

Filed on behalf of: Agios Pharmaceuticals, Inc.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

AGIOS PHARMACEUTICALS, INC.,
Patent Owner.

IPR2026-00351
Patent 11,878,049

PATENT OWNER'S PRELIMINARY RESPONSE

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USPTO, P.T.A.B. Trial Practice Guide, § II.B.6 (Claim Construction) (last updated Dec. 12, 2025), https://www.uspto.gov/patents/ptab/trial-practice-guide	17

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
2011	Yonggoo Kim et al., <i>Diagnostic Approaches for Inherited Hemolytic Anemia in the Genetic Era</i> , 52 BLOOD RSCH. 84 (2017) (“Kim 2017”)

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2012	Bernadette Modell & Matthew Darlison, <i>Global Epidemiology of Haemoglobin Disorders and Derived Service Indicators</i> , 86 BULL. WORLD HEALTH ORG. 480 (2008) (“Modell 2008”)
2013	Declaration of Kevin H.M. Kuo in Support of Patent Owner's Preliminary Response (“Kuo Decl.”)
2014	<i>Curriculum Vitae</i> of Kevin H.M. Kuo
2015	Patrick Foy et al., <i>Overall Survival of Patients With Pyruvate Kinase Deficiency in the UK: A Real World Study</i> , 6 eJ. HAEMATOLOGY 1–4 (2025) (“Foy 2025”)
2016	Rachael F. Grace et al., <i>Clinical Spectrum of Pyruvate Kinase Deficiency: Data from the Pyruvate Kinase Deficiency Natural History Study</i> , 131 BLOOD 2183 (2018) (“Grace 2018”)
2017	Ali T. Taher & Maria Domenica Cappellini, <i>How I Manage Medical Complications of β-Thalassemia in Adults</i> , 132 BLOOD 1781 (2018) (“Taher 2018”)
2018	Rachael F. Grace et al., <i>Erythrocyte Pyruvate Kinase Deficiency: 2015 Status Report</i> , 90 AM. J. HEMATOLOGY 825 (2015) (“Grace 2015”)
2019	FDA, <i>FDA Approves First Oral Treatment for Anemia in Thalassemia, An Inherited Blood Disorder</i> (as of Jan. 5, 2026), https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-oral-treatment-anemia-thalassemia-inherited-blood-disorder (last visited Aug. 18, 2026) (“FDA Aqvesme™ Approval”)

Exhibit	Description
2020	Press Release, Agios Pharmaceuticals, Inc., <i>Agios Presents Positive Results from Phase 3 ENERGIZE Study of Mitapivat in Non-Transfusion- Dependent Thalassemia in Plenary Session at the European Hematology Association 2024 Hybrid Congress</i> (June 15, 2024), https://investor.agios.com/news-releases/news-release-details/agios-presents-positive-results-phase-3-energize-study-mitapivat (last visited Aug. 18, 2026) (“ENERGIZE Press Release”)
2021	MALCOLM ROWLAND & THOMAS N. TOZER, CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS: CONCEPTS AND APPLICATIONS (4th ed. 2011) (EXCERPT) (“Rowland & Tozer”)
2022	U.S. Dep’t of Health & Hum. Servs., FDA, Ctr. For Drug Evaluation & Rsch., <i>In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies, Guidance for Industry (DRAFT GUIDANCE)</i> , 47 pp. (Oct. 2017), https://www.fda.gov/media/108130/download (last visited Aug. 19, 2026) (“FDA, In Vitro Metabolism- and Transporter- Mediated DDI Studies”)
2023	U.S. Dep’t of Health & Hum. Servs., FDA, Ctr. For Drug Evaluation & Rsch., <i>Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications, Guidance for Industry (DRAFT GUIDANCE)</i> , 32 pp. (Oct. 2017), https://www.regulations.gov/document/FDA-2017-D-5961-0002 (last visited Aug. 19, 2026) (“FDA, Clinical Drug Interaction Studies”)
2024	Jukka Hakkola et al., <i>Inhibition and Induction of CYP Enzymes in Humans: An Update</i> , 94 ARCHIVES TOXICOLOGY 3671 (2020) (“Hakkola 2020”)
2025	CAPRELSA® (vandetanib) tablets, Prescribing Information, Sanofi Genzyme (Revised Oct. 2018)

Exhibit	Description
2026	AFINITOR [®] (everolimus) / AFINITOR DISPERZ [®] (everolimus) tablets, Prescribing Information, Novartis Pharma Stein AG Novartis Pharms. Corp. (Revised Apr. 2018)
2027	VENCLEXTA [®] (venetoclax) tablets, Prescribing Information, Abbvie Inc. Genentech USA, Inc. (Revised May 2019)
2028	SPRYCEL (dasatinib) tablets, Prescribing Information, Bristol-Myers Squibb Co. (Revised Dec. 2018)

I. Introduction

The first and only FDA-approved drug of its kind, mitapivat is a life-changing drug for treating two inherited hemolytic anemias,¹ rare and debilitating genetic diseases characterized by destruction of red blood cells. But, for patients taking mitapivat, drug-drug interactions (“DDIs”) with concomitant medications (i.e., moderate CYP3A4/5 inducers), which accelerate the breakdown of mitapivat in the body, can force patients to discontinue or avoid therapy with mitapivat altogether. United States Patent No. 11,878,049 (the “’049 Patent”) teaches Agios’s solution to that problem: methods of treating hemolytic anemia with specific doses of mitapivat (about 10, 40, 100 or 200 mg/day) in patients taking a moderate inducer of CYP3A4/5.

Apotex’s Petition is fatally defective. None of the asserted prior art discloses the key claim limitation of co-administration of mitapivat with a moderate CYP3A4/5 inducer. None of the asserted prior art has any data, discussion or disclosure supporting such co-administration. With its anticipation and obviousness challenges, Apotex recycles prior art that is the same or substantially the same as the

¹ Mitapivat is the first and only approved “pyruvate kinase activator”; PYRUKYND[®] is approved to treat pyruvate kinase deficiency (“PKD”) and AQVESME[™] is approved to treat alpha- and beta-thalassemia.

prior art that was already vetted and found deficient by the Examiner in allowing the claims. Apotex's alleged anticipation reference (Sizemore) is directed to crystalline forms of mitapivat, not co-administration of drugs and DDIs. Apotex's obviousness references (Agresta, Dana-Farber and Grace Presentation/Abstract) are directed to clinical trials for mitapivat alone – not to co-administration of drugs or DDIs. And the conclusory opinions of Apotex's expert, Dr. Thirman – that merely parrot Apotex's bare assertions – cannot fill the gap of that critical claim limitation that is missing in the asserted prior art. Nor can Dr. Thirman's hindsight opinions transform complete silence in the asserted prior art into an affirmative teaching.

