

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
U.S. PATENT NO. 11,878,049
ISSUED: JANUARY 23, 2024

TITLE:
MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450

PETITION FOR *INTER PARTES* REVIEW

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- 1001 U.S. Patent No. 11,878,049 to Iyer et al. (the “’049 patent”).
- 1002 Prosecution History for U.S. Patent No. 11,878,049 (“’049 prosecution history”).
- 1003 Declaration of Michael J. Thirman (“Thirman Decl.”).
- 1004 International Publication No. WO 2019/104134 A1 to Sizemore et al. (“Sizemore”).
- 1005 International Publication No. WO 2016/201227 A1 to Agresta et al. (“Agresta”).
- 1006 E.C. Gordon-Smith, *Pyruvate kinase deficiency*, 27 J. Clin. Path. 128 (1974) (“Gordon-Smith”).
- 1007 Affidavit of Mina Ching, March 21, 2026 & Exhibit A (Dana-Farber Cancer Institute, *A Study of AG-348 in Adult Patients With Pyruvate Kinase Deficiency*, Aug. 23, 2016) (“Dana-Farber”).
- 1008 Affidavit of Mina Ching, March 21, 2026, Exhibit B (Rachael F. Grace et al., *Results Update from the DRIVE PK Study: Effects of AG-348, a Pyruvate Kinase Activator, in Patients with Pyruvate Kinase Deficiency*, (presentation at the 22nd Congress of the European Hematology Association, Madrid, Spain, June 22–25, 2017)) (“Grace Presentation”).
- 1009 Rachael F. Grace et al., *Results Update from the DRIVE PK Study: Effects of AG-348, a Pyruvate Kinase Activator, in Patients with Pyruvate Kinase Deficiency*, 30 Blood 2194 (2017) (“Grace Abstract”).
- 1010 Madhav Mutalik & Dhara Sanghavi, *Review of Drug Interactions: A Comprehensive Update*, 4 Brit. J. Pharm. Rsch. 954 (2014) (“Mutalik”).
- 1011 U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., *Integrated Review: NDA 216916, Pyrukynd (mitapivat)* (2021) (“FDA”).
- 1012 Nathan P. Clark, *Warfarin Interaction With Hepatic Cytochrome P-450 Enzyme-Inducing Anticonvulsants*, 24 Clin. & Applied Thrombosis/Hemostasis 172 (2018) (“Clark”).

- 1013 Pamela S. Hackman, *“Spleen Baby”: A Case Presentation of Pyruvate Kinase Deficiency in an Amish Neonate*, 35 Neonatal Network 375 (2016) (“Hackman”).
- 1014 Neshan B. Ilangaratne et al., *Phenobarbital: missing in action*, 90 Bull World Health Organ 871 (2012) (“Ilangaratne”).
- 1015 Paul L. M. van Giersbergen et al., *In vivo and in vitro studies exploring the pharmacokinetic interaction between bosentan, a dual endothelin receptor antagonist, and glyburide*, 71 Clin. Pharmacol. & Therapeutics 253 (2002) (“van Giersbergen”).
- 1016 C. Bachmeyer et al., *Idiopathic pulmonary arterial hypertension in a patient with pyruvate kinase deficiency and paravertebral extramedullary hematopoiesis*, 88 Annals of Hematology 603 (2008) (“Bachmeyer”).
- 1017 Kha Le et al., *Population Pharmacokinetics and Pharmacodynamics of AG-348 in Healthy Human Volunteers Guide Dose Selection for the Treatment of Pyruvate Kinase Deficiency*, 126 Blood 3336 (2015) (“Le”).
- 1018 CV of Michael J. Thirman

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I. Introduction

Petitioner Apotex Inc. seeks *inter partes* review of Claims 1, 8, 9, 14, and 19 (the “challenged claims”) of U.S. Patent No. 11,878,049 (the “’049 patent”) (Ex. 1001). The ’049 patent, assigned to Agios Pharmaceuticals, Inc. (“Agios” or “Patent Owner”), is directed to methods of treating hemolytic anemia, a disorder characterized by excessive red blood cell breakdown. Those methods employ a combination of two known drugs: (1) mitapivat and (2) what is referred to as a “moderate inducer” of the liver enzymes cytochrome P450 3A4 or cytochrome P450 3A5 (collectively “CYP3A4/5”).

Critically, when the moderate inducer is administered with mitapivat, it induces the CYP3A4/5 enzymes to metabolize mitapivat. Ex. 1001 (’049 patent), 2:3-8. The inventors apparently sought to solve this problem, and their solution is as unremarkable as it is unpatentable. To wit, the inventors simply adjusted the dose of mitapivat to account for its metabolism by the CYP3A4/5 enzymes. *Id.* at 7:19-39.

To that end, the specification provides a myriad of proposed mitapivat doses and dosing ranges falling within an overarching range of between about 2 mg/day to about 3,000 mg/day. *Id.* at 12:31-14:17. The specification, however, provides no rationale for choosing a particular mitapivat dose or how to do so when it is co-administered with a moderate inducer. Section IV.B, *infra*. Without explanation,

the inventors incorporated four daily dosages into independent Claim 1: about 10 mg/day, about 40 mg/day, about 100 mg/day, and about 200 mg/day. Notably, the extrinsic evidence reveals that Agios appears to have chosen at least two of these dosages, namely the “about 100 mg/day” and “about 200 mg/day” dosages, in light of dosing recommendations made by FDA employees during the drug approval process for Pyrukynd® (mitapivat tablets). Sections IV.C-D, *infra*. Those FDA employees, who contributed post-filing work to arrive at the claimed doses, were not named as inventors to the '049 patent.

Given the simplistic nature of the claimed invention, which at bottom is the concept that the mitapivat dose may be adjusted in view of its metabolism, it is not surprising that the prior art renders the claimed invention anticipated and obvious. Section V, *infra*. To summarize, the prior art taught methods of treating hemolytic anemia, including a type known as pyruvate kinase deficiency (“PKD”), by co-administering mitapivat with other drugs. Drugs that would have been logical options for co-administration with mitapivat would have included certain moderate CYP3A4 inducers, as the art likewise taught administration of those inducers to patients suffering from PKD. The prior art further taught that administration of such moderate inducers would have been expected to increase metabolism of mitapivat, thereby reducing its concentration in the body. And as if that were not enough, it was well known that such a reduction may be countered by simply

adjusting the dose of mitapivat, and the art provided a menu of safe and effective doses from which the POSA could choose. These disclosures from the prior art flow into the following four grounds of this petition:

Ground 1 demonstrates that Sizemore—a PCT publication directed to pharmaceutical compositions using mitapivat—expressly discloses each limitation recited in the challenged claims, rendering those claims anticipated.

Ground 2 shows that the challenged claims would have been obvious over three references, Agresta, Dana-Farber, and Grace Presentation, coupled with the knowledge of a POSA. These references each relate to a Phase 2 study of mitapivat for the treatment of PKD. Agresta, a PCT publication, discloses the protocol for the study; Dana-Farber, a webpage, discloses inclusion and exclusion criteria for the study; and Grace Presentation, a slide deck delivered at a hematology conference, discloses the study's results. Together these references disclose all of the limitations of the challenged claims, as well as provide motivation and reasonable expectation of success to arrive at the claimed invention.

Ground 3 likewise shows how the challenged claims would have been obvious, this time over Agresta, Dana-Farber, Grace Abstract, and the knowledge of a POSA. This ground shares two of three references with Ground 2. Further, Grace Abstract provides similar teachings to Grace Presentation, though in the

form of an abstract. Thus, the challenged claims would have been obvious for similar reasons to Ground 2.

Ground 4, addressing a single dependent claim, Claim 19, relating to tablet ingredients, builds upon prior art in Grounds 2 and 3 with the addition of the formulation-related teachings of Sizemore, the anticipatory reference set forth in Ground 1. Those collective teachings render this challenged claim obvious.

The Board should therefore institute *inter partes* review and hold all challenged claims unpatentable.

II. Mandatory Notices

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

In accordance with 37 C.F.R. § 42.8(b)(1), Petitioner Apotex Inc. is a real party-in-interest. Additional real parties-in-interest are Apotex Holdco Inc., SK Artemis Holdings II, LLC, Apotex Corp., Artemis Parent, Inc., Artemis Intermediate Holdings, Inc., and Aposherm Delaware Holdings Corp.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Petitioner is not aware of any related matter involving the '049 patent.

C. Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

Petitioner identifies the following:

Lead counsel:	John J. Molenda (Reg. No. 47,804)
Back-up counsel:	Jordan P. Markham (Reg. No. 68,667)
Back-up counsel:	Michael I. Green (Reg. No. 80,436)

Back-up counsel: Fievel Lim (Limited Recognition No.
800,170)

D. Notice of Service Information (37 C.F.R. § 42.8(b)(4))

Petitioner identifies the following:

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Mailing address:	STEPTOE LLP 1114 Avenue of the Americas New York, NY 10036
Telephone number:	212-506-3900
Fax number:	212-506-3950

Please address all correspondence to the above email address. Petitioner consents to electronic service at that address.

III. Requirements for *Inter Partes* Review

A. Grounds for Standing (37 C.F.R. §§ 42.104, 42.204(a))

Petitioner certifies that (1) the '049 patent is available for *inter partes* review and (2) Petitioner is not barred or estopped from requesting review of any claim on the grounds identified in this petition.

B. Payment of Fees

Pursuant to 37 C.F.R. § 42.103, the fee set forth in § 42.15(a) accompanies this petition. The Office is authorized to charge all fees due in connection with this matter to Deposit Account No. 19-4293.

C. Identification of Challenge

Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancellation of the claims of the '049 patent as follows:

Ground	Claims	Description
1	1, 8, 9, 14, 19	§ 102 over Ex. 1004 (Sizemore)
2	1, 8, 9, 14	§ 103 over Ex. 1005 (Agresta), Ex. 1007 (Dana-Farber), Ex. 1008 (Grace Presentation), and the knowledge of a POSA
3	1, 8, 9, 14	§ 103 over Ex. 1005 (Agresta), Ex. 1007 (Dana-Farber), Ex. 1009 (Grace Abstract), and the knowledge of a POSA
4	19	§ 103 over Ex. 1005 (Agresta), Ex. 1007 (Dana-Farber), Ex. 1008 (Grace Presentation) or Ex. 1009 (Grace Abstract), Ex. 1004 (Sizemore), and the knowledge of a POSA

Petitioner's detailed grounds for unpatentability are set forth below. In support of these grounds, Petitioner submits the exhibits identified herein, including the expert declaration of Michael J. Thirman, M.D., Ex. 1003.

IV. Background

A. Technical Background and State of the Art

A POSA would have known the following information as of the effective filing date of the '049 patent. Ex. 1003 (Thirman Decl.) ¶ 11; Section IV.B, *infra*.

