Ex. 2002.

² Apotex's file history exhibit notably omits Agios's IDS, as well as the Examiner's statement that he “considered” these references. See Ex. 1002.

³ Apotex asserts that “Dana-Farber teaches that ... patients taking moderate inducers were not excluded.” Pet. 32; see also *id.* 45. This overstates Dana-Farber. There is no mention of moderate inducers anywhere in that reference.

added); Pet. 32, 45. But Apotex also (incorrectly) asserts⁴ that Sizemore has the same disclosure: “[i]n certain embodiments, [the] subject is not taking ... *strong* inducers of CYP3A4.” See Pet. 23 (first alteration in original) (emphasis added); Ex. 1004, [0053]. Given Petitioner’s concession that Dana-Farber’s relied-upon teachings are cumulative of what it contends Sizemore already discloses, Dana-Farber also satisfies *Advanced Bionics* step 1.

B. *Advanced Bionics* Step 2 (*Becton* Factors (c), (e), and (f)): Apotex Has Failed To Identify Any Material Error

Apotex likewise has not met—and cannot meet—its burden under *Advanced Bionics* step 2 to show that the Examiner materially erred in allowing the claims. *Ecto World*, IPR2024-01280, Paper 13 at 6-7.

First, Apotex does not identify a specific alleged mistake in the Examiner’s analysis. Instead, Apotex recycles the same references the Examiner already considered and properly rejected, and attempts to fill in claim-critical gaps with a skilled artisan’s general knowledge. But discretionary denial is appropriate for a petitioner who “merely disagrees with the Examiner’s treatment of the art without showing material error.” See *Ascentcare Dental Prods., Inc. v. Solmetex, LLC*, PGR2025-00058, Paper 10 at 3 (P.T.A.B. Oct. 17, 2025) (citation omitted).

⁴ As explained further below, both references are silent as to moderate CYP3A4/5 inducers.

Second, the Examiner did not materially err. To establish material error, Apotex “must demonstrate that ... the previously presented art teaches the limitations of the challenged claims, and that no reasonable examiner could have found otherwise.” *Ecto World*, IPR2024-01280, Paper 13 at 6 (citation omitted). Apotex cannot make that showing as to any reference.

Sizemore. The Examiner expressly relied on Sizemore in rejecting claims under 35 U.S.C. § 103. Ex. 2001, 1281. Specifically, the Examiner rejected claims directed to co-administering mitapivat tablet compositions and a moderate CYP3A4/5 inducer over a combination of Agresta, Sizemore, and two additional references not re-raised by Apotex. *Id.* 1280-1281. Following two Examiner interviews and a formal response by Agios, the Examiner concluded in the Reasons for Allowance that “there are no teaching or suggestions within the prior art to combine a moderate inducer of cytochrome P450 enzyme 3A4/5 (CYP 3A4/5) with the claimed doses of mitapivat or a pharmaceutically acceptable salt thereof in order to treat hemolytic anemia in a subject in need” *Id.* 1607-1608. The Examiner did not materially err in so finding.

Tellingly, Apotex does not identify *any* disclosure in Sizemore of co-administration of mitapivat with a *moderate* CYP3A4/5 inducer. Nor can it. *None of Apotex's prior art references*—Sizemore included—*are directed to drug-drug interactions, and none disclose co-administration of mitapivat with a moderate*

CYP3A4/5 inducer. Instead, Apotex improperly relies on what skilled artisans allegedly would have inferred. *See* Pet. 23 (“By excluding all inhibitors of CYP3A4 while excluding only strong inducers of CYP3A4, a POSA would have understood Sizemore to contemplate administration of moderate inducers of CYP3A4.” (emphasis omitted)). As the forthcoming POPR will demonstrate, that inference is wrong: nothing in Sizemore would have led a skilled artisan to read in the missing co-administration limitation. An examiner does not err—let alone materially—by declining to import non-existent teachings into a prior art reference. *See, e.g., Samsung Elecs. Co. v. Neodron Ltd.*, IPR2020-00334, Paper 11 at 10-12 (P.T.A.B. July 10, 2020) (granting § 325(d) denial and rejecting petitioner’s material error arguments based on limitations “infer[red]” from the prior art).

Agresta. The Examiner relied on Agresta throughout prosecution, both as an anticipatory reference and as the primary reference in multiple § 103 rejections. Ex. 2001, 1236-1243, 1277-1283. And yet, the Examiner recognized that “Agresta does not specifically teach incorporating a CYP 3A4/5 inducer with the mitapivat regimen.” *Id.* 1242. Apotex does not—and cannot—identify any Agresta disclosure of co-administering mitapivat with a moderate CYP3A4/5 inducer; it again improperly resorts to attributing that teaching to the general knowledge of skilled artisans. The Examiner understood and applied Agresta’s full disclosure before allowing the claims, and did not materially err in declining to find in Agresta a

disclosure that it does not contain.