Apotex's Petition falls short. DDIs for a new drug – especially one that is the first and only in its therapeutic class – are inherently unpredictable; as such, FDA guidelines mandate clinical studies specifically designed to assess DDIs for a new drug. As of the June 14, 2019 priority date, no clinical DDI trials had been reported for mitapivat. With the '049 Patent, Agios was the first to characterize mitapivat DDIs based on mitapivat-specific clinical DDI data. In acknowledgement of such unpredictability, PTAB has denied obviousness challenges directed to DDI patents. *See, e.g., Roxane Laboratories, Inc. v. Vanda Pharms. Inc.*, IPR2016-00690, Paper 8 at 19 (P.T.A.B. Aug. 30, 2016) (denying institution of obviousness challenge to DDI patent because the clinical significance of any DDI “is unpredictable and needs to

be empirically determined”). Such is the case here. Apotex's Petition should be denied.

II. Background

A. Treatment of Rare Hemolytic Anemias With Mitapivat

Inherited hemolytic anemias are a class of rare, debilitating – and even life-threatening – genetic diseases that are characterized by destruction of red blood cells. Ex.2011 (Kim 2017), 001;² Ex.2012 (Modell 2008), 002; Ex.2013 (Kuo Decl.) ¶¶39-40. Examples of inherited hemolytic anemias are PKD (pyruvate kinase deficiency) and thalassemia. Ex.2011 (Kim 2017), 006; Ex.2013 (Kuo Decl.) ¶¶40-42. PKD is extremely rare (3.2 to 8.5 cases per million people in Western populations), but those afflicted have a wide array of chronic complications that affect their quality of life, including iron overload, gallstones, low bone density (increasing fracture risk), as well as high blood pressure in the lung arteries and leg ulcers; from the moment of birth they also have *five times* the risk of death as compared to the normal population. Ex.2015 (Foy 2025), 001-2; Ex.2016 (Grace 2018), 009; Ex.2013 (Kuo Decl.) ¶41. While not as rare, thalassemia is often deadly without treatment, with patients suffering from many of the same complications.

² Except for cites to certain patent documents (Ex.1001, Ex.1004) and expert declarations (Ex.1003, Ex. 2013), all cites are to the stamped pagination.

Ex.2012 (Modell 2008), 002; Ex.2017 (Taher 2018), 001-3, 005; Ex.2013 (Kuo Decl.) ¶42. As of the priority date of the '049 Patent (June 14, 2019), treatment options for inherited hemolytic anemias were invasive (e.g., regular transfusions or splenectomy (for PKD)), and non-curative. Ex.2012 (Modell 2008), 002; Ex.2018 (Grace 2015), 002-3; Ex.2013 (Kuo Decl.) ¶¶43-44.

Mitapivat is a life-changing drug for PKD and thalassemia patients. Ex.1011 (FDA 2022), 21-22, 27, 29; Ex.2019 (FDA Aqvesme™ Approval); Ex.2020 (ENERGIZE Press Release); Ex.2013 (Kuo Decl.) ¶¶43-44. A tablet that is taken twice daily, it is the first and only approved “pyruvate kinase activator,” capable of stimulating the pyruvate kinase enzyme that provides energy in red blood cells and keeps them from breaking down prematurely. Ex.1011 (FDA 2022), 2, 21-22, 27, 29; Ex.2013 (Kuo Decl.) ¶43. Mitapivat is the first and only drug approved to treat PKD, the first FDA-approved oral treatment for beta-thalassemia, and the first drug approved to treat alpha-thalassemia. Ex.1011 (FDA 2022), 21; Ex.2019 (FDA Aqvesme™ Approval); Ex.2013 (Kuo Decl.) ¶¶43-44. Mitapivat provides a substantial improvement in hemoglobin response in both PKD and thalassemia patients, reduces transfusions in patients who regularly receive them, and improves key quality of life metrics such as fatigue, shortness of breath, and jaundice. Ex.1011 (FDA 2022), 21; Ex.2019 (FDA Aqvesme™ Approval); Ex.2020 (ENERGIZE Press Release); Ex.2013 (Kuo Decl.) ¶¶43-44.

B. State of the Art of Mitapivat DDIs as of June 14, 2019

Drugs can interact in ways that compromise their safety and/or efficacy; as such, before prescribing any drug, clinicians must consider the other drugs a patient is taking. Ex.2021 (Rowland & Tozer), 004-5, 007; Ex.2013 (Kuo Decl.) ¶¶45-46. Identifying and overcoming such DDIs for a new drug is not routine or predictable; clinical testing is essential for characterizing such interactions and required by the FDA. Ex.2022 (FDA, In Vitro Metabolism- and Transporter- Mediated DDI Studies), 006-7 (“if the enzyme is responsible for $\geq 25\%$ of the drug’s elimination ... the sponsor should conduct clinical DDI studies using strong index inhibitors and/or inducers of the enzyme”); Ex.2023 (FDA, Clinical Drug Interaction Studies), 006 (“Proper and thorough DDI evaluations that can inform regulatory decision-making generally require studies specifically designed for this purpose.”); Ex.2013 (Kuo Decl.) ¶¶46-47, 60-61. As of June 14, 2019, FDA’s draft guidance on evaluating DDIs for investigational drugs required initial *in vitro* testing as well as clinical trials to evaluate DDIs for new drugs (and optionally, further modeling or simulations). Ex.2022 (FDA, In Vitro Metabolism- and Transporter- Mediated DDI Studies), 005-18; Ex.2023 (FDA, Clinical Drug Interaction Studies), 006-9; Ex.2013 (Kuo Decl.) ¶¶46-47, 60-61. As of June 14, 2019, no clinical DDI trials or further modeling had been reported for mitapivat.

DDIs can manifest in different ways. Ex.2021 (Rowland & Tozer), 004-7; Ex.2013 (Kuo Decl.) ¶¶48-50. Some examples are:

- Two drugs can bind together in the gut to form a complex that cannot be absorbed into the blood. Ex.2021 (Rowland & Tozer), 005; Ex.2013 (Kuo Decl.) ¶49.
- A drug can impact blood flow through the liver and change how fast another drug is cleared from the body by the liver. Ex.2021 (Rowland & Tozer), 032; Ex.2013 (Kuo Decl.) ¶49.
- Drugs can also interact when their actions are additive, e.g., blood pressure medications that each work in a different way, such that the combination reduces blood pressure more than either drug would alone. Ex.2021 (Rowland & Tozer), 004, 036-39; Ex.2013 (Kuo Decl.) ¶48.