Hemolytic anemia is a disorder characterized by excessive breakdown of red blood cells. Ex. 1003 (Thirman Decl.) ¶ 12; Ex. 1005 (Agresta) at 4. PKD is “a congenital hemolytic anemia caused by mutations in the PKLR gene.” Ex. 1003

(Thirman Decl.) ¶ 12; Ex. 1009 (Grace Abstract) at 2; *see also* Ex. 1005 (Agresta) at 3-4. Mitapivat, known in the prior art as N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide, Compound 1, formula (I), or AG-348, was taught to be a treatment for both hemolytic anemia generally and PKD specifically.¹ Ex. 1003 (Thirman Decl.) ¶ 12; Ex. 1005 (Agresta) at 25, 37-38, 51 (disclosing treatment); *see also id.* at 37 (identifying the compound), 44 (referring to the compound as AG-348); Ex. 1004 (Sizemore) at ¶ 0003 (same); Section IV.G, *infra* (defining mitapivat).

Mitapivat was one of many drugs known to be metabolized by CYP3A4, a type of cytochrome P450 enzyme. Ex. 1003 (Thirman Decl.) ¶ 14; Ex. 1005 (Agresta) at 42; Ex. 1010 (Mutalik) at 12. Drug interactions between co-administered drugs were known to commonly arise where one drug is metabolized by a cytochrome P450 enzyme, while another drug modulates that enzyme's activity. Ex. 1003 (Thirman Decl.) ¶ 15; Ex. 1010 (Mutalik) at 12-13. Such interactions were a "known factor" in how patients respond to drugs. Ex. 1003 (Thirman Decl.) ¶ 15; Ex. 1010 (Mutalik) at 2, 12-13.

¹ For ease of reference, this Petition solely uses "mitapivat" to refer to this compound.

A drug that increases a CYP450 enzyme's activity, and thus reduces drug concentration in a patient's body, was known as an inducer. Ex. 1003 (Thirman Decl.) ¶ 16; Ex. 1010 (Mutalik) at 12. Inducers known to decrease concentration of a drug by 50-80% were categorized as "moderate." Ex. 1003 (Thirman Decl.) ¶ 16; Ex. 1010 (Mutalik) at 13-14. A common way to combat decreased drug concentration resulting from co-administration with an inducer was to simply increase the drug's dose. Ex. 1003 (Thirman Decl.) ¶ 16; Ex. 1010 (Mutalik) at 19, 24; Ex. 1012 (Clark) at 1, 2, 4, 5, 6.

Several examples of cytochrome P450 modulators were known and in clinical use, including moderate CYP3A4 inducers. Ex. 1003 (Thirman Decl.) ¶ 17; Ex. 1010 (Mutalik) at 13-14; Ex. 1015 (van Giersbergen) at 7. These examples included inducers that complemented mitapivat treatment for hemolytic anemia by treating co-morbidities such as hyperbilirubinemia and pulmonary arterial hypertension. Ex. 1003 (Thirman Decl.) ¶ 17; Ex. 1006 (Gordon-Smith) at 9-10; Ex. 1013 (Hackman) at 1, 3; Ex. 1016 (Bachmeyer) at 2-3; Ex. 1015 (van Giersbergen) at 1.

B. The Filing of the '049 Patent and Its Specification

The '049 patent is titled "Mitapivat Therapy and Modulators of Cytochrome P450." Ex. 1001 ('049 patent) at Cover; Ex. 1003 (Thirman Decl.) ¶ 18. The '049 patent was filed on June 12, 2020 as Application No. 16/900,610 and claims

priority to U.S. Provisional Application No. 62/861,600 (filed June 14, 2019). Ex. 1001 ('049 patent) at Cover; Ex. 1003 (Thirman Decl.) ¶ 18. For the purpose of this IPR only, Petitioner assumes the effective filing date of the '049 patent is June 14, 2019.

The '049 patent is directed to methods of treating hemolytic anemias, e.g., PKD, using mitapivat in combination with, or in the absence of, cytochrome P450 modulators. Ex. 1001 ('049 patent) at Abstract; Ex. 1003 (Thirman Decl.) ¶ 20.

The first 35 columns, i.e., three quarters, of the '049 patent's specification are largely an assemblage of generalized boilerplate, which in many cases are in the form of lengthy laundry lists. Ex. 1001 ('049 patent) at 1:1-35:61; Ex. 1003 (Thirman Decl.) ¶ 21. After providing nine columns of introductory material, including a brief description of PKD and mitapivat's development to treat that disorder, the specification provides a generalized description of pharmaceutical compositions. Ex. 1001 ('049 patent) at 1:12-8:67, 9:1-10:28; Ex. 1003 (Thirman Decl.) ¶ 21. The latter section, in turn, is followed by eighteen laundry-list heavy columns relating to dosing of mitapivat and administration of concomitant medications that may yield drug-drug interactions. Ex. 1001 ('049 patent) at 10:29-28:51; Ex. 1003 (Thirman Decl.) ¶ 21. Two columns alone are devoted to a vast laundry list of daily doses and dosage ranges, with options broadly ranging

from 2 to 3000 mg per day.² Ex. 1001 ('049 patent) at 12:31-14:17; Ex. 1003 (Thirman Decl.) ¶ 21. The subsequent seven columns list types of diseases to be treated using mitapivat. Ex. 1001 ('049 patent) at 28:52-35:61; Ex. 1003 (Thirman Decl.) ¶ 21.

Following the extensive boilerplate, are three examples. Ex. 1001 ('049 patent) at 35:61-45:22; Ex. 1003 (Thirman Decl.) ¶ 22. Example 1 indicates that mitapivat is primarily metabolized by CYP3A4/5. Ex. 1001 ('049 patent) at 36:5-12; Ex. 1003 (Thirman Decl.) ¶ 22. Example 2 provides a drug-drug interaction clinical study testing the effects of a strong CYP3A4/5 inhibitor (itraconazole) and a strong CYP3A4/5 inducer (rifampicin) on mitapivat, with the specification's figures reporting results from the study. Ex. 1001 ('049 patent) at 36:42-67, 37:18-29; Ex. 1003 (Thirman Decl.) ¶ 22. The specification's conclusions drawn from this example are limited to a strong inhibitor and a strong inducer, Ex. 1001 ('049

² This laundry list includes dosing ranges including from about 5 mg to about 500 mg, about 5 mg to about 200 mg, about 300-360 mg, and about 5 mg to about 10 mg. Ex. 1001 ('049 patent), 12:31-14:17; Ex. 1003 (Thirman Decl.) ¶ 21. This list also includes individual daily doses from about 5 mg to 60 mg in 5 mg intervals, along with individual daily doses from about 60 to about 300 mg in 10 mg intervals. *Id.*

patent) at 43:36-40, and thus do **not** address the moderate inducers recited in the challenged claims. Ex. 1003 (Thirman Decl.) ¶ 22.

Example 3 generally describes the development of a pharmacokinetic model to evaluate drug-drug interactions, including the effect of a moderate CYP3A4/5 inducer on mitapivat at doses of 5, 20, and 50 mg twice daily. Ex. 1001 ('049 patent) at 43:41-50, 44:22-25; Ex. 1003 (Thirman Decl.) ¶ 23. But at the time of filing, the inventors had **not** performed that modeling or even completed developing it. Ex. 1001 ('049 patent) at 43:41-50, 44:22-25; Ex. 1003 (Thirman Decl.) ¶ 23. Rather, the specification states that the modeling “is being developed” and “will be used to assess DDI liability.” Ex. 1001 ('049 patent) at 43:41-50, 44:22-25; Ex. 1003 (Thirman Decl.) ¶ 23.

While the specification instructs that when a drug-drug interaction occurs, “the amount of mitapivat . . . should be adjusted,” Ex. 1001 ('049 patent) at 7:33-39, it does not explain how to make that adjustment when mitapivat is co-administered with a moderate CYP3A4/5 inducer. Ex. 1003 (Thirman Decl.) ¶ 24. At the same time, nowhere in the specification’s laundry list of doses do the inventors explain how to select a dose from that list. Ex. 1001 ('049 patent) at 12:31-14:17; Ex. 1003 (Thirman Decl.) ¶ 24. Rather, the list is agnostic as to whether the doses are co-administered with a CYP3A4/5 inducer, inhibitor, or neither, let alone whether the CYP3A4/5 inducer is weak, moderate, or strong. *Id.*

Further, the specification provides no experimental data involving co-administration of a moderate CYP3A4/5 inducer and mitapivat. Ex. 1001 ('049 patent) at 35:61-45:22; Ex. 1003 (Thirman Decl.) ¶ 24. The disclosed studies regarding that scenario were “being developed,” Ex. 1001 ('049 patent) at 43:41-50, 44:22-25, while the studies that were actually performed address different scenarios involving a strong inducer or inhibitor, *id.* at 36:42-67. Ex. 1003 (Thirman Decl.) ¶ 24.

C. FDA Review Relating to Mitapivat

After filing for the challenged patent, on June 17, 2021, Patent Owner filed a New Drug Application (NDA) with the FDA for a mitapivat drug called Pyrukynd[®]. Ex. 1003 (Thirman Decl.) ¶ 25; Ex. 1011 (FDA) at 2. In response to a request from the FDA—seemingly after filing the NDA, and thus after filing for the '049 patent, too—Patent Owner finally performed modeling of the effect of a moderate CYP3A inducer on mitapivat doses of 5 mg, 20 mg, and 50 mg twice daily. Ex. 1003 (Thirman Decl.) ¶ 25; Ex. 1011 (FDA) at 217 (Table 108 and caption). Based upon that modeling, the FDA “recommend[ed] titration beyond 50 mg twice daily dose if necessary but not to exceed 100 mg twice daily” of mitapivat when co-administered with a moderate inducer in its February 16, 2022 review of the Pyrukynd[®] NDA. Ex. 1003 (Thirman Decl.) ¶ 26; Ex. 1011 (FDA) at 119; *see also id.* at 2 (listing date). Notably, nowhere had the inventors

specifically disclosed such a recommendation in their specification. Ex. 1003 (Thirman Decl.) ¶ 27; Section IV.B, *supra*. It thus appears that the FDA conceived of administration of mitapivat doses beyond 50 mg twice daily, i.e., about 100 mg daily, and about 100 mg twice daily, i.e., about 200 mg per day³ for patients also taking moderate CYP3A inducers.

D. The Prosecution History

The initial claims, filed on June 12, 2020, recited methods of treatment by administering an “effective amount” of mitapivat together with a CYP3A4/5 inducer. Ex. 1002 (’049 prosecution history, Jun. 12, 2020 Originally Filed Claims) at 84-89; Ex. 1003 (Thirman Decl.) ¶ 28. A subsequent preliminary amendment on August 19, 2020, presented claims reciting administering an “effective amount” of mitapivat either (1) together with a CYP3A4/5 inducer or inhibitor or (2) in the absence of an inhibitor or inducer. Ex. 1002 (’049 prosecution history, Aug. 19, 2020 preliminary amendment) at 99-102; Ex. 1003 (Thirman Decl.) ¶ 28. Then-pending Claim 36, depending from Claim 1, recited co-administration of mitapivat and a moderate CYP3A4/5 inducer. Ex. 1003

³ The term “about” provides a “range of tolerance[]”, such that, for example, “about 50 mg” encompasses doses beyond 50 mg and “about 100 mg” encompasses doses beyond 100 mg. Ex. 1001 (’049 patent) at 8:59-67.