Dana-Farber. By Apotex's own logic, Dana-Farber adds nothing that Sizemore does not already supply. Apotex relies on Dana-Farber for a single proposition—that mitapivat should not be administered with strong CYP3A4 inducers—but that is the very disclosure Apotex extracts from Sizemore's exclusion of strong inducers. *Supra* Section III.B (Sizemore). Dana-Farber is substantially the same as art the Examiner already considered; it cannot supply the material error Apotex must show.

Grace Presentation and Grace Abstract. Apotex cannot show that the Examiner materially erred by issuing the claims over Grace Presentation and Grace Abstract. Because these references were “listed on an IDS” but “the Examiner did not issue any prior art rejections during examination,” Apotex must show “the Examiner materially erred by overlooking certain teachings in” Grace Presentation and Grace Abstract. *Ecto World*, IPR2024-01280, Paper 13 at 5-6. It cannot, because the Examiner did not overlook those teachings at all—he relied on the same disclosures, found in other art, during prosecution.

Apotex asserts Grace Presentation and Grace Abstract “teach[] positive results from the same Phase 2 study discussed in Agresta and Dana-Farber”—i.e., “that

Phase 2 Study patients were effectively treated for PKD.” Pet. 33, 45.⁵ But the Examiner expressly recognized that “Agresta teaches the method of treating pyruvate kinase deficiency.” *See* Ex. 2001, 1236; *see also id.* 1237-1243, 1278-1283.

Apotex similarly asserts that Grace Presentation and Grace Abstract teach specified mitapivat dosing regimens. Pet. 35, 47. But the Examiner already found that the prior art teaches mitapivat dosing: Agresta discloses “a therapeutic range of 10 mg-3000 mg, administered once or twice a day” and that “700 mg doses of mitapivat yields undesirable Grade 1-2 nausea and vomiting in patients,” as well as “administering mitapivat in a dose of 50-300 mg, once or twice per day.” Ex. 2001, 1242, 1237. The Examiner had before him—and applied—the very teachings Apotex now attributes to the Grace references. Apotex cannot establish materiality: neither Grace Presentation nor Grace Abstract mentions drug-drug interactions or CYP3A4/5 modulators, let alone the claimed moderate CYP3A4/5 inducers.

Background References. Apotex’s background references—which are not

⁵ Apotex also asserts that Grace Presentation and Grace Abstract “do[] not report any difficulty with treating patients receiving both mitapivat and moderate CYP3A4 inducers as permitted by Dana-Farber.” Pet. 33, 45. But Apotex provides no evidence that patients on moderate CYP3A4 inducers were actually included in the Phase 2 Study, let alone that a POSA would have known that.

asserted in any Ground for unpatentability—cannot salvage the Petition. The Board squarely rejected such reasoning in *Sandoz Inc. v. Acerta Pharma B.V.*, where the petitioner alleged material error because “the Examiner failed to consider” certain references that “neither ground of unpatentability asserted by Petitioner relie[d] on.” IPR2023-00478, Paper 17 at 18-19 (P.T.A.B. Aug. 7, 2023). The Board held “that Petitioner’s reliance in the Petition on references that ... are not even asserted against the claims in Petitioner’s asserted grounds for unpatentability as set out in the Petition[] fails to demonstrate ‘that the Office erred in a manner material to the patentability of challenged claims.’” *Id.* (citation omitted). And so too here. The Examiner considered and applied the principal references, confronted the precise moderate-inducer issue, and allowed the application only after determining that the prior art lacked the claimed co-administration teaching.

IV. THE PETITION’S WEAK MERITS WARRANT DENIAL

The Director should decline to institute because Apotex’s unpatentability challenge is particularly weak. Apotex fails to show a reasonable likelihood of prevailing as to any claim.

The defect is fundamental. Apotex builds every Ground on the same prior art the Examiner found lacking during prosecution, then tries to fill the gap in the prior art with *ipse dixit* expert testimony. That is impermissible. As then-Acting Director Stewart explained, a petition must “specify where each element of the claim is found

in the prior art patents or printed publications relied upon.” 7/31/2025 Acting Dir. Mem. at 1 (“expert testimony, common sense, and other evidence that is not ‘prior art consisting of patents or printed publications’ ... may not be used to supply a missing claim limitation”); *see also* 37 C.F.R. § 42.104(b)(4).