Of particular relevance here, one drug can increase or decrease the amount of a second drug in the body by increasing or decreasing that second drug's breakdown. Ex.2021 (Rowland & Tozer), 014-32; Ex.2013 (Kuo Decl.) ¶¶50-54. For example, Agios reported that the CYP3A4 enzyme breaks down mitapivat in the body.³

³ Multiple distinct types of cytochrome P450 (CYP) exist in the body (e.g., CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2). Different drugs are broken down by one

Ex.1005 (Agresta), 42; Ex.1017⁴ (Le), 2; Ex.2013 (Kuo Decl.) ¶62. This flagged that drugs that induce or inhibit the activity of CYP3A4 (or the related CYP3A5 enzyme) could potentially lead to DDIs with mitapivat. *See, e.g.*, Ex.2024 (Hakkola 2020), 030; Ex.2022 (FDA, In Vitro Metabolism- and Transporter- Mediated DDI Studies), 006-7; Ex.2013 (Kuo Decl.) ¶¶56, 62. Agios also reported that mitapivat itself could potentially induce the activity of CYP3A4, i.e., mitapivat could potentially induce its own breakdown in the body (as well as other drugs that are broken down by CYP3A4). Ex.1005 (Agresta), 42; Ex.1017 (Le), 2; Ex.2013 (Kuo Decl.) ¶63.

And yet, as of June 14, 2019, it was not known whether, or to what extent, *any* “CYP3A4/5 inducers” or “CYP3A4/5 inhibitors” would diminish the safety and/or efficacy of mitapivat when those drugs are taken at the same time by a patient suffering from hemolytic anemia. Ex.2013 (Kuo Decl.) ¶¶62-63. FDA’s classification system for the strength of a CYP3A4/5 inducer/inhibitor applied only

or more CYPs or other metabolizing enzymes, and/or eliminated from the body in other ways (e.g., being shuttled out of cells by “transporter” proteins); such breakdown and clearance is drug-dependent and not predictable absent preclinical and clinical testing. Ex.2013 (Kuo Decl.) ¶51.

⁴ Exhibit 1017 is incorrectly stamped as Exhibit 1016.

to certain drugs (“sensitive index substrates”) having well-characterized sensitivity to such inducers/inhibitors; there was no such classification in relation to mitapivat. Ex.2013 (Kuo Decl.) ¶¶55-59, 62. For example, a “strong” CYP3A4/5 inducer reduces the amount of a sensitive index substrate in the blood⁵ by $\geq 80\%$, a moderate CYP3A4/5 inducer reduces the amount of sensitive index substrate by $\geq 50\%$ to $< 80\%$, and a weak (aka mild) CYP3A4/5 inducer reduces the amount of sensitive index substrate by $\geq 20\%$ to $< 50\%$. Ex.2023 (FDA, Clinical Drug Interaction Studies), 024, 31-32; Ex.2013 (Kuo Decl.) ¶¶54-55. But context matters. As shown in the table below, a strong inducer can have widely varying effects on different drugs broken down by CYP3A4/5 – i.e., a person of ordinary skill in the art (“POSA”) could not predict whether any particular inducer would be “strong,” “moderate” or “weak/mild” with respect to mitapivat. Ex.2024 (Hakkola 2020), 003⁶; Ex.2013 (Kuo Decl.) ¶¶54-59. Moreover, a POSA would have understood that

⁵ One common measure of the amount of drug in a patient’s blood is the AUC (area under the curve), which measures the total amount of a drug in the blood over time. Another is $C_{\max}$, which is the maximum drug concentration in the blood.

⁶ This unpredictability in 2020 demonstrates unpredictability as of the earlier June 14, 2019 priority date.

mitapivat's own induction of CYP3A4 further contributed to the unpredictability of the effects of CYP3A4/5 inducers on mitapivat. Ex.2013 (Kuo Decl.) ¶63.

Clinical Effect of Strong CYP3A4/5 Inducer Rifampin (aka Rifampicin) on Different Drugs

Drug	AUC Reduction	C_{max} Reduction	Reference⁷
Vandetanib	40%	None	Ex.2025 (CAPRELSA (October 2018 label))
Everolimus	63%	58%	Ex.2026 (AFINITOR/AFINITOR DISPERZ (April 2018 label))
Venetoclax	71%	42%	Ex.2027 (VENCLEXTA (May 2019 label))
Dasatinib	82%	81%	Ex.2028 (SPRYCEL (December 2018 label))

C. The '049 Patent

The '049 Patent is titled “Mitapivat Therapy and Modulators of Cytochrome P450.” Ex.1001 ('049 Patent), Cover. Based on preclinical and clinical trial data – as well as corresponding modeling described in the patent – the '049 Patent claims methods of treating hemolytic anemia with specific doses of mitapivat (about 10, 40, 100 or 200 mg/day) in patients taking a moderate inducer of CYP3A4/5.

As explained in the '049 Patent, a “CYP3A4/5 inducer[’s] activity may cause mitapivat or a pharmaceutically acceptable salt thereof that is co-administered with the CYP3A4/5 inducer to be metabolized and eliminated more quickly from the

⁷ Each of the references is the current label as of the priority date of June 14, 2019.

body, as determined by the measured plasma levels of the compound and its metabolites.” *Id.* 5:21-26. Such DDIs can also lead to a “decrease in the therapeutic efficacy of the first drug (e.g., mitapivat),” as well as other DDI effects, including fatigue, back pain, hemolysis and dizziness because of the decrease in mitapivat levels. *Id.* 21:59-22:2; *see also id.* 21:44-47 (“An increase in activity or expression level of the detoxification enzyme will tend to decrease the concentration of the first drug in the patient and its consequential effect on the patient ...”). Because “[d]rugs that are being co-administered with mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate), ... will sometimes be CYP3A4/5 inducers or CYP3A4/5 inhibitors,” there is a need for reliable dose adjustment “to reduce effects of a drug-drug interaction between mitapivat or a pharmaceutically acceptable salt thereof (e.g., mitapivat sulfate) and the co-administered drug.” *Id.* 7:26-39.

The patent recognizes that classification of CYP inducers is conventionally “based on its effect on an index CYP substrate” – i.e., not based on the effect on mitapivat. *Id.* 5:44-53. To address that gap, the ’049 Patent discloses mitapivat-specific examples, and corresponding tables and figures of data, in which – among other things – “the drug-drug interactions between mitapivat sulfate and a CYP3A4/5 inducer (e.g., rifampin) or a CYP3A4/5 inhibitor (e.g., itraconazole) are studied.” *Id.* 35:65-36:1.

Example 1 is directed to *in vitro* studies on the breakdown of mitapivat by various CYP enzymes, as well as the ability of mitapivat itself to inhibit and/or induce CYP enzymes and other proteins. Of particular relevance here, the patent reports:

- “mitapivat sulfate was primarily metabolized [broken down] by CYP3A4/5 (>90%)”;
- “minor contributions from CYP2C9, CYP2C8, and CYP1A2” to the breakdown of mitapivat;
- “inhibition of ... CYP3A4 (largely irreversible)” by mitapivat itself; and
- mitapivat is “a potential inducer of human ... CYP3A4.”