(Thirman Decl.) ¶ 28; Ex. 1002 ('049 prosecution history, Aug. 19, 2020 preliminary amendment) at 101. But that claim did not specify which doses would be effective. *Id.*

Substantive prosecution of the preliminarily amended claims began July 18, 2022, five months after the FDA review of the Pyrukynd® (mitapivat tablets) NDA was completed. Ex. 1002 ('049 prosecution history, Jul. 18, 2022 Non-Final Rejection) at 106-07; Ex. 1003 (Thirman Decl.) ¶ 29; Section IV.C, *supra*. The Examiner issued a Non-Final Office Action rejecting the then-pending claims on multiple grounds. Ex. 1003 (Thirman Decl.) ¶ 29; Ex. 1002 ('049 prosecution history, Jul. 18, 2022 Non-Final Rejection) at 108-20. As for claims reciting co-administration of mitapivat with a CYP3A4/5 inhibitor or inducer, the Examiner relied upon prior art directed to co-administration with the CYP3A4/5 inhibitor boceprevir and the CYP3A4/5 inducer dexamethasone. Ex. 1003 (Thirman Decl.) ¶ 29; Ex. 1002 ('049 prosecution history, Jul. 18, 2022 Non-Final Rejection) at 110-17.

On November 18, 2022, Applicants cancelled every pending claim and submitted new claims directed to methods of treating hemolytic anemia by administering mitapivat with a moderate CYP3A4/5 inducer, which was narrower than the prior claims that encompassed any CYP3A4/5 inducer (or inhibitor). Ex. 1003 (Thirman Decl.) ¶ 30; Ex. 1002 ('049 prosecution history, Nov. 18, 2022

Claims) at 127-28. Those new claims introduced numerical doses for the first time: about 10, about 40, and about 50 mg/day. *Id.*

Applicants further argued that the Examiner's prior art was inapplicable to the new claims. Ex. 1003 (Thirman Decl.) ¶ 31; Ex. 1002 ('049 prosecution history, Nov. 18, 2022 Response to Non-Final Office Action) at 129-33.

Applicants distinguished the boceprevir prior art by arguing that it taught co-administration of a CYP inhibitor, not an inducer. Ex. 1003 (Thirman Decl.) ¶ 31; Ex. 1002 ('049 prosecution history, Nov. 18, 2022 Response to Non-Final Office Action) at 129-31. Applicants distinguished the dexamethasone prior art by arguing that the drug is a strong inducer, not a moderate inducer. Ex. 1003 (Thirman Decl.) ¶ 31; Ex. 1002 ('049 prosecution history, Nov. 18, 2022 Response to Non-Final Office Action) at 132-33.

The Examiner then issued a Final Office Action on February 7, 2023, advancing a new obviousness theory based upon co-administration of mitapivat with the CYP3A4/5 inducer rifampicin. Ex. 1002 ('049 prosecution history, Feb. 7, 2023 Final Rejection) at 140-42; Ex. 1003 (Thirman Decl.) ¶ 32.

On April 7, 2023, Applicants responded by arguing that rifampicin is a strong inducer and therefore does not satisfy the moderate-inducer claim limitation, nor did the Examiner explain how it does. Ex. 1002 ('049 prosecution history, Apr. 7, 2023 Applicant Arguments and Remarks to Final) at 154; Ex. 1003

(Thirman Decl.) ¶ 33. Nor was the Examiner later able to identify prior art that provided teachings relating to a moderate inducer, as evident from the remainder of the prosecution history.⁴ Ex. 1003 (Thirman Decl.) ¶ 33. Applicants also cancelled the pending claims and submitted amended Claims 59-77), *infra*. Ex. 1002 ('049 prosecution history, Apr. 7, 2023 Claims) at 150-52; Ex. 1003 (Thirman Decl.) ¶ 34. Notably, the amendment modified the claimed dosing. Ex. 1002 ('049 prosecution history, Apr. 7, 2023 Applicant Arguments and Remarks to Final) at 153; Ex. 1003 (Thirman Decl.) ¶ 34. While the earlier November 2022 claims recited doses of about 10, about 40, or about 50 mg/day, the new claim set removed about 50 mg/day and added about 100 or about 200 mg/day. Ex. 1003 (Thirman Decl.) ¶ 34; Ex. 1002 ('049 prosecution history, Apr. 7, 2023 Applicant

⁴ Petitioner, however, identifies prior art doing so in both its anticipation and obviousness grounds. Ex. 1003 (Thirman Decl.) ¶ 33; Sections V.A.1, (anticipation argument relying upon Ex. 1004 (Sizemore) utilizing teachings not relied upon by the Examiner), *infra*; V.B.1, V.C.1 (obviousness arguments relying upon references not cited to or utilized by the Examiner in an office action including Ex. 1007 (Dana-Farber), Ex. 1010 (Mutalik), Ex. 1006 (Gordon-Smith), Ex. 1013 (Hackman), Ex. 1015 (van Giersbergen), Ex. 1016 (Bachmeyer)), *infra*; Ex. 1001 ('049 patent) References Cited; Ex. 1002 ('049 prosecution history).

Arguments and Remarks to Final) at 153; *compare* Ex. 1002 ('049 prosecution history, Apr. 7, 2023 Claims) at 150-52 *with* Ex. 1002 ('049 prosecution history, Nov. 18, 2022 Claims) at 127-28.

Significantly, it appears that FDA reviewers had conceived of the “about 100 mg/day” and the about “200 mg/day” dosing limitations in its review of the Pyrukynd[®] NDA. Section IV.C, *supra*. However, the April 2023 response did not disclose the FDA reviewers’ role. Ex. 1002 ('049 prosecution history, Apr. 7, 2023 Applicant Arguments and Remarks to Final) at 153-55; Ex. 1003 (Thirman Decl.) ¶ 35. Nor did the Applicants otherwise disclose the FDA review to the Examiner. Ex. 1003 (Thirman Decl.) ¶ 35; Ex. 1001 ('049 patent) References Cited.

On May 3, 2023, the Examiner issued a Notice of Allowance for Claims 59-77, stating that “Applicant’s arguments submitted 04/07/2023 are sufficient to overcome the rejection of record.” Ex. 1002 ('049 prosecution history, May 3, 2023 Notice of Allowance) at 163; Ex. 1003 (Thirman Decl.) ¶ 36. In a subsequent Notice of Allowance, the Examiner elaborated, stating that “there are no teaching[s] or suggestions within the prior art to combine a moderate inducer of [CYP 3A4/5] with the claimed doses of mitapivat . . . in order to treat hemolytic anemia.” Ex. 1002 ('049 prosecution history, Aug. 30, 2023 Notice of Allowance) at 451-52; Ex. 1003 (Thirman Decl.) ¶ 36.

E. The Issued Claims

Claim 1, the only independent claim, recites as follows:

1. A method of treating hemolytic anemia in a subject, comprising administering to the subject about 10 mg/day, about 40 mg/day, about 100 mg/day, or about 200 mg/day of mitapivat or a pharmaceutically acceptable salt thereof and a moderate inducer of cytochrome P450 3A4/5 (CYP3A4/5).

Ex. 1001 ('049 patent), Claim 1; Ex. 1003 (Thirman Decl.) ¶ 37. Claim 8 depends from Claim 1 and specifies that the subject is administered about 200 mg/day of mitapivat. Ex. 1001 ('049 patent), Claim 8; Ex. 1003 (Thirman Decl.) ¶ 37. Claim 9 depends from Claim 8 and further specifies that the subject is administered about 100 mg of mitapivat twice per day. Ex. 1001 ('049 patent), Claim 9; Ex. 1002 ('049 prosecution history, Certificate of Correction) at 459; Ex. 1003 (Thirman Decl.) ¶ 37. Claim 14 depends from Claim 9 and further specifies that the mitapivat is orally administered as part of a tablet composition. Ex. 1001 ('049 patent), Claim 14; Ex. 1003 (Thirman Decl.) ¶ 37. Claim 19 depends from Claim 14 and further specifies that the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl

fumarate. Ex. 1001 ('049 patent), Claim 19; Ex. 1003 (Thirman Decl.) ¶ 37.⁵ As noted previously, the about 100 and about 200 mg/day doses reflect FDA's recommendations for what Agios should employ for its Pyrukynd[®] product upon co-administration with a moderate CYP3A4 inducer. Section IV.C, *supra*.

F. Level of Skill

Petitioner proposes that a POSA would have had at least the following qualifications: a medical degree and at least three years of experience in treating hematologic diseases or developing drugs for treating hematologic diseases, or would have had equivalent education, training, or experience. Ex. 1003 (Thirman Decl.) ¶ 60. A POSA may be part of a team that includes other scientists in related fields, for example a pharmacologist or pharmaceutical formulator. *Id.*

G. Claim Construction

Petitioner proposes that “mitapivat” be construed as “N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide.” Ex. 1003 (Thirman Decl.) ¶ 63. The specification confirms that those two names, as

⁵ A certificate of correction issued on February 27, 2024, correcting the dependency of Claim 9 from “claim 6” to “claim 8.” Ex. 1002 ('049 prosecution history, Certificate of Correction) at 459; Ex. 1003 (Thirman Decl.) ¶ 38.

well as AG-348, are synonymous. Ex. 1001 ('049 patent) at 1:33-51; Ex. 1003 (Thirman Decl.) ¶ 63.

The specification contains several definitions. Ex. 1003 (Thirman Decl.) ¶ 64. Petitioner proposes that the Board should adopt those definitions. *Id.* Many of those definitions appear in a part of the specification entitled “Definitions.” *Id.*; Ex. 1001 ('049 patent) at 4:55-8:67. The specification additionally defines “CYP3A4/5” as “cytochrome P450 3A4 (CYP3A4) *or* 3A5 (CYP3A5).” Ex. 1001 ('049 patent) at 2:22-23 (emphasis added); Ex. 1003 (Thirman Decl.) ¶ 65.

V. Detailed Explanation of Grounds for Unpatentability

A. Ground 1: Claims 1, 8, 9, 14, and 19 Are Anticipated Under 35 U.S.C. § 102 by Sizemore

Claims 1, 8, 9, 14, and 19 are anticipated by Sizemore under 35 U.S.C. § 102. Ex. 1003 (Thirman Decl.) ¶ 67. As explained by Sizemore, the reference provides, *inter alia*, uses for pharmaceutical compositions comprising mitapivat for treating conditions associated with pyruvate kinase. Ex. 1003 (Thirman Decl.) ¶ 67; Ex. 1004 (Sizemore) at ¶¶ 0005-06; *see also id.* at Abstract.

Sizemore qualifies as prior art under 35 U.S.C. § 102(a)(1). It was published on May 31, 2019, Ex. 1004 (Sizemore) at Cover, before the effective filing date of the '049 patent. Ex. 1003 (Thirman Decl.) ¶ 68. Petitioner is not aware of any exception under 35 U.S.C. § 102(b)(1) that would remove Sizemore as prior art. *Id.* For example, there is no overlap in inventorship between Sizemore and the

'049 patent. *Compare* Ex. 1004 (Sizemore) at Cover *with* Ex. 1001 ('049 patent) at Cover; Ex. 1003 (Thirman Decl.) ¶ 68.

1. Claim 1

Claim 1 recites a method of treating hemolytic anemia by administering about 10, about 40, about 100, or about 200 mg/day of mitapivat and a moderate inducer of CYP3A4/5. Ex. 1001 ('049 patent), Claim 1; Ex. 1003 (Thirman Decl.) ¶ 69. Sizemore anticipates Claim 1 for the following reasons. Ex. 1003 (Thirman Decl.) ¶ 69.