Apotex's Petition runs headlong into that prohibition. In *all four Grounds*, Apotex impermissibly relies on expert testimony to supply a claim limitation missing from the prior art: the co-administration of mitapivat and a moderate CYP3A4/5 inducer. *See* Pet. 23 (Ground 1: “[b]y excluding all inhibitors of CYP3A4 while excluding only strong inducers of CYP3A4, a POSA would have understood Sizemore to contemplate administration of moderate inducers of CYP3A4”), 32 (Ground 2: “Dana-Farber teaches that patients taking strong CYP3A4 inducers were excluded from the study A POSA would thus have understood PKD patients taking moderate CYP3A4 inducers ... could be enrolled and treated with mitapivat.”), 45 (same for Ground 3), 53 (Ground 4 relies on Grounds 2-3) (all emphases added, except “moderate”). In each Ground, this limitation appears nowhere in any reference, but only in Apotex's allegations about what “a POSA would have understood.”

The Board recently rejected a similar attempt in *CyberSecure IPS, LLC v. Network Integrity Systems, Inc.*, IPR2025-01441, Paper 18 (P.T.A.B. May 26, 2026). There, “[a]ll of the challenged claims ... require[d] detecting movement.” *Id.* 2.

Although one ground met the institution threshold “because it relie[d] on a reference that expressly disclose[d] detecting movement,” the Director nonetheless discretionarily denied institution because “Petitioner’s remaining grounds” rested on “inherency arguments relying on expert testimony” that “d[id] not explain sufficiently how the prior art inherently discloses the detecting movement limitation.” *Id.* Apotex’s Petition is even more defective: Apotex lacks even a single compliant ground. Every one of its four Grounds depends on expert testimony to supply the missing moderate-inducer limitation. As such, the Petition fails to comply with 37 C.F.R. § 42.104(b)(4) and should be denied.

Apotex’s reliance on expert testimony to bridge gaps in the prior art is even more problematic because that testimony is conclusory and warrants little weight. The Board affords “little or no weight” to expert “testimony [that] repeats, almost verbatim, the language in the Petition without any further explanation or supporting reasoning or evidence.” *Tiktok Inc. v. Ntech Props., Inc.*, IPR2024-01339, Paper 9 at 16 (P.T.A.B. Feb. 25, 2025) (citation omitted). But that is precisely the testimony Apotex’s expert, Dr. Thirman, offers. *See* Ex. 2003 (Apotex Petition/Expert Declaration comparison). There is clear overlap with Apotex’s Petition—in addition to the large swaths of identical or nearly identical language (*id.*), the declaration also includes typographical errors that appear identically in the Petition. *Compare* Pet. 21, *with* Ex. 1003 ¶ 71 (missing quotation marks before “about 20 mg” and

“about 50 mg”), Pet. 32, *with* Ex. 1003 ¶ 100 (“while at the same patients”), Pet. 40, *with* Ex. 1003 ¶ 118 (citing to corresponding nonexistent sections), Pet. 44, *with* Ex. 1003 ¶ 132 (superfluous “these”), Pet. 54, *with* Ex. 1003 ¶ 166 (superfluous comma at “Claims, 9”). Testimony that merely parrots the Petition cannot bridge a gap in the prior art’s disclosure. *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15-16 (P.T.A.B. Aug. 24, 2022) (precedential).

For these reasons—and for the additional merits deficiencies Agios’s forthcoming POPR will detail—the Director should deny institution.

V. DENIAL IS WARRANTED BECAUSE THE PETITION IS NOT A TRUE ALTERNATIVE TO DISTRICT COURT LITIGATION

The Director consistently declines to institute trial when, as here, an AIA challenge is not an alternative to litigation. *Magnolia Med. Techs., Inc. v. Kurin, Inc.*, IPR2026-00097, Paper 17 at 3-4 (P.T.A.B. May 14, 2026) (precedential) (“Congress intended AIA reviews to narrow disputes—not create another forum where litigation can be expanded.”). Here, the Petition will not meaningfully narrow the parties’ dispute. Instead, institution will unnecessarily expand the parties’ dispute—the same prior art and arguments will be re-litigated in forthcoming Hatch-Waxman litigation.

While no parallel litigation between Agios and Apotex *presently* exists, it is all but certain. Apotex—a well-known, major generic manufacturer that routinely engages in Hatch-Waxman litigation—has indicated that it intends to market a

generic mitapivat product. *See* Ex. 2004 (Apotex Head of IP Strategy proposing “a license under the ’049 patent to further [its] goal of bringing affordable generic options to patients”). The Petition underscores Apotex’s intent to challenge the patent in district court by repeatedly previewing validity attacks that *cannot be adjudicated via IPR*. Apotex indicates its intent to challenge the ’049 patent’s inventorship. *See* Pet. 2 (arguing “Agius appears to have chosen at least two of [the claimed] dosages, ... in light of dosing recommendations made by FDA employees” who “were not named as inventors to the ’049 patent”).⁶ Apotex also broadcasts an impending § 112 attack. *See* Pet. 1 (arguing “the specification provides a myriad of proposed mitapivat doses and dosing ranges” but “no rationale for choosing a particular mitapivat dose or how to do so when it is co-administered with a moderate inducer”). It is no secret that Apotex will imminently challenge the ’049 patent’s validity in district court based on grounds that are by statute outside the scope of this *inter partes* review.