Ex.1001 ('049 Patent), 36:8-17.

Example 2 is directed to the first clinical trial characterizing DDIs in human subjects taking mitapivat with either rifampin (a strong CYP3A4/5 inducer with respect to sensitive index substrates) or itraconazole (a strong CYP3A4/5 inhibitor with respect to sensitive index substrates). The data from that clinical trial is reported in Tables 1-4 and Figures 1-4.

As depicted in Table 3 and Figure 4 below, the inventors showed that mitapivat stability in the blood is *extremely* sensitive to co-administration with rifampin. Co-administration of rifampin reduced the amount of mitapivat in the

blood (AUC) by approximately 91% (i.e., more than an 11-fold reduction), and reduced the peak concentration of mitapivat (C_{max}) by 77% (i.e., more than a 4-fold reduction). *Id.* 42:22-62 (“The geometric mean AUC_{0-t} and AUC_{0-inf} ratios of mitapivat in the presence and absence of rifampin were 0.09 [9%]. The geometric mean C_{max} ratio of mitapivat in the presence and absence of rifampin was 0.23 [23%].”).

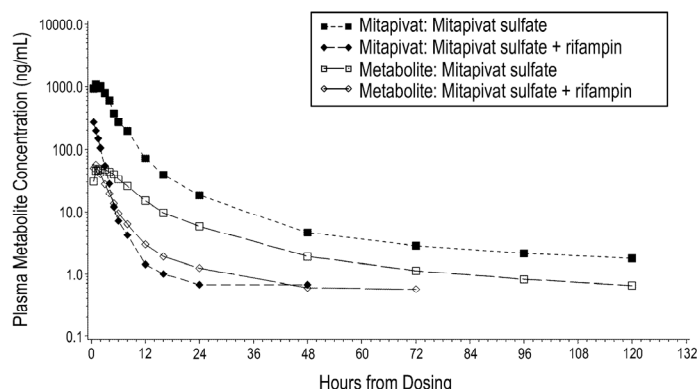


FIG. 4

Ex.1001 ('049 Patent), Fig. 4; *id.* 42:28-53.

The clinical trial data in the '049 Patent also flagged that even moderate CYP3A4/5 inducers could potentially have DDIs with mitapivat. Moderate CYP3A4/5 inducers can still be very potent inducers, decreasing levels of a sensitive index substrate by ≥ 50 percent to < 80 percent. Ex.2023 (FDA, Clinical Drug Interaction Studies), 024; Ex.1001 ('049 Patent), 5:50-51.

TABLE 3

Summary of Statistical Comparisons of Plasma Mitapivat Pharmacokinetic Parameters Following 50 mg Mitapivat Sulfate Co-Administered With Multiple Doses of 600 mg Rifampin Versus Administered Alone (Part 2)						
Parameter (unit)	Geometric LSM	n	Geometric LSM	n	GMR	90% Confidence Interval
AUC_{0-t} (ng*hr/mL)	486.4	14	5565	14	0.0874	0.0719-0.1062
AUC_{0-inf} (ng*hr/mL)	496.4	14	5681	14	0.0874	0.0719-0.1062
C_{max} (ng/mL)	292.4	14	1263	14	0.2316	0.1933-0.2773

Mitapivat sulfate alone: 50 mg mitapivat sulfate (1 x 50 mg tablet) at Hour 0 on Day 1 (Period 1)
 Mitapivat sulfate + rifampin: 600 mg rifampin (2 x 300 mg capsules) QD on Day 1 to Day 12 inclusive (within ± 1 hour of dosing time on Day 1) with 50 mg mitapivat sulfate (1 x 50 mg tablet) coadministered at Hour 0 on Day 8 (Period 2)
 Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the linear mixed effect model.
 Geometric Mean Ratio (GMR) = test/reference
 Intra-subject CV % = $100 \times (\text{square root}(\exp[\text{MSE}] - 1))$, where MSE = Residual variance from linear mixed effect model.

Example 3 addresses potential DDIs between mitapivat and a moderate CYP inducer by describing the development of a “physiologically based pharmacokinetic [PK] model (“PBPK model”) for mitapivat sulfate based on the currently available in-vitro and clinical PK data.” Ex.1001 (’049 Patent), 43:41-45:11. This modeling characterizes both the effect of moderate CYP inducers on mitapivat, and also the effect of mitapivat on a number of other drugs that are broken down by a variety of CYP and other enzymes. *Id.* 44:1-67. For example, “[t]he impact of the co-administration of the moderate CYP3A4 inducer efavirenz on the PK of mitapivat sulfate will be determined following single and multiple dose administration of 5, 20 and 50 mg BID.” *Id.* 44:22-25. The modeling also characterizes the effects of 5 to 50 mg BID mitapivat sulfate on drugs broken down or otherwise cleared by the following enzymes: CYP3A4, CYP2B6, CYP2C9, CYP2C8/CYP3A4, CYP2C19, OATP1B1/OATP1B3, P-gp, metformin and OAT3.⁸ Ex.1001 (’049 Patent), 44:26-67. Such modeling for moderate inducers is accepted by the FDA *only after* clinical trials with a strong inducer – the exact trials reported in the ’049 Patent. Ex.2023 (FDA, Clinical Drug Interaction Studies), 008-9; Ex.2022 (FDA, In Vitro Metabolism- and Transporter- Mediated DDI Studies), 038.

⁸ The modeling was also designed to account for the effect of an increase in stomach pH. Ex.1001 (’049 Patent), 45:1-11.

Agios's modeling confirmed that about 10, 40, 100 or 200 mg/day were appropriate doses of mitapivat in combination with moderate CYP3A4/5 inducers – as described and claimed in the '049 Patent. *See, e.g.*, Ex.1001 ('049 Patent), 14:18-15:10 (“mitapivat or a pharmaceutically acceptable salt thereof is formulated for administration at a dose equivalent to about 5 mg of mitapivat thereof twice per day” up to “about 100 mg of mitapivat twice per day”). And in approving mitapivat to treat PKD, the FDA expressly accepted Agios's clinical data and modeling. Ex.1011 (FDA 2022), 210-224 (Agios physiologically based pharmacokinetic (PBPK) analyses “adequate to predict the interaction effect of CYP3A inducers”); *see also id.* 184-185 (clinical DDI study), 215 (in the PBPK analyses, the “relative contribution of the CYP3A4 pathway to the total clearance of mitapivat ... was optimized ***using clinical DDI data*** (Study 012) with the strong CYP3A inhibitor itraconazole [and] tested against the ***clinical DDI*** [data] with the strong CYP3A inducer rifampin” (emphases added)).

Consistent with the teachings of the patent, claim 1, the patent's sole independent claim, recites:

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), 45:25-30.