Sizemore satisfies the method of treatment and mitapivat claim limitations by disclosing “methods for treating hemolytic anemia in a subject in need thereof comprising administering to the subject an effective amount of [mitapivat], or a pharmaceutical composition thereof” Ex. 1003 (Thirman Decl.) ¶ 70; Ex. 1004 (Sizemore) at ¶ 00137; *see also id.* at ¶ 00125, Claim 35 (similar). As Sizemore notes, “pyruvate kinase deficiency results in life-long hemolytic anemia,” which mitapivat treats because it is a pyruvate kinase activator. Ex. 1003 (Thirman Decl.) ¶ 70; Ex. 1004 (Sizemore) at ¶¶ 0003, 00122; *see also id.* at ¶ 0002.

Sizemore satisfies the dosing claim limitation by disclosing administration of “about 5 mg,” about 20 mg,” about 50 mg,” and “about 100 mg” of mitapivat “twice per day,” i.e., about 10 mg, about 40 mg, about 100 mg, and about 200

mg/day. Ex. 1003 (Thirman Decl.) ¶ 71; Ex. 1004 (Sizemore) at ¶ 00113; *see also id.* at ¶ 00114 (disclosing tablet compositions containing “about 5 mg,” “about 20 mg,” “about 50 mg,” and “about 100 mg”).

Sizemore satisfies the moderate CYP3A4/5 inducer limitation based upon its disclosures regarding combination therapy and CYP3A4 modulators viewed with the knowledge and understanding of a POSA. Ex. 1003 (Thirman Decl.) ¶ 72. Anticipation analysis is undertaken from a POSA’s perspective and, “therefore, **must** take account of the knowledge of such a person.” *Sage Prods., LLC v. Stewart*, 133 F.4th 1376, 1384 n.5 (Fed. Cir. 2025) (emphasis added).

So “[e]ven if a piece of prior art does not expressly disclose a limitation, it anticipates if a person of ordinary skill in the art would understand the prior art to disclose the limitation and could combine the prior art description with his own knowledge to make the claimed invention.” *Id.* (quoting *Arthrocare Corp. v. Smith & Nephew, Inc.*, 406 F.3d 1365, 1373-74 (Fed. Cir. 2005)).

Indeed, the Federal Circuit has repeatedly held claims anticipated under those circumstances. *See, e.g., id.* at 1383-84 & n.5 (rejecting argument that anticipatory reference lacked “explicit disclosure” and crediting expert testimony as to a POSA’s knowledge); *Arthrocare*, 406 F.3d at 1373-74 (crediting testimony of expert who agreed that the anticipatory reference “does not explicitly identify” the claim limitation, but stated that a POSA “would understand” that the limitation

was disclosed); *VirnetX Inc. v. Apple Inc.*, No. 2022-1523, 2023 WL 6933812, at *4 (Fed. Cir. Oct. 20, 2023) (“[T]he limitation in question . . . would be understood to be disclosed . . . even though not expressly stated as such in the reference itself.”).

Here, a POSA would read Sizemore as disclosing co-administration of mitapivat with a moderate CYP3A4 inducer. Ex. 1003 (Thirman Decl.) ¶ 73. Sizemore discloses administration of a therapeutic agent, i.e., mitapivat, “alone or in combination with other therapies.” Ex. 1004 (Sizemore) at ¶ 0046; Ex. 1003 (Thirman Decl.) ¶ 73. Sizemore then limits the other therapies taken by the treated subjects. Ex. 1004 (Sizemore) at ¶ 0053; Ex. 1003 (Thirman Decl.) ¶ 73. Sizemore discloses that, “[i]n certain embodiments, such subject is not taking inhibitors of cytochrome P450 (CYP)3A4, strong inducers of CYP3A4, strong inhibitors of P-glycoprotein (P-gp), or digoxin.” *Id.* 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. Ex. 1003 (Thirman Decl.) ¶ 73. That is because a POSA would have viewed Sizemore’s disclosure with his or her background knowledge, for example, that mitapivat was a CYP3A4 substrate and that moderate CYP3A4 inducers were publicly available. *Id.*; Section IV.A, *supra*.

2. Claims 8 and 9

Claim 8 depends from Claim 1 and further recites that the subject is administered about 200 mg/day of mitapivat. Ex. 1001 ('049 patent), Claim 8; Ex. 1003 (Thirman Decl.) ¶ 74. Claim 9 depends from Claim 8 and further recites that the subject is administered about 100 mg of mitapivat twice per day. Ex. 1001 ('049 patent), Claim 9; Ex. 1002 ('049 prosecution history, Certificate of Correction) at 459; Ex. 1003 (Thirman Decl.) ¶ 74. Sizemore anticipates Claims 8 and 9 for the same reasons as Claim 1 and the further reasons below. Ex. 1003 (Thirman Decl.) ¶ 74; Section V.A.1, *supra*.

As discussed above, Sizemore discloses a dose of “about 100 mg of compound 1 twice per day.” Ex. 1004 (Sizemore) at ¶¶ 00113, 00114; Ex. 1003 (Thirman Decl.) ¶ 75. This disclosure satisfies Claim 9’s limitation of about 100 mg twice per day. Ex. 1003 (Thirman Decl.) ¶ 75. It simultaneously satisfies Claim 8’s limitation of about 200 mg/day because about 100 mg twice per day totals about 200 mg/day. *Id.*

3. Claims 14 and 19

Claim 14 depends from Claim 9 (and therefore from Claims 8 and 1) and additionally recites that the mitapivat is orally administered as part of a tablet composition. Ex. 1001 ('049 patent), Claim 14; Ex. 1003 (Thirman Decl.) ¶ 76. Claim 19 depends from Claim 14 (and therefore from Claims 9, 8, and 1) and

additionally recites that the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate. Ex. 1001 ('049 patent), Claim 19; Ex. 1003 (Thirman Decl.) ¶ 76. Sizemore anticipates Claims 14 and 19 for the same reasons as Claims 1, 8, and 9 and the further reasons below. Ex. 1003 (Thirman Decl.) ¶ 76; Sections V.A.1-2, *supra*.

Sizemore discloses that its compositions “may be administered orally” in an orally acceptable dosage form “including . . . tablets.” Ex. 1004 (Sizemore) at ¶ 00110; *see also id.* at ¶ 00114 (disclosing that mitapivat “is formulated as a tablet composition together with a pharmaceutically acceptable carrier”); Ex. 1003 (Thirman Decl.) ¶ 77.

Sizemore further discloses a mitapivat tablet formulation comprising the inactive ingredients recited by Claim 19: microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate. Ex. 1004 (Sizemore) at ¶¶ 00114, 00116, 00219, Claims 29-30; *see also id.* ¶¶ 0093-110; Ex. 1003 (Thirman Decl.) ¶ 78.

4. Conclusion

For the foregoing reasons, Claims 1, 8, 9, 14, and 19 are unpatentable as anticipated under 35 U.S.C. § 102 by Sizemore. Ex. 1003 (Thirman Decl.) ¶ 79.

B. Ground 2: Claims 1, 8, 9, and 14 Would Have Been Obvious Under 35 U.S.C. § 103 over Agresta, Dana-Farber, Grace Presentation, and the Knowledge of a POSA

Claims 1, 8, 9, and 14 are unpatentable as obvious under 35 U.S.C. § 103 over Agresta, Dana-Farber, Grace Presentation, and the knowledge of a POSA. Ex. 1003 (Thirman Decl.) ¶ 80.

We begin by providing a brief overview of these references' disclosures. Agresta, a PCT publication, Ex. 1005 (Agresta) at Cover, teaches treating PKD, a type of hemolytic anemia, using mitapivat, including by providing a protocol for a Phase 2 clinical study. Section V.B.1.a, *infra*; Ex. 1003 (Thirman Decl.) ¶ 81. Agresta further teaches co-administration of mitapivat with other drugs. Section V.B.1.a, *infra*; Ex. 1003 (Thirman Decl.) ¶ 81. Dana-Farber, a webpage, Ex. 1007 (Dana-Farber) at 5, discloses the Agresta study's inclusion and exclusion criteria, with the latter notably prohibiting patients taking strong CYP3A4 inducers but **not** moderate CYP3A4 inducers. Section V.B.1.b, *infra*; Ex. 1003 (Thirman Decl.) ¶ 81. Grace Presentation, delivered at a hematology conference, Ex. 1008 (Grace Presentation) at 16, discloses the Agresta study's results, including which mitapivat dosages were safe and effective. Section V.B.1.c, *infra*; Ex. 1003 (Thirman Decl.) ¶ 81. Together, these references satisfy all the limitations of Claims 1, 8, 9, and 14. Ex. 1003 (Thirman Decl.) ¶ 81.

As discussed further below, a POSA would have been motivated to combine these references, because the references all address treatment of the same disease (PKD) using the same drug (mitapivat) in the same Phase 2 clinical study. Section V.B.3, *infra*; Ex. 1003 (Thirman Decl.) ¶¶ 82-83. A POSA would further have been motivated to combine these references in view of the nature of the problem to be solved, i.e., a drug-drug interaction between mitapivat and CYP3A4 inducers. Section V.B.3, *infra*; Ex. 1003 (Thirman Decl.) ¶ 83. And a POSA would have had a reasonable expectation of success given the study’s positive results and the routine nature of handling drug-drug interactions. Section V.B.4, *infra*; Ex. 1003 (Thirman Decl.) ¶ 83.

Each of Agresta, Dana-Farber, and Grace Presentation qualify as prior art for the following reasons:

Reference	Prior Art Status
Agresta	Agresta was published on December 15, 2016 and is therefore prior art under 35 U.S.C. § 102(a)(1). Ex. 1005 (Agresta) at Cover; Ex. 1003 (Thirman Decl.) ¶ 84.
Dana-Farber	Dana-Farber was published on August 23, 2016 and is therefore prior art under 35 U.S.C. § 102(a)(1). Ex. 1007 (Dana-Farber) at 5; Ex. 1003 (Thirman Decl.) ¶ 84. The reference’s publication date is demonstrated by an affidavit from the Internet Archive bearing that date. <i>Id.</i> at 1-2; <i>Valve Corp. v. Ironburg Inventions Ltd.</i> , 8 F.4th 1364, 1374-75 (Fed. Cir. 2021); MPEP § 2128(II)(E); Ex. 1003 (Thirman Decl.) ¶¶ 85-86.
Grace Presentation	Grace Presentation was published on October 7, 2017 and is therefore prior art under 35 U.S.C. § 102(a)(1). Ex. 1008

	(Grace Presentation) at 15; Ex. 1003 (Thirman Decl.) ¶ 84. The reference’s publication date is demonstrated by an affidavit from the Internet Archive bearing that date. <i>Id.</i> at 1-2; <i>Valve</i> , 8 F.4th at 1374-75; MPEP § 2128(II)(E); Ex. 1003 (Thirman Decl.) ¶¶ 87-88.
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1. Claim 1 Would Have Been Obvious

Claim 1 recites a method of treating hemolytic anemia by administering about 10, about 40, about 100, or about 200 mg/day of mitapivat and a moderate inducer of CYP3A4/5. Ex. 1001 (’049 patent), Claim 1; Ex. 1003 (Thirman Decl.) ¶ 89. Claim 1 would have been obvious over the combination of Agresta, Dana-Farber, Grace Presentation, and the knowledge of a POSA. Ex. 1003 (Thirman Decl.) ¶ 89.

a. Agresta Discloses Treatment of Hemolytic Anemia Using Mitapivat and Co-Administering Mitapivat with Other Drugs

Agresta teaches methods for treating hemolytic anemia by administering mitapivat. Ex. 1005 (Agresta) at 25 (disclosing “a method for treating hemolytic anemia . . . comprising administering to a subject in need thereof a therapeutically effective amount of . . . [mitapivat]”), 51 (Claim 17 reciting same); Ex. 1003 (Thirman Decl.) ¶ 90; Section IV.A, *supra*. One type of hemolytic anemia that Agresta discloses treating is PKD, including in a Phase 2 clinical study. Ex. 1003 (Thirman Decl.) ¶ 90; Ex. 1005 (Agresta) at 37-38; *see also id.* at 19 (disclosing a

method of treating PKD); 37-47 (disclosing examples relating to PKD treatment, including Phase 2 clinical study protocol).