To market a generic mitapivat product, Apotex must first seek FDA approval by filing an abbreviated new drug application (“ANDA”). In order to seek approval

⁶ Apotex’s FDA inventorship narrative is inaccurate and irrelevant to this proceeding. Apotex’s argument underscores why this Petition will not resolve the parties’ dispute.

prior to the expiration of the '049 patent, Apotex must include with its ANDA a certification that the '049 patent is invalid, unenforceable, or not infringed. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV). Here, whether Apotex's ANDA references PYRUKYND®, AQVESMETM, or both, Apotex will need to certify as to the '049 patent because it is listed in the Orange Book for both products. *See* Exs. 2005, 2006. Filing such a certification is an act of infringement that will trigger Hatch-Waxman litigation.⁷ *See* 35 U.S.C. § 271(e)(2)(A).

The present IPR will not avoid or meaningfully simplify that litigation; it will merely add a parallel AIA challenge. Indeed, Apotex has made no *Sotera* stipulation (nor any other stipulation) stipulating that it will not raise the same or overlapping arguments in district court as it has before the Board. As such, Apotex is preserving similar arguments and overlapping prior art for district court. If instituted, nothing would stop Apotex from raising “the same arguments as the AIA review” and “pursuing alternative theories under a ‘wait and see’ approach presumably to gain a litigation advantage and/or settlement leverage.” *Magnolia*, IPR2026-00097, Paper 17 at 3-4 (citation omitted). The Petition itself proves that even a Final

⁷ Because Apotex's certification is an act of infringement triggering district court litigation, Apotex has control of when litigation begins and can delay until after the Director's decision on institution.

Written Decision will not resolve the dispute. Apotex devotes pages to inventorship and § 112 grounds that cannot be resolved in IPR. Institution will not simplify the real dispute because Apotex is *already* preserving theories outside IPR. Agios will be forced to repeatedly defend the validity of the '049 patent, exactly the result the AIA sought to prevent.

Moreover, district court litigation involving the '049 patent is already underway with another generic challenger. *See* Ex. 2007. Institution would risk inconsistent outcomes, waste the Board's resources, and require Agios to defend the '049 patent in two forums simultaneously. This contravenes the purpose of AIA reviews. *See Magnolia*, IPR2026-00097, Paper 17 at 2 ("Congress was clear that AIA reviews should not be used 'for ... repeated litigation and administrative attacks' for fear that this type of abuse would 'frustrate the purpose' of these reviews to provide 'quick and cost effective alternatives to litigation.'" (citations omitted)).

VI. DENIAL IS WARRANTED IN LIGHT OF THE PUBLIC INTEREST

The Director should also grant denial because institution would be contrary to the public interest, given Agios's domestic investment and small size. *Magnolia*, IPR2026-00097, Paper 17 at 6-8; Mem. from the Under Sec'y of Com. for Intell. Prop. & Dir. of the USPTO to All P.T.A.B. Users at 2 (Mar. 11, 2026).

Agios is a Massachusetts-based company that employs approximately 500 people, all but three in the United States. Ex. 2008 ¶¶ 3-4. Agios invested at least

six hundred eighty-eight million dollars (\$688,000,000) in the development of mitapivat, [REDACTED] to support the marketing and sale of PYRUKYND[®] and AQVESME[™], and at least approximately [REDACTED] specifically in the inventions claimed in the '049 patent—in particular, the dosing regimens that permit physicians to prescribe mitapivat safely and effectively for rare hemolytic anemias to vulnerable patients when also taking a moderate CYP3A4/5 inducer. *See id.* ¶¶ 5-7. In stark contrast, Apotex is a large, Canadian-based corporation employing more than 6,000 people worldwide. Ex. 2009, 1-2. And yet, Apotex is not seeking to market its own innovative treatment. By all indications, Apotex, a well-known generic manufacturer, will seek to market a generic version of mitapivat, leveraging *Agios's* innovations. *Agios's* investment produced a rare disease therapy that Congress intended to reward with meaningful market protection, as evidenced by FDA's grant of orphan drug exclusivity for both PYRUKYND[®] and AQVESME[™]. *See* 21 U.S.C. § 360cc(a). As a small U.S. innovator, *Agios* reasonably relied on its patent for protecting its investment.

VII. CONCLUSION

For the foregoing reasons, *Agios* respectfully requests that the Director exercise discretion to deny the Petition for *inter partes* review of the '049 patent.

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 27th day of July, 2026, a true and correct copy of the foregoing **Patent Owner's Brief on Discretionary Denial and all Exhibits** were served by electronic mail on Petitioner's lead and backup counsel at the following email addresses:

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