D. Prosecution History

During prosecution, the Examiner thoroughly vetted the claims of the '049 Patent, including over substantially the same prior art that Apotex relies on in its Petition. All of the Examiner's anticipation and obviousness rejections were directed to Agresta – with the Examiner highlighting precisely the same passage that Apotex emphasizes, referring to the breakdown of mitapivat by CYP3A4. Ex.2001 ('049 Patent FH), 1236-1243, 1277-1283; *id.* 1237 (CYP3A4 as “the major route of mitapivat’s metabolic pathway”); Pet. 31 (citing Ex.1005 (Agresta), 42). But the Examiner went on to acknowledge that “Agresta does not specifically teach incorporating a CYP 3A4/5 inducer with the mitapivat regimen.” Ex.2001 ('049 Patent FH), 1242. The Examiner also expressly considered the other references that Apotex relies on in its Petition: Sizemore (which includes substantially the same disclosure that Apotex relies on from Dana-Farber), as well as the Grace Presentation and Abstract. *Id.* 1249-1258. After extensive consideration, the Examiner allowed the claims over the prior art, finding 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 (Reasons for Allowance).

III. Level of Ordinary Skill in the Art

Apotex asserts that a POSA (person of ordinary skill in the art), for purposes of the '049 Patent, would have had “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.” Pet. 19; Ex.1003 (Thirman Decl.) ¶60. Apotex further argues that “[a] POSA may be part of a team that includes other scientists in related fields, for example a pharmacologist or pharmaceutical formulator.” Pet. 19; Ex.1003 (Thirman Decl.) ¶60.

Solely for the purpose of responding to this Petition for *inter partes* review, Agios does not dispute Apotex's definition.⁹

⁹ Agios reserves the right to propose a definition in this proceeding and/or future proceedings (including in district court).

IV. Claim Construction

Apotex proposes construction of only two claim terms, “mitapivat” and “CYP3A4/5.”¹⁰ Pet. 19-20. Agios agrees that, in the claims at issue, “mitapivat” means “N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl) quinoline-8-

¹⁰ Apotex also vaguely proposes that the Board adopt “several definitions” from the specification, without specifying in the Petition the particular claim terms it seeks to construe or the proposed definitions. Apotex’s request is deficient on its face; it does not satisfy the requirement to identify *in the Petition* how the challenged claim is to be construed. 37 C.F.R. § 42.104(b)(3); *see also* USPTO, P.T.A.B. Trial Practice Guide, § II.B.6 (Claim Construction) (last updated Dec. 12, 2025), <https://www.uspto.gov/patents/ptab/trial-practice-guide> (“If a petitioner believes that a claim term requires an express construction, the petitioner **must** include a **statement identifying a proposed construction of the particular term** and where the **intrinsic and/or extrinsic evidence** supports that meaning.” (emphases added)). Moreover, there is no indication that any such terms are necessary to resolve the dispute. *E.g.*, *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (per curiam) (only terms that are necessary to resolve the dispute need be construed).

sulfonamide,” and “CYP3A4/5” means “cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5).”

V. Ground 1: Sizemore Does Not Anticipate Claims 1, 8, 9, 14 and 19

A. Sizemore Does Not Disclose Co-Administration of Mitapivat With a Moderate CYP3A4/5 Inducer

It is indisputable that Sizemore does not disclose a key limitation of every challenged claim: “administering to the subject... a moderate inducer of cytochrome P450 3A4/5 (CYP3A4/5).” Ex.2013 (Kuo Decl.) ¶¶95-98. Indeed, there is no mention of moderate inducers anywhere in Sizemore. *Id.* ¶79. The absence of any such disclosure is dispositive and ends the anticipation inquiry.

The lack of such a disclosure is also not surprising; Sizemore is a patent publication directed to *crystalline forms* of mitapivat, not DDIs. *See, e.g.*, Ex.1004 (Sizemore), Title (“CRYSTALLINE FORMS OF [MITAPIVAT]”). The working examples in the disclosure (spanning nearly 40 pages), and all 25 figures, are directed to the preparation and characterization of various forms of mitapivat. *Id.* [0161]-[0249]; Ex.2013 (Kuo Decl.) ¶¶78, 96. Only mitapivat was administered to animals (rats); no other drugs were co-administered and no DDIs were evaluated. Ex.1004 (Sizemore), [0233]-[0249]; Ex.2013 (Kuo Decl.) ¶¶78, 96. In the 116-page Sizemore specification, the term “inducer” appears *once* – in a passing reference to a subject that “is *not* taking inhibitors of cytochrome P450 (CYP)3A4, *strong* inducers of CYP3A4, strong inhibitors of P-glycoprotein (P-gp), or digoxin.”

Ex.1004 (Sizemore), [0053] (emphases added); Ex.2013 (Kuo Decl.) ¶¶79, 97. The terms “cytochrome” and “CYP” likewise appear only in that same isolated sentence that makes no mention of a moderate CYP3A4/5 inducer – much less a teaching of administering a moderate inducer with mitapivat, as required by the challenged claims. Ex.2013 (Kuo Decl.) ¶¶79, 97.

B. Expert Testimony Cannot Supply a Missing Limitation

Instead of pointing to any actual disclosure in Sizemore, Apotex improperly relies on the opinion of its expert (Dr. Thirman) to argue that “a POSA would have *understood* Sizemore to *contemplate* administration of moderate inducers of CYP3A4.” Pet. 23 (emphases added). Yet, a Petition must “specify where each element of the claim is found in the prior art patents or printed publications relied upon,” and “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.” Memorandum from the Acting Under Sec’y of Com. for Intell. Prop. & Acting Dir. of the USPTO to Members of the P.T.A.B. (July 31, 2025), <https://www.uspto.gov/subscription-center/2025/uspto-issues-memorandum-clarifying-enforcement-rule-104b4-ipr-proceedings> (“USPTO July 31, 2025 Mem.”), 1 (citing 37 C.F.R. § 42.104(b)(4)). As such, Apotex’s Petition is facially defective.