Agresta contemplates administering mitapivat in combination with “one or more additional therapeutic or prophylactic agents” as part of a “multiple dose regimen.” Ex. 1005 (Agresta) at 36; Ex. 1003 (Thirman Decl.) ¶ 91. Indeed, a POSA would have understood that co-administration of multiple drugs is common, given the multiple medical conditions that patients may have and the need to treat those conditions. Ex. 1010 (Mutalik) at 2; Ex. 1003 (Thirman Decl.) ¶ 91.

Because, as discussed above, the prior art taught administering mitapivat to treat PKD, a POSA would have understood that logical candidates for co-administered drugs are those also administered to those suffering from PKD, for example, to treat a comorbidity. Ex. 1003 (Thirman Decl.) ¶ 92; *In re Kerkhoven*, 626 F.2d 846, 850 (C.C.P.A. 1980) (holding “*prima facie* obvious” combining two compositions, reasoning it “flows logically” to combine compositions having the same purpose but taught individually in the prior art). A POSA would have been aware of such drugs. Ex. 1003 (Thirman Decl.) ¶ 92.

One example would have been phenobarbitone (also known as phenobarbital), Ex. 1006 (Gordon-Smith) at 10; Ex. 1013 (Hackman) at 3, which, as discussed below, a POSA would have known to be a moderate CYP3A4 inducer. Ex. 1003 (Thirman Decl.) ¶ 93. A POSA would have known that PKD

causes not only hemolytic anemia but also hyperbilirubinemia (elevated bilirubin levels in the blood). Ex. 1003 (Thirman Decl.) ¶ 93; Ex. 1006 (Gordon-Smith) at 9-10; Ex. 1013 (Hackman) at 375. To manage hyperbilirubinemia, the prior art taught administering phenobarbital.⁶ Ex. 1003 (Thirman Decl.) ¶ 93; Ex. 1006 (Gordon-Smith) at 10; Ex. 1013 (Hackman) at 3.

Another example would have been bosentan, which, as discussed below, a POSA would also have known to be a moderate CYP3A4 inducer. Ex. 1003 (Thirman Decl.) ¶ 95. A POSA would have known that pulmonary arterial hypertension (PAH) is a “well-known complication in patients with hemoglobinopathies” and that PAH is “closely related to the hemolytic anemia.” *Id.*; Ex. 1016 (Bachmeyer) at 2. Thus PAH was a potential complication of PKD. *Id.* To manage PAH, the prior art taught administering bosentan, including, as in Bachmeyer, to a PKD patient. Ex. 1016 (Bachmeyer) at 3; Ex. 1015 (van Giersbergen) at 1; Ex. 1003 (Thirman Decl.) ¶ 95.

⁶ A POSA would further have known, for example, that co-administration of mitapivat and phenobarbital may arise in the treatment of patients who have both hemolytic anemia and epilepsy, as phenobarbital is an “effective anti-epileptic drug.” Ex. 1014 (Ilangaratne) at 1; Ex. 1003 (Thirman Decl.) ¶ 94.

At the same time, a POSA would have been aware that when co-administering drugs, interactions between those drugs may arise, commonly when one drug is metabolized by cytochrome P450 enzyme, while another drug modulates that enzyme's activity. Ex. 1010 (Mutalik) at 1-2; Ex. 1012 (Clark) at 1; Ex. 1003 (Thirman Decl.) ¶ 96; Section IV.A, *supra*. Here, Agresta identifies CYP3A4 as “the major route of . . . metabolism” for mitapivat. Ex. 1005 (Agresta) at 42; Ex. 1003 (Thirman Decl.) ¶ 96. A POSA would thus have recognized a potential drug-drug interaction when co-administering mitapivat with a CYP3A4 inducer such as phenobarbital, which a POSA would have known is a moderate inducer. Ex. 1003 (Thirman Decl.) ¶ 96; Ex. 1010 (Mutalik) at 12-13. A POSA would have likewise understood bosentan to be a moderate CYP3A4 inducer. Ex. 1003 (Thirman Decl.) ¶ 96; Ex. 1015 (van Giersbergen) at 259; *see also* Ex. 1010 (Mutalik) at 12-13 (describing bosentan as a “common inducer” of cytochrome P450). Indeed, a POSA would have been aware of several examples of such inducers. Ex. 1010 (Mutalik) at 13-14; Ex. 1003 (Thirman Decl.) ¶ 97. A POSA would have co-administered those inducers with mitapivat when the need for those inducers arose. Ex. 1010 (Mutalik) at 2; Ex. 1003 (Thirman Decl.) ¶ 97.

Agresta thus teaches treating a hemolytic anemia patient by co-administering mitapivat with other drugs. Ex. 1003 (Thirman Decl.) ¶ 98. Further, a POSA

would have understood such drugs to include moderate CYP3A4 inducers and that such drugs may give rise to a drug-drug interaction with mitapivat. *Id.*

b. Dana-Farber Teaches Exclusion Criteria for a Mitapivat Clinical Trial that Prohibit Strong CYP3A4 Inducers but Not Moderate Inducers

Dana-Farber further details the protocol for the Agresta Phase 2 study of mitapivat in PKD patients, including inclusion and exclusion criteria⁷. Ex. 1007 (Dana-Farber) at 5-6; Ex. 1003 (Thirman Decl.) ¶ 99; Section V.B.1.a, *supra*.

Dana-Farber teaches that patients taking strong CYP3A4 inducers were excluded from the study, while at the same patients taking moderate inducers were not excluded. Ex. 1007 (Dana-Farber) at 6 (Exclusion Criterion #12); Ex. 1003 (Thirman Decl.) ¶ 100. A POSA would thus have understood PKD patients taking moderate CYP3A4 inducers—such as those receiving phenobarbitone or bosentan—could be enrolled and treated with mitapivat. Ex. 1003 (Thirman Decl.) ¶ 100. That understanding, taken together with the positive results of this study, as discussed below, demonstrates that a POSA would have been able to co-administer

⁷ Inclusion criteria define which patients are permitted to enroll in a clinical trial, while exclusion criteria define which patients are prohibited from enrolling in a clinical trial. Ex. 1003 (Thirman Decl.) ¶ 99; Ex. 1007 (Dana-Farber) at 5-6.

mitapivat and a moderate CYP3A4 inducer. Ex. 1003 (Thirman Decl.) ¶ 100; Section V.B.1.c, *infra*.

c. Grace Presentation Teaches Positive Results for the Mitapivat Clinical Trial, Including Safe and Effective Doses

Grace Presentation teaches positive results from the same Phase 2 study discussed in Agresta and Dana-Farber. Ex. 1008 (Grace Presentation) at 21-31; Ex. 1003 (Thirman Decl.) ¶ 101. Specifically, Grace Presentation teaches that Phase 2 study patients were effectively treated for PKD and does not report any difficulty with treating patients receiving both mitapivat and moderate CYP3A4 inducers as permitted by Dana-Farber. *Id.*; Ex. 1007 (Dana-Farber) at 5-6. A POSA would thus have understood that he or she would have been able to co-administer mitapivat and a moderate CYP3A4 inducer. Ex. 1003 (Thirman Decl.) ¶ 101.

Indeed, a POSA would have known that drug-drug interactions, such as those involving moderate CYP3A4 inducers and mitapivat are routinely managed by physicians, when aware of such interactions. *Id.* ¶ 102; Ex. 1010 (Mutalik) at 24 (“With all the due awareness of possibility of a potential drug interaction, the prescriber should be able to recognise it and then plan the appropriate action.”). Here, a POSA would have been aware of an interaction between mitapivat and a CYP3A4 inducer, as discussed above, permitting a physician to manage the

interaction. Ex. 1003 (Thirman Decl.) ¶ 102; Ex. 1010 (Mutalik) at 24; Section IV.A, *supra*.

A POSA would further have known that a key way to manage a drug-drug interaction, when necessary, was to adjust the dose of a drug affected by the interaction. Ex. 1003 (Thirman Decl.) ¶ 103; Ex. 1010 (Mutalik) at 24; *see also id.* at 19. That is because a POSA would have recognized that administration of a cytochrome P450 inducer reduced the concentration of the affected drug in the body, Ex. 1010 (Mutalik) at 12-13, which could be counteracted by an increased dose to increase that concentration, Ex. 1017 (Le) at 2-4 (disclosing that increasing mitapivat dose increases drug concentration, as well as the drug's effects); Ex. 1012 (Clark) at 1, 2, 4, 5, 6 (disclosing increasing dose of the drug warfarin to counteract reduced concentration resulting from administering a cytochrome P450 inducer). Ex. 1003 (Thirman Decl.) ¶ 103.

A POSA would thus have selected a mitapivat dose for co-administration with a moderate CYP3A4 inducer that is sufficient to compensate for the interaction between the drugs. Ex. 1003 (Thirman Decl.) ¶ 104. A POSA would have utilized Grace Presentation's disclosures to do so, given that patients in the disclosed study were permitted to receive moderate CYP3A4 inducers. *Id.*; Section V.B.1.b, *supra*.

Regarding dosing, Grace Presentation taught that the Phase 2 study protocol provided 50 mg and 300 mg twice daily of mitapivat as starting doses, and further permitted dose adjustment. Ex. 1003 (Thirman Decl.) ¶ 105; Ex. 1008 (Grace Presentation) at 23; *see also* Ex. 1005 (Agresta) at 45. Accounting for dose adjustments, study patients received mitapivat doses in a range between 5 mg once daily and 300 mg twice daily (5 to 600 mg/day) of mitapivat. *Id.*

Grace Presentation further taught that doses of < 25, 25, 50, 100, 150, 200, and 300 mg twice daily were effective, as indicated by hemoglobin increases, and were “well tolerated.” Ex. 1008 (Grace Presentation) at 19 (disclosing that hemoglobin changes are “indicators of clinical activity”), 21, 26-31 (reporting results); Ex. 1003 (Thirman Decl.) ¶ 106; *see also* Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8 (disclosing dosage amounts); *id.* at 46 (disclosing that hemoglobin changes are “indicators of clinical activity”). Significantly, 50 and 100 mg twice daily total 100 mg and 200 mg per day, respectively, thus meeting the “about 100 mg” and “about 200 mg” doses recited in Claim 1. Ex. 1003 (Thirman Decl.) ¶ 106.

Moreover, arriving at doses recited in the claims would have been a matter of routine optimization. Ex. 1017 (Le) at 2 (publication by several Agios authors, including inventor Yang, describing dose selection as “optimiz[ation]”); Ex. 1003 (Thirman Decl.) ¶ 107. A POSA would have optimized the mitapivat dose because

it was recognized as a result-effective variable. *Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1348 (Fed. Cir. 2024) (holding that routine optimization of a parameter recognized as result-effective by the prior art is “normally obvious”); Ex. 1003 (Thirman Decl.) ¶ 107. That is because, as discussed above, adjusting dose was recognized as a routine way to manage a drug-drug interaction to ensure adequate drug concentration, and thus efficacy. Ex. 1003 (Thirman Decl.) ¶ 107; Ex. 1010 (Mutalik) at 24; *see also id.* at 19; Ex. 1017 (Le) at 2-4; Ex. 1012 (Clark) at 1, 2, 4, 5, 6.

Here, a POSA would have been able to arrive at an optimal mitapivat dose by routine adjustment within the dosage options provided by the prior art. Ex. 1003 (Thirman Decl.) ¶ 108; *Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1062 (Fed. Cir. 2024) (holding claimed daily dose obvious, reasoning that “where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.”) (citation omitted); *Amgen Inc. v. Sandoz Inc.*, 66 F.4th 952, 968 (Fed. Cir. 2023) (holding claims obvious, explaining that dose adjustments are “well-known and obvious” to a POSA); *Merck & Co. v. Biocraft Lab’ys, Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (holding claims obvious, reasoning that the claimed dosages were “reached by means of routine procedures, and produc[ed] only predictable results”).

Indeed, in the Phase 2 study, the investigators performed such adjustment when dosing the subjects, Ex. 1008 (Grace Presentation) at 23, 26, illustrating the routine nature of dose adjustment. Ex. 1003 (Thirman Decl.) ¶ 109. As taught by Grace Presentation, safety and efficacy results were assessed at regular intervals, permitting selection of a dose that appropriately balanced those results. Ex. 1008 (Grace Presentation) at 19, 26; Ex. 1003 (Thirman Decl.) ¶ 109.

Moreover, the claimed mitapivat doses would have been obvious to try, as there were a finite number of predictable solutions and a design need to select a dose. Ex. 1003 (Thirman Decl.) ¶ 110; *See In re Copaxone Consol. Cases*, 906 F.3d 1013, 1025-29 (Fed. Cir. 2018) (explaining obvious to try framework and holding claimed dosing obvious under that framework).

As for a finite number of predictable solutions, Grace Presentation discloses just seven mitapivat dosing levels to be effective. Ex. 1008 (Grace Presentation) at 19, 21, 26-31; Ex. 1003 (Thirman Decl.) ¶ 111. Grace Presentation presents those seven dosing levels as follows:

	< 25 m g B I D
	25 m g B I D
	50 m g B I D
	100 m g B I D
	150 m g B I D
	200 m g B I D
	300 m g B I D

Ex. 1008 (Grace Presentation) at 26; Ex. 1003 (Thirman Decl.) ¶ 111. As for a design need, for the reasons discussed above, there was a design need to utilize a mitapivat dose to counteract the known interaction with CYP3A4 inducers. Ex. 1003 (Thirman Decl.) ¶ 111.

As such, selecting from among seven identified dosing levels in view of the design need would have been obvious to try. *Id.* ¶ 112; *Amgen*, 66 F.4th at 967-68 (holding dosing regimen obvious where patent challenger asserted there were eighteen possible options).

* * *

For the foregoing reasons, Claim 1 would have been obvious. Ex. 1003 (Thirman Decl.) ¶ 113.

2. Claims 8, 9, and 14 Would Have Been Obvious

a. It Would Have Been Obvious to Administer About 200 mg/Day and About 100 mg Twice Per Day (Claims 8 and 9)

Claim 8 depends from Claim 1 and further recites that the subject is administered about 200 mg/day of mitapivat. Ex. 1001 ('049 patent), Claim 8; Ex. 1003 (Thirman Decl.) ¶ 114. Claim 9 depends from Claim 8 and further recites that the subject is administered about 100 mg of mitapivat twice per day. Ex. 1001 ('049 patent), Claim 9; Ex. 1003 (Thirman Decl.) ¶ 114. Claims 8 and 9 would have been obvious over Agresta in view of Dana-Farber, Grace Presentation, and

the knowledge of a POSA for the reasons discussed above regarding Claim 1 and the reasons that follow. Ex. 1003 (Thirman Decl.) ¶ 114; Section V.B.1, *supra*.

Administering about 100 mg/dose twice daily would have been obvious for each of the same reasons that the claimed doses of Claim 1 would have been obvious. Ex. 1003 (Thirman Decl.) ¶ 115. First, Agresta expressly discloses “about 100 mg” as a dose for twice-daily oral administration, totaling 200 mg/day. *Id.*; Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8. Second, Grace Presentation confirms that this dose was safe and effective in PKD patients. Ex. 1008 (Grace Presentation) at 23, 26-31; Ex. 1003 (Thirman Decl.) ¶ 115. Third, a POSA would have arrived at the dose via routine optimization. Ex. 1003 (Thirman Decl.) ¶ 115; *see* Section V.B.1.c, *supra*. Fourth, it would have been obvious to try. *Id.*

For the foregoing reasons, Claims 8 and 9 would have been obvious. Ex. 1003 (Thirman Decl.) ¶ 116.

b. It Would Have Been Obvious to Orally Administer Mitapivat as Part of a Tablet Composition (Claim 14)

Claim 14 depends from Claim 9 (and therefore from Claims 8 and 1) and additionally recites that the mitapivat is orally administered as part of a tablet composition. Ex. 1001 ('049 patent), Claim 14; Ex. 1003 (Thirman Decl.) ¶ 117. Claim 14 would have been obvious over Agresta in view of Dana-Farber, Grace Presentation, and the knowledge of a POSA for the reasons discussed above

regarding Claims 1, 8, and 9 and the reasons that follow. Ex. 1003 (Thirman Decl.) ¶ 117; Sections V.B.1-2.a, *supra*.

Agresta expressly discloses that mitapivat may be formulated as “tablets” and administered “orally.” Ex. 1003 (Thirman Decl.) ¶ 118; Ex. 1005 (Agresta) at 35. Further, the Phase 2 clinical study described in Agresta specifically administered mitapivat to PKD patients using oral capsules. Ex. 1005 (Agresta) at 45; Ex. 1003 (Thirman Decl.) ¶ 118. The positive results of the study support use of tablets because tablets, like capsules, are solid oral dosage forms. Ex. 1005 (Agresta) at 35 (explaining that “any orally acceptable dosage form,” including tablets and capsules, may be used); Ex. 1003 (Thirman Decl.) ¶ 118. Section V.B.2.c, *supra*.

For the foregoing reasons, Claim 14 would have been obvious. Ex. 1003 (Thirman Decl.) ¶ 119.

3. A POSA Would Have Been Motivated to Combine the References

A POSA would have been motivated to combine Agresta, Dana-Farber, and Grace Presentation. Ex. 1003 (Thirman Decl.) ¶ 120. That is because those references all address treatment of the same disease (PKD) using the same drug (mitapivat) in the same Phase 2 clinical study. *Id.*; Section V.B.1, *supra*.

A POSA would also have been motivated to combine these references in view of the nature of the problem to be solved, i.e., a drug-drug interaction

between mitapivat and CYP3A4 inducers. Ex. 1003 (Thirman Decl.) ¶ 121.

Agresta teaches co-administration of mitapivat with other drugs, during which a POSA would have recognized a potential drug-drug interaction between mitapivat and CYP3A4 inducers. Ex. 1003 (Thirman Decl.) ¶ 121; Section V.B.1.a, *supra*.

A POSA would thus have been motivated to investigate co-administration of mitapivat and a moderate CYP3A4 inducer when treating PKD, and how to dose mitapivat when doing so. Ex. 1003 (Thirman Decl.) ¶ 121; Section V.B.1.a, *supra*.

A POSA would have looked to Dana-Farber and Grace Presentation, which provide procedures and results from the Phase 2 trial that would have allowed a POSA to confirm that such administration is feasible and to arrive at a mitapivat dose. Ex. 1003 (Thirman Decl.) ¶ 121; Sections V.B.1.b-c, *supra*.

For the foregoing reasons, a POSA would have been motivated to combine Agresta, Dana-Farber, and Grace Presentation. Ex. 1003 (Thirman Decl.) ¶ 122.

4. A POSA Would Have Had a Reasonable Expectation of Success

A POSA would have had a reasonable expectation of success in arriving at the claimed invention based on the prior art teachings discussed above. Section V.B.1, *supra*; Ex. 1003 (Thirman Decl.) ¶ 123.

In particular, the results of the Phase 2 trial would have provided a reasonable expectation of success. Section V.B.1.c, *supra*; Ex. 1003 (Thirman Decl.) ¶ 124. In that trial, patients were treated in a manner that meets the claims:

the patients were treated for PKD using mitapivat at two of the claimed dosing alternatives, and were permitted to receive a moderate CYP3A4 inducer. *Id.* And Grace Presentation indicates that the disease was effectively treated without raising any concerns about co-administration of mitapivat with a moderate CYP3A4 inducer. *Id.*

A reasonable expectation of success would further have been supported by the fact that POSAs routinely, and successfully, managed drug-drug interactions and would have been able to do so by routine dose adjustment. Section V.B.1.c, *supra*; Ex. 1003 (Thirman Decl.) ¶ 125.

A POSA would also have had a reasonable expectation of success for the reasons that a POSA would have had motivation to combine. Section V.B.3, *supra*; Ex. 1003 (Thirman Decl.) ¶ 126.

For the foregoing reasons, a POSA would have had a reasonable expectation of success in arriving at the claimed invention. Ex. 1003 (Thirman Decl.) ¶ 127.

5. Lack of Secondary Considerations

Petitioner is not aware of any evidence of secondary considerations of nonobviousness. Ex. 1003 (Thirman Decl.) ¶ 128. Notably, Patent Owner made no assertion of secondary considerations during the prosecution of the '049 patent. *Id.*; Ex. 1002 ('049 prosecution history).

6. Conclusion

For the foregoing reasons, the combination of Agresta, Dana-Farber, Grace Presentation, and the knowledge of a POSA satisfy each of the limitations of the challenged claims. Ex. 1003 (Thirman Decl.) ¶ 129. Further, a POSA would have been motivated to combine those references and had a reasonable expectation of success at arriving at the claimed invention. *Id.*

C. Ground 3: Claims 1, 8, 9, and 14 Would Have Been Obvious Under 35 U.S.C. § 103 over Agresta, Dana-Farber, Grace Abstract, and the Knowledge of a POSA

Claims 1, 8, 9, and 14 are unpatentable as obvious under 35 U.S.C. § 103 over Agresta, Dana-Farber, Grace Abstract, and the knowledge of a POSA. Ex. 1003 (Thirman Decl.) ¶ 130.