Apotex's improper reliance on expert opinion to supply a missing claim limitation likewise runs afoul of controlling caselaw on anticipation. The Federal Circuit has repeatedly held that, "[t]o anticipate, a reference must do more than 'suggest' the claimed subject matter." *Eli Lilly & Co. v. L.A. Biomedical Rsch. Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1076 (Fed. Cir. 2017); *id.* at 1075 (disclosure of dosing for at least three days or "as long as the patient suffers from [the disease]" is not disclosure of daily dosing for at least 45 days); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1054-56 (Fed. Cir. 2010) (disclosure that "dose should be the lowest dose which keeps the patient symptom-free" is not disclosure of once-daily dosing); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274-75 (Fed. Cir. 2017) (rejecting proposition that "a reference missing a limitation can anticipate a claim if a skilled artisan viewing the reference would 'at once envisage' the missing limitation" (citation omitted)); *Galderma Laboratories, L.P. v. Teva Pharms. USA, Inc.*, 799 F. App'x 838, 845 (Fed. Cir. 2020) ("[D]istrict court was not permitted 'to fill in missing limitations simply because a skilled artisan would immediately envision them.'").¹¹

¹¹ Apotex's cited cases (Pet. 22-23), are distinguishable. In all of the cited cases, the relevant claim limitations were ***necessarily present*** in the prior art disclosures; they were not altogether missing, as is the case here. *Sage Prods., LLC v. Stewart*,

C. Exclusion of Strong CYP3A4 Inducers Does Not Suggest Administration of Moderate CYP3A4/5 Inducers

Equally fatal to Ground 1 of the Petition is that there is no suggestion in Sizemore of co-administering mitapivat with a moderate CYP3A4/5 inducer. Apotex is wrong that a POSA would have made that inference from the single passing reference to a subject that is *not* taking a *strong* CYP3A4 inducer. Ex.2013 (Kuo Decl.) ¶¶99-100. A POSA would not have understood silence as to moderate CYP3A4/5 inducers to be an implicit endorsement of their use with mitapivat – especially in view of the additional unpredictability resulting from mitapivat's own induction of CYP3A4 (auto-induction). *Id.* ¶¶99-104. Apotex improperly uses

133 F.4th 1376, 1382-83 (Fed. Cir. 2025) (prior art disclosure of “sterile” was “unequivocal[.]” disclosure of “sterilized” claim limitation in view of the relevant regulatory standards); *ArthroCare Corp. v. Smith & Nephew, Inc.*, 406 F.3d 1365, 1373-74 (Fed. Cir. 2005) (prior art disclosure of “electrical leads attach[ed] to the power source from near the proximal end of the endoscope” satisfies claim limitation requiring “a connector near the proximal end of the shaft for electrically coupling the electrode terminal to the electrosurgical power supply”); *VirnetX Inc. v. Apple Inc.*, No. 2022-1523, 2023 WL 6933812, at *4 (Fed. Cir. Oct. 20, 2023) (nonprecedential) (authentication failure disclosed in prior art “would result in an error message being returned,” as claimed).

hindsight, working backwards from the claims of the '049 Patent to identify a treatment step – co-administration of mitapivat with a moderate CYP3A4/5 inducer – that Sizemore nowhere discloses. *Id.* ¶¶79-80, 100.

Because mitapivat was reported to be broken down by CYP3A4, it was reasonable and expected for a POSA to avoid co-administering mitapivat with **strong** CYP3A4/5 inducers; such inducers were most likely to cause DDIs. *Id.* ¶101. But a POSA's avoidance of strong CYP3A4/5 inducers says nothing about whether other inducers also cause DDIs or whether such DDIs can be overcome with dose adjustments of mitapivat. *Roxane*, IPR2016-00690, Paper 8 at 19 (denying institution of obviousness challenge to DDI patent because the clinical significance of any DDI "is unpredictable and needs to be empirically determined"). Avoidance of strong inducers certainly does not affirmatively teach or suggest co-administering moderate CYP3A4/5 inducers with mitapivat. Ex.2013 (Kuo Decl.) ¶101. If anything, given the concern with co-administering strong CYP3A4/5 inducers with mitapivat, a POSA would have likewise **avoided** co-administering moderate CYP3A4/5 inducers absent the preclinical and clinical data necessary to characterize potential DDIs. *Id.*

Even if a POSA would have understood Sizemore's single mention of a subject not taking a strong inducer to reflect DDI studies – and there is no basis for that – a POSA would have understood that such disclosure was missing critical

context, i.e., DDI data or analysis, necessary to inform a POSA about co-administration of mitapivat with moderate inducers. *Id.* ¶102. A POSA would have known that it is standard practice to study DDIs with strong CYP inducers **before** conducting such studies with moderate inducers. *Id.* Under FDA's draft guidance, "clinical DDI studies should start with a strong index inhibitor and a strong index inducer." Ex.2023 (FDA, Clinical Drug Interaction Studies), 013. If DDIs are found with a strong CYP inhibitor/inducer, further clinical studies or modeling/simulation approaches with moderate inhibitors/inducers are required. *Id.* 014. Still further, a POSA would have understood that DDIs between mitapivat and CYP3A4/5 inducers were particularly challenging to predict because mitapivat itself was believed to induce CYP3A4. Ex.1005 (Agresta), 42; Ex.2013 (Kuo Decl.) ¶103. As explained above, it was unpredictable how a moderate CYP3A4/5 inducer affected the safety and efficacy of mitapivat; the combined effect of auto-induction and a moderate CYP3A4/5 inducer was all the more unpredictable. Ex.2013 (Kuo Decl.) ¶103. Without clinical DDI data and associated pharmacokinetic analysis to substantiate that mitapivat could be co-administered with moderate CYP3A4/5 inducers, a POSA would not have assumed that such co-administration was advisable or safe. *Id.*

Apotex makes much of the fact that Sizemore refers to a subject that "is not taking **inhibitors** of cytochrome P450 (CYP)3A4" – without classifying the strength of the inhibitors. According to Apotex, "[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.” Pet. 23 (emphasis omitted). Not so. A POSA would not have understood Sizemore to exclude “all inhibitors” as Apotex suggests; that argument is contradicted by the other prior art Apotex relies on. Ex.1007 (Dana-Farber), 6; Ex.2013 (Kuo Decl.) ¶104. In the Dana-Farber reference related to the Phase II DRIVE-PK trial of mitapivat (which a POSA is presumed to be aware of), only patients taking strong inhibitors – not “all inhibitors” – were excluded. Ex.1007 (Dana-Farber), 6; Ex.2013 (Kuo Decl.) ¶104. There is no basis for Apotex’s hindsight-fueled speculation, and the Board should reject Ground 1 of Apotex’s Petition.

VI. Grounds 2-4: Claims 1, 8, 9, 14 and 19 Would Not Have Been Obvious Over the Asserted Prior Art

A. None of the Asserted Prior Art Discloses Co-Administration of Mitapivat With a Moderate CYP3A4/5 Inducer

In Grounds 2-4 (obviousness), Apotex again does not – because it cannot – identify any prior art disclosure of co-administering mitapivat with a moderate CYP3A4/5 inducer. That lack of disclosure of a key claim limitation is dispositive.