Agresta and Dana-Farber were each references that served as part of the obviousness combination in Ground 2, along with Grace Presentation. Section V.B, *supra*; Ex. 1003 (Thirman Decl.) ¶ 131. In Ground 3, Grace Abstract replaces Grace Presentation. Ex. 1003 (Thirman Decl.) ¶ 131. Grace Abstract provides similar teachings to Grace Presentation, though in the form of an abstract. *Id.*; Ex. 1009 (Grace Abstract) at 1; Section V.B.1.c, *supra*; Section V.C.1, *infra*. Together, these references satisfy all the limitations of Claims 1, 8, 9, and 14. Ex. 1003 (Thirman Decl.) ¶ 131.

A POSA would have thus been motivated to combine these Agresta, Dana-Farber, and Grace Abstract, for the same reasons that a POSA would have been motivated to combine the references of Ground 2. Ex. 1003 (Thirman Decl.) ¶ 132; Section V.C.3, *infra*. And a POSA would have had a reasonable expectation of success for the same reasons set forth in Ground 2. *Id.*

Each of Agresta and Dana-Farber qualify as prior art for the reasons discussed above. Ex. 1003 (Thirman Decl.) ¶ 133; Section V.B, *supra*. Grace Abstract qualifies as prior art for the following reasons:

Reference	Prior Art Status
Grace Abstract	Grace Abstract was published on December 7, 2017 and is therefore prior art under 35 U.S.C. §102(a)(1). Ex. 1009 (Grace Abstract) at 1; Ex. 1003 (Thirman Decl.) ¶ 133.

1. Claim 1 Would Have Been Obvious

Claim 1 recites a method of treating hemolytic anemia by administering about 10, about 40, about 100, or about 200 mg/day of mitapivat and a moderate inducer of CYP3A4/5. Ex. 1001 ('049 patent), Claim 1; Ex. 1003 (Thirman Decl.) ¶ 134. Claim 1 would have been obvious over Agresta, Dana-Farber, Grace Abstract, and the knowledge of a POSA. Ex. 1003 (Thirman Decl.) ¶ 134.

As discussed above, Agresta discloses treatment of hemolytic anemia using mitapivat, including in a Phase 2 clinical trial, and further discloses co-administering mitapivat with other drugs. *Id.* ¶ 135; Section V.B.1.a, *supra*.

Further, a POSA would have understood such drugs to include moderate CYP3A4 inducers, such as phenobarbitone and bosentan, and that such drugs may give rise to a drug-drug interaction with mitapivat. Ex. 1003 (Thirman Decl.) ¶ 135; Section V.B.1.a, *supra*.

As also discussed above, Dana-Farber teaches that in Agresta's Phase 2 trial, patients taking strong CYP3A4 inducers were prohibited from participating in the trial, while at the same time patients taking moderate inducers were **not** prohibited. Ex. 1003 (Thirman Decl.) ¶ 136; Section V.B.1.b, *supra*. Taken together with the disclosures of Grace Abstract, discussed below, a POSA would have understood that PKD patients taking moderate CYP3A4 inducers could be treated with mitapivat. *Id.*

Grace Abstract teaches positive results from the same Phase 2 study discussed in Agresta and Dana-Farber. Ex. 1009 (Grace Abstract) at 1-3; Ex. 1003 (Thirman Decl.) ¶ 137. Specifically, Grace Abstract teaches that Phase 2 study patients were effectively treated for PKD and does not report any difficulty with treating patients receiving both mitapivat and moderate CYP3A4 inducers as permitted by Dana-Farber. *Id.*; Ex. 1007 (Dana-Farber) at 5-6. A POSA would thus have understood that he or she would have been able to co-administer mitapivat and a moderate CYP3A4 inducer. Ex. 1003 (Thirman Decl.) ¶ 137.

Indeed, a POSA would have known that drug-drug interactions, such as those involving moderate CYP3A4 inducers and mitapivat are routinely managed by physicians, when aware of such interactions. *Id.* ¶ 138; Ex. 1010 (Mutalik) at 24. Here, a POSA would have been aware of an interaction between mitapivat and a CYP3A4 inducer, as discussed above, permitting a physician to manage the interaction. Ex. 1003 (Thirman Decl.) ¶ 138; Ex. 1010 (Mutalik) at 24; Section IV.A, *supra*.

A POSA would further have known that a key way to manage a drug-drug interaction, when necessary, was to adjust the dose of a drug affected by the interaction. Ex. 1003 (Thirman Decl.) ¶ 139; Ex. 1010 (Mutalik) at 24; *see also id.* at 19. That is because a POSA would have recognized that administration of a cytochrome P450 inducer reduced the concentration of the affected drug in the body, Ex. 1010 (Mutalik) at 12-13, which could be counteracted by an increased dose to increase that concentration, Ex. 1017 (Le) at 2-4; Ex. 1012 (Clark) at 1, 2, 4, 5, 6; Ex. 1003 (Thirman Decl.) ¶ 139.

A POSA would thus have selected a mitapivat dose for co-administration with a moderate CYP3A4 inducer that is sufficient to compensate for the interaction between the drugs. Ex. 1003 (Thirman Decl.) ¶ 140. A POSA would have utilized Grace Abstract's disclosures to do so, given that patients in the

disclosed study were permitted to receive moderate CYP3A4 inducers, as discussed above. *Id.*; Section V.B.1.b, *supra*.

Regarding dosing, Grace Abstract taught that the Phase 2 study protocol provided 50 mg and 300 mg twice daily of mitapivat as starting doses, and further permitted dose adjustment. Ex. 1003 (Thirman Decl.) ¶ 141; Ex. 1009 (Grace Abstract) at 2-3; *see also* Ex. 1005 (Agresta) at 45. Accounting for dose adjustments, study patients received mitapivat doses in a range between 5 mg once daily and 300 mg twice daily (5 to 600 mg/day) of mitapivat. *Id.*

Grace Abstract further taught that doses in the range of 5 to 300 mg twice daily were effective, as indicated by hemoglobin increases, and were “well tolerated.” Ex. 1009 (Grace Abstract) at 2-3; Ex. 1003 (Thirman Decl.) ¶ 142; *see also* Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8 (disclosing dosage amounts); *id.* at 46 (disclosing that hemoglobin changes are “indicators of clinical activity”).

Each dose recited in the challenged claims—about 10 mg/day, about 40 mg/day, about 100 mg/day, or about 200 mg/day—thus falls within the range of safe and effective doses reported by Grace Abstract. Ex. 1009 (Grace Abstract) at 2-3; Ex. 1003 (Thirman Decl.) ¶ 143. Where, as here, a claimed value falls within a range disclosed in the prior art, a *prima facie* case of obviousness exists. *Gen. Hosp. Corp. v. Sienna Biopharms., Inc.*, 888 F.3d 1368, 1373–74 (Fed. Cir. 2018); *Galderma Lab’ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013).

Further, claimed doses do not merely appear in the prior art within a range; two of them (about 100 mg and about 200 mg) are expressly disclosed by Agresta. Ex. 1003 (Thirman Decl.) ¶ 144; Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8.

Moreover, arriving at the claimed doses would have been a matter of routine optimization. Ex. 1017 (Le) at 2 (describing dose selection as “optimiz[ation]”); Ex. 1003 (Thirman Decl.) ¶ 145. A POSA would have optimized the mitapivat dose because it was recognized as a result-effective variable. *Pfizer*, 94 F.4th at 1348; Ex. 1003 (Thirman Decl.) ¶ 145. As discussed above, adjusting dose was recognized as a routine way to manage a drug-drug interaction to ensure adequate drug concentration, and thus efficacy. Ex. 1003 (Thirman Decl.) ¶ 145; Ex. 1010 (Mutalik) at 24; *see also id.* at 19; Ex. 1017 (Le) at 2-4; Ex. 1012 (Clark) at 1, 2, 4, 5, 6.

Here, a POSA would have been able to arrive at an optimal mitapivat dose by routine adjustment within the dosage options provided by the prior art. Ex. 1003 (Thirman Decl.) ¶ 146; *Salix*, 98 F.4th at 1062; *Amgen*, 66 F.4th at 968; *Merck*, 874 F.2d at 809.

Indeed, in the Phase 2 study, the investigators performed such adjustment when dosing the subjects, Ex. 1009 (Grace Abstract) at 2-3, illustrating the routine nature of dose adjustment. Ex. 1003 (Thirman Decl.) ¶ 147. As taught by Grace Abstract, safety and efficacy results were assessed at regular intervals, permitting

selection of a dose that appropriately balanced those results. Ex. 1009 (Grace Abstract) at 2-3; Ex. 1003 (Thirman Decl.) ¶ 147.

Moreover, the claimed mitapivat doses would have been obvious to try, as there were a finite number of predictable solutions and a design need to select a dose. Ex. 1003 (Thirman Decl.) ¶ 148; *see Copaxone*, 906 F.3d at 1025-29.

As for a finite number of predictable solutions, a POSA would have understood from Agresta that there were eleven possible twice-daily dosing options within Grace Abstract's effective range: about 50–300 mg at 25 mg increments. Ex. 1003 (Thirman Decl.) ¶ 149; Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8 (disclosing “. . . about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg”); *see also id.* at 45 (disclosing 25 mg dosage form size for use in Phase 2 study).⁸ As for a design need, for the reasons discussed above, there was a design need to utilize a mitapivat dose to counteract the known interaction between mitapivat and CYP3A4 inducers. Ex. 1003 (Thirman Decl.) ¶ 151. Selecting from among eleven identified dosing levels in view of the design need

⁸ Even considering a 5 mg dose option, as well as an additional option or options between 5 mg and 50 mg, the number of options would remain finite. Ex. 1003 (Thirman Decl.) ¶ 150.

would have been obvious to try. *Id.*; *Amgen*, 66 F.4th at 967-68 (holding dosing regimen obvious where patent challenger asserted there were eighteen possible options).

For the foregoing reasons, Claim 1 would have been obvious. Ex. 1003 (Thirman Decl.) ¶ 152.

2. Claims 8, 9, and 14 Would Have Been Obvious

a. It Would Have Been Obvious to Administer About 200 mg/Day and About 100 mg Twice Per Day (Claims 8 and 9)

Claim 8 depends from Claim 1 and further recites that the subject is administered about 200 mg/day of mitapivat. Ex. 1001 ('049 patent), Claim 8; Ex. 1003 (Thirman Decl.) ¶ 153. Claim 9 depends from Claim 8 and further recites that the subject is administered about 100 mg of mitapivat twice per day. Ex. 1001 ('049 patent), Claim 9; Ex. 1003 (Thirman Decl.) ¶ 153. Claims 8 and 9 would have been obvious over Agresta in view of Dana-Farber, Grace Abstract, and the knowledge of a POSA for the reasons discussed above regarding Claim 1 and the reasons that follow. Ex. 1003 (Thirman Decl.) ¶ 153; Section V.C.1, *supra*.

Administering about 100 mg/dose twice daily would have been obvious for each of the same reasons that the claimed doses of Claim 1 would have been obvious. Ex. 1003 (Thirman Decl.) ¶ 154. First, Agresta expressly discloses “about 100 mg” as a dose for twice-daily oral administration, totaling 200 mg/day.

Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8; Ex. 1003 (Thirman Decl.) ¶ 154.

Second, Grace Abstract confirms that this dose fell within the range of safe and effective doses in PKD patients. Ex. 1009 (Grace Abstract) at 2-3; Ex. 1003 (Thirman Decl.) ¶ 154.