With respect to claim 1 (on which all challenged claims depend), Apotex relies on Agresta, Dana-Farber and Grace Presentation/Abstract.¹² Pet. 26, 28. But those references are all directed to clinical trials of **mitapivat alone**, not to characterizing DDIs or co-administering mitapivat with moderate CYP3A4/5 inducers. *See Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1382-83 (Fed. Cir. 2021) (POSA would not extrapolate co-administration dosing from dosing of drug alone); Ex.2013 (Kuo Decl.) ¶¶81, 84, 87, 92, 108-116. Agresta mentions a CYP enzyme **once** in its nearly 70 pages to state that mitapivat is broken down by, and itself is potentially an inducer of, CYP3A4/5. Ex.1005 (Agresta), 42; Ex.2013 (Kuo Decl.) ¶83, 110. There is no mention in Agresta of co-administration with **any** CYP3A4/5 inducers. Ex.2013 (Kuo Decl.) ¶¶81-83, 110. Dana-Farber (like Sizemore in Ground 1) discloses **avoiding** co-administration of **strong** CYP3A4 inducers. Ex.1007 (Dana-Farber), 6. There is no mention of moderate CYP3A4/5 inducers at all – let alone that they could be co-administered with

¹² Ground 2 relies on Agresta, Dana-Farber, and Grace Presentation, as well as “the knowledge of a POSA.” Pet. 26, 28. Ground 3 applies the same combination, substituting Grace Abstract for Grace Presentation. *Id.* 43. Ground 4 adds Sizemore to the combinations of Grounds 2 and 3, solely to address claim limitations regarding excipients in dependent claim 19 – not claim 1. *Id.* 53-56.

mitapivat. *Id.*; Ex.2013 (Kuo Decl.) ¶¶85, 114. And the Grace Presentation and Grace Abstract do not mention *any* CYP enzymes, inducers, or DDIs. Ex.2013 (Kuo Decl.) ¶¶89, 93, 116.

Apotex manufactures the missing limitation by improperly arguing that “a POSA would have understood” a moderate CYP3A4/5 inducer could have been co-administered with mitapivat. Pet. 31-33 (Ground 2)¹³, 45 (Ground 3)¹⁴. But a Petition must “specify where each element of the claim is found in the prior art

¹³ See Pet. 31-32 (Agresta: “a ***POSA would have understood*** such drugs to include moderate CYP3A4 inducers”), 32 (Dana-Farber: “[a] ***POSA would thus have understood*** PKD patients taking moderate CYP3A4 inducers ... could be enrolled and treated with mitapivat”), 33 (Grace Presentation: “a ***POSA would thus have understood*** that he or she would have been able to co-administer mitapivat and a moderate CYP3A4 inducer”) (all emphases added).

¹⁴ See Pet. 45 (Agresta: “a ***POSA would have understood*** such drugs to include moderate CYP3A4 inducers”); *id.* (Dana-Farber: “a ***POSA would have understood*** that PKD patients taking moderate CYP3A4 inducers could be treated with mitapivat”); *id.* (Grace Abstract: “[a] ***POSA would thus have understood*** that he or she would have been able to co-administer mitapivat and a moderate CYP3A4 inducer”) (all emphases added).

patents or printed publications relied upon,” and “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.” USPTO July 31, 2025 Mem. 1 (citing 37 C.F.R. § 42.104(b)(4)). The lack of disclosure of a key claim limitation in the asserted prior art mandates a finding of nonobviousness.

B. A POSA Would Not Have Understood the Asserted Prior Art to Disclose Co-Administration of a Moderate CYP3A4/5 Inducer With Mitapivat

Apotex's hindsight-driven obviousness argument is similarly defective. A POSA would not have “understood” the asserted prior art – alone or in combination – to teach co-administration of a moderate CYP3A4/5 inducer with mitapivat. Ex.2013 (Kuo Decl.) ¶¶105-107. Apotex points to Agresta for the generic disclosure of a possible “combination of Compound 1 [mitapivat] and one or more additional therapeutic or prophylactic agents.” Ex.1005 (Agresta), 36 (quoted in Petition at 29). Apotex then relies on a POSA's purported general knowledge of moderate CYP3A4/5 inducers that *theoretically could* be co-administered with mitapivat. *Id.* 29-31, 45-47. That is a far cry from a teaching of the claimed co-administration of a moderate CYP3A4/5 inducer with mitapivat. To the contrary, a POSA would have *avoided* co-administering the two drugs since there was no data about the impact of moderate CYP3A4/5 inducers. Ex.2013 (Kuo Decl.) ¶¶62-65, 118-120. Agresta separately disclosed that mitapivat is broken down by,

and is itself potentially an inducer of, CYP3A4. Ex.1005 (Agresta), 42. As Apotex freely concedes, “a POSA would have understood ... that such drugs may give rise to a drug-drug interaction with mitapivat.” Pet. 31-32, 45. And yet, DDIs with any CYP3A4/5 inducers had not been characterized. Ex.2013 (Kuo Decl.) ¶62. This flaw is fatal to Apotex's obviousness challenge. *See Roxane*, IPR2016-00690, Paper 8 at 19, 22-23. With the '049 Patent, Agios was the first to address the unpredictability of mitapivat DDIs by characterizing such DDIs in a clinical trial, per FDA standards. Ex.2013 (Kuo Decl.) ¶¶60-64.

Dana-Farber likewise does not disclose co-administering a moderate CYP3A4/5 inducer with mitapivat. Nor would it, as Dana-Farber is a list of eligibility criteria for a clinical trial of *mitapivat alone*; that clinical trial did not assess DDIs. Ex.1007 (Dana-Farber), 6; Ex.2013 (Kuo Decl.) ¶¶84-86. Instead, Apotex points to a single exclusion criteria referencing drugs known to “strongly induce” CYP3A4. Pet. 32 (citing Ex.1007 (Dana-Farber), 6), 45. Because the criteria does not exclude moderate CYP3A4 inducers, Apotex's expert makes the bare and unsupported assertion that patients taking such inducers “*could* be enrolled and treated with mitapivat.” *Id.* 32-33 (emphasis added) (citing 1003 (Thirman Decl.) ¶100), 45-46 (citing Ex.1003 (Thirman Decl.) ¶¶136, 137). Apotex's argument is pure speculation based on hindsight that cannot support a finding of obviousness.

Dana-Farber says nothing of moderate CYP3A4/5 inducers or their co-administration with mitapivat, and a POSA would not have assumed that such co-administration was advisable or safe based on Dana-Farber's silence. Ex.2013 (Kuo Decl.) ¶¶68, 113-114, 121-124. Exclusion criteria in early-phase clinical trials (like the one in Dana-Farber) manage variables that are likely to confound the investigation in the trial. *Id.* ¶¶67, 123-124. For drugs that are broken down by a particular CYP enzyme, it was standard practice to avoid strong inducers of that enzyme, since they are most likely to cause DDIs affecting safety and/or efficacy. *Id.* ¶67. A POSA would have understood that Dana-Farber's exclusion of strong CYP3A4 inducers – with no discussion of DDIs – followed standard practice and provides no guidance as to any potential DDIs with moderate CYP3A4/5 inducers. *Id.* ¶¶68, 122-124. If anything, a POSA would have likewise ***avoided*** co-administering moderate CYP3A4/5 inducers given the lack of data on the potential effect of such co-administration on patients. *Id.* ¶124.