Third, a POSA would have arrived at the dose via routine optimization. Ex. 1003 (Thirman Decl.) ¶ 155; *see* Section V.C.1, *supra*. Fourth, it would have been obvious to try. *Id.*

For the foregoing reasons, Claims 8 and 9 would have been obvious. Ex. 1003 (Thirman Decl.) ¶ 156.

b. It Would Have Been Obvious to Orally Administer Mitapivat as Part of a Tablet Composition (Claim 14)

Claim 14 depends from Claim 9 (and therefore from Claims 8 and 1) and additionally recites that the mitapivat is orally administered as part of a tablet composition. Ex. 1001 ('049 patent), Claim 14; Ex. 1003 (Thirman Decl.) ¶ 157. Claim 14 would have been obvious over Agresta in view of Dana-Farber, Grace Abstract, and the knowledge of a POSA for the reasons discussed above regarding Claims 1, 8, and 9 and the reasons that follow. Ex. 1003 (Thirman Decl.) ¶ 157; Sections V.C.1, V.C.2.a, *supra*.

Agresta expressly discloses that mitapivat may be formulated as “tablets” and administered “orally.” Ex. 1005 (Agresta) at 35; Ex. 1003 (Thirman Decl.) ¶ 158. Further, the Phase 2 clinical study described in Agresta specifically

administered mitapivat to PKD patients using oral capsules. Ex. 1005 (Agresta) at 45; Ex. 1003 (Thirman Decl.) ¶ 158. The positive results of the study support use of tablets, because tablets, like capsules, are solid oral dosage forms. Ex. 1005 (Agresta) at 35 (explaining that “any orally acceptable dosage form,” including tablets and capsules, may be used); Ex. 1003 (Thirman Decl.) ¶ 158; Section V.C.1, *supra*.

For the foregoing reasons, Claim 14 would have been obvious. Ex. 1003 (Thirman Decl.) ¶ 159.

3. A POSA Would Have Been Motivated to Combine the References

Given the similar disclosures of the references of Grounds 2 and 3, a POSA would have been motivated to combine the references of Ground 3, the same reasons that a POSA would have been motivated to combine the references of Ground 2. Section V.B.3, *supra*; Ex. 1003 (Thirman Decl.) ¶ 160.

4. A POSA Would Have Had a Reasonable Expectation of Success

Given the similar disclosures of the references of Grounds 2 and 3, a POSA would have had a reasonable expectation of success as to Ground 3 for the same reasons that a POSA would have had a reasonable expectation of success as to Ground 2. Section V.B.4, *supra*; Ex. 1003 (Thirman Decl.) ¶ 161.

5. Lack of Secondary Considerations

Petitioner is not aware of any evidence of secondary considerations of nonobviousness. Ex. 1003 (Thirman Decl.) ¶ 162. Notably, Patent Owner made no assertion of secondary considerations during the prosecution of the '049 patent. *Id.*; Ex. 1002 ('049 prosecution history).

6. Conclusion

For the foregoing reasons, the combination of Agresta, Dana-Farber, Grace Abstract, and the knowledge of a POSA satisfy each of the limitations of the challenged claims. Ex. 1003 (Thirman Decl.) ¶ 163. Further, a POSA would have been motivated to combine those references and had a reasonable expectation of success at arriving at the claimed invention. *Id.*

D. Ground 4: Claim 19 Would Have Been Obvious Under 35 U.S.C. § 103 over Agresta, Dana-Farber, Grace Presentation or Grace Abstract, Sizemore, and the Knowledge of a POSA

Claim 19 is unpatentable as obvious under 35 U.S.C. § 103 over Agresta, Dana-Farber, Grace Presentation or Grace Abstract, Sizemore, and the knowledge of a POSA. Ex. 1003 (Thirman Decl.) ¶ 164. Claim 19 depends from claims previously addressed in Grounds 2 and 3 (Claims 1, 8, 9, and 14). *Id.*; Sections V.B-C, *supra*. As discussed above, those claims would have been obvious over Agresta, Dana-Farber, Grace Presentation, and the knowledge of a POSA (Ground 2), or, alternatively, Agresta, Dana-Farber, Grace Abstract, and the knowledge of a POSA (Ground 3). *Id.* Ground 4 relies upon the foregoing arguments and adds

Sizemore to address Claim 19. Ex. 1003 (Thirman Decl.) ¶ 164. Together, these references satisfy all the limitations of Claim 19. *Id.*

As discussed further below, a POSA would have been motivated to combine these references, because the references all address treatment of the same disease (PKD) using the same drug (mitapivat) and address the same clinical study.

Section V.D.2, *infra*; Ex. 1003 (Thirman Decl.) ¶ 165. A POSA would further have been motivated to combine these references in view of the nature of the problem to be solved, i.e., a drug-drug interaction between mitapivat and CYP3A4 inducers. *Id.* And a POSA would have had a reasonable expectation of success for the same reasons discussed in Grounds 2 and 3, as well as based upon Sizemore's disclosures. Section V.D.3, *infra*; Ex. 1003 (Thirman Decl.) ¶ 165.

1. Claim 19 Would Have Been Obvious

Claim 19 depends from Claim 14 (and therefore from Claims, 9, 8, and 1) and additionally recites that the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate. Ex. 1001 ('049 patent), Claim 19; Ex. 1003 (Thirman Decl.) ¶ 166. Claim 19 would have been obvious over Agresta in view of Dana-Farber, Grace Presentation or Grace Abstract, Sizemore and the knowledge of a POSA for the reasons discussed above regarding Claims 1, 8, 9, and 14 in Grounds 2 or 3 and the reasons that follow. Ex. 1003 (Thirman Decl.) ¶ 166; Sections V.B-C, *supra*.

As explained above in Ground 1, Sizemore discloses, *inter alia*, uses for pharmaceutical compositions comprising mitapivat for treating conditions associated with pyruvate kinase. Section V.A, *supra*; Ex. 1003 (Thirman Decl.) ¶ 167. Sizemore specifically discloses that scientists developed mitapivat to treat PKD and investigated mitapivat in the same Phase 2 trial discussed in the other combination references of this Ground. Ex. 1004 (Sizemore) at ¶¶ 0003, 0004; Ex. 1003 (Thirman Decl.) ¶ 167; Sections V.B.1, V.C.1, *supra*. As pertinent here, Sizemore discloses pharmaceutical compositions comprising mitapivat for treating PKD. Ex. 1003 (Thirman Decl.) ¶ 167; Ex. 1004 (Sizemore) at ¶ 0006; *see also id.* at Abstract.

Sizemore discloses a mitapivat tablet formulation comprising the ingredients recited by Claim 19: microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate. Ex. 1004 (Sizemore) at ¶¶ 00114, 00116, 00219, Claims 29-30; Ex. 1003 (Thirman Decl.) ¶ 168; *see also* Ex. 1004 (Sizemore) at ¶ 0003 (identifying disclosed compound as mitapivat). Further, Sizemore taught helpful information to a POSA to make a tablet using those ingredients, including exemplary ingredient amounts, procedures to make the tablets, as well as further ingredients to bolster the tablets' properties. Ex. 1004 (Sizemore) at ¶¶ 00114, 00116, 00219, Claim 30; *see also id.* ¶¶ 0093-110; Ex. 1003 (Thirman Decl.) ¶ 168.

For the foregoing reasons, Claim 19 would have been obvious. Ex. 1003 (Thirman Decl.) ¶ 169.

2. A POSA Would Have Been Motivated to Combine the References

A POSA would have been motivated to combine Agresta, Dana-Farber, and Grace Presentation or Grace Abstract, and Sizemore. Ex. 1003 (Thirman Decl.) ¶ 170.

Sizemore, like the other combination references, addresses treatment of the same disease (PKD) using the same drug (mitapivat), and further addresses the same Phase 2 clinical study. Ex. 1003 (Thirman Decl.) ¶ 171; Sections V.B-C, V.D.1, *supra*. Moreover, Sizemore, like the other combination references, addresses the problem to be solved, namely the interaction between mitapivat and a CYP3A4 inducer. Ex. 1003 (Thirman Decl.) ¶ 171; Sections V.B-C, V.D.1, *supra*. Sizemore contemplates co-administering mitapivat and a moderate CYP3A4 inducer given that it discloses administering mitapivat (1) with other drugs, (2) to patients not taking **any** CYP3A4 inhibitor, and (3) to patients not taking a **strong** CYP3A4 inducer. Ex. 1003 (Thirman Decl.) ¶ 171; Ex. 1004 (Sizemore) at ¶¶ 0046, 0053.

For the foregoing reasons, a POSA would have been motivated to combine Agresta, Dana-Farber, Grace Presentation or Grace Abstract, and Sizemore. Ex. 1003 (Thirman Decl.) ¶ 172.

3. A POSA Would Have Had a Reasonable Expectation of Success

Given that the references of Grounds 2 and 3 are utilized in Ground 4, a POSA would have had a reasonable expectation of success as to Ground 4 for the same reasons that a POSA would have had a reasonable expectation of success as to Grounds 2 and 3. Sections V.B.4, V.C.4, *supra*; Ex. 1003 (Thirman Decl.) ¶ 173. A POSA would further have had a reasonable expectation of success based on the prior art disclosures discussed immediately above, as well as the reasons that a POSA would have been motivated to combine the references of Ground 4. Sections V.B.3, V.C.3, V.D.2, *supra*; Ex. 1003 (Thirman Decl.) ¶ 173.

4. Lack of Secondary Considerations

Petitioner is not aware of any evidence of secondary considerations of nonobviousness. Ex. 1003 (Thirman Decl.) ¶ 174. Notably, Patent Owner made no assertion of secondary considerations during the prosecution of the '049 patent. *Id.*; Ex. 1002 ('049 prosecution history).

5. Conclusion

For the foregoing reasons, the combination of Agresta, Dana-Farber, Grace Presentation or Grace Abstract, Sizemore, and the knowledge of a POSA satisfy each of the limitations of the challenged claims. Ex. 1003 (Thirman Decl.) ¶ 175. Further, a POSA would have been motivated to combine those references and had a reasonable expectation of success at arriving at the claimed invention. *Id.*

VI. Discretionary Considerations Favor Institution

Discretionary considerations favor institution. If Patent Owner requests discretionary denial, Apotex will separately respond pursuant to the March 26, 2025, Interim Processes for PTAB Workload Management Memorandum.

VII. Conclusion

For the reasons set forth above, the challenged claims are unpatentable as anticipated and obvious. Petitioner respectfully requests *inter partes* review and cancellation of these claims.

Dated: May 18, 2026

Respectfully submitted,

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

Under the provisions of 37 C.F.R. § 42.24(d), the undersigned attorney hereby certifies that the word count for the foregoing petition, excluding table of contents, table of authorities, mandatory notices under 37 C.F.R. § 42.8, certificate of service, and appendix of exhibits or claim listing, is 12,430 according to Microsoft Word. *See* 37 C.F.R. § 42.24(a)(1); 81 Fed. Reg. 24,702–03 (April 27, 2016).

Dated: May 18, 2026

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Lead Counsel for Petitioner

CERTIFICATE OF SERVICE

I hereby certify that on May 18, 2026, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review and accompanying exhibits to be served by Federal Express on the Patent Owner at the following correspondence address of record as listed on the USPTO's Patent Center website:

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Dated: May 18, 2026

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