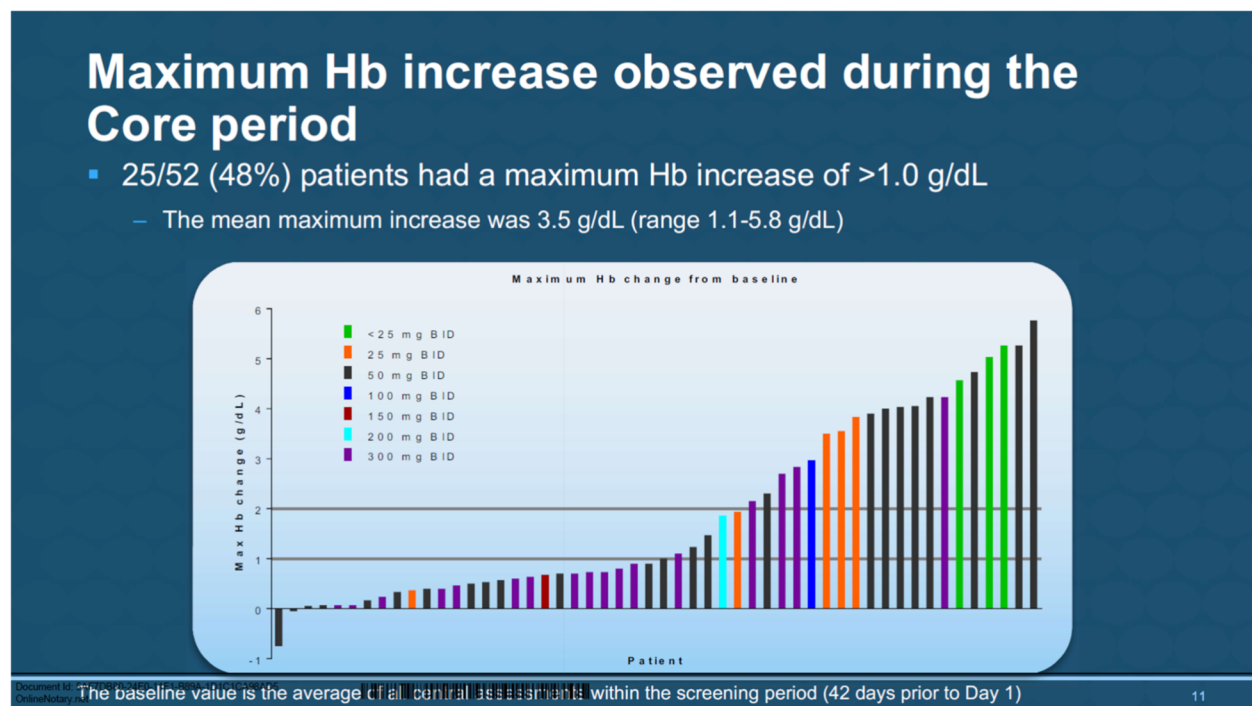
As for the remaining asserted prior art references – the Grace Presentation and Abstract – Apotex does not contend that they independently disclose co-administration of moderate CYP3A4/5 inducers with mitapivat. Nor could Apotex do so. Those references disclose interim results of the same clinical trial as Dana-Farber – for ***mitapivat alone***; they make no mention of ***any*** CYP enzymes, inducers or DDIs. *Id.* ¶¶89, 93, 116. Apotex instead relies on these references to argue that

co-administration (as purportedly taught in *Dana-Farber*), was possible and could be done without difficulty. Pet. 33, 45 (Grace references “do[] not report any difficulty with treating patients receiving both mitapivat and moderate CYP3A4 inducers *as permitted by Dana-Farber*” (emphasis added)).

Combining the asserted prior art does not render the claimed co-administration obvious. Ex.2013 (Kuo Decl.) ¶¶131-143. Instead, the references collectively reinforce a POSA's cautious skepticism of co-administering mitapivat with a moderate CYP3A4/5 inducer. *Id.* ¶¶120, 122-124, 126, 130, 131-134. Agresta and Dana-Farber each flag potential DDIs between mitapivat and inducers of CYP3A4/5. *Id.* ¶¶111-112, 120, 122-124, 126, 132. Neither provides any data supporting their co-administration. *Id.* ¶¶81-84, 109-110, 114, 132. The Grace references are silent on DDIs; there is no evidence that any such data was collected or evaluated. *Id.* ¶¶89, 93, 115-116, 127, 133. After all, the trial underlying the Grace references was directed to mitapivat alone. *Id.* ¶¶87-88, 92, 116. Such silence would not have motivated a POSA to co-administer mitapivat with a moderate CYP3A4/5 inducer. *Id.* ¶¶133-134.

A POSA would also have had no reasonable expectation of success. *Id.* ¶¶135-139. None of the asserted prior art references has any data, discussion, or disclosure supporting co-administration with a moderate CYP3A4/5 inducer. *Id.* ¶136. None of the references disclose whether *any* patients in the Phase II

DRIVE-PK study were actually taking a moderate CYP3A4/5 inducer. *Id.* ¶¶127-130, 137. And even if certain patients in the trial had been concurrently taking moderate CYP3A4/5 inducers, the Grace references do not disclose whether mitapivat was effective and/or well-tolerated in those patients. *Id.* As shown in the slide below from the Grace Presentation, certain patients did not respond to mitapivat.



Ex.1008 (Grace Presentation), 26; Ex.2013 (Kuo Decl.) ¶¶129-130. Apotex also ignores the adverse events reported in the Grace references – including that withdrawal of mitapivat exacerbated destruction of red blood cells. Ex.1008 (Grace Presentation), 21; Ex.1009 (Grace Abstract), 2; Ex.2013 (Kuo Decl.) ¶¶90, 134, 138. Instead of providing a reasonable expectation of success, the data in the Grace

references underscores the unpredictable consequences of changes in mitapivat blood levels.¹⁵ Ex.2013 (Kuo Decl.) ¶138.

At bottom, Apotex argues that the claimed co-administration would have been obvious in view of the fact that *mitapivat alone* performed well in clinical trials. That is squarely contradicted by the fact that Agios took on the substantial burden and expense – per FDA's guidelines – to conduct an additional clinical trial specifically investigating DDIs. Ex.2023 (FDA, Clinical Drug Interaction

¹⁵ To the extent Apotex relies on references other than the asserted prior art – i.e., Mutalik (Ex.1010) and Clark (Ex.1012) – those references also do not support a reasonable expectation of success. Pet. 33-36 (citing Ex.1010 (Mutalik), 24, Ex.1012 (Clark), 1, 2, 4, 5, 6). Mutalik's generic reference to "recogni[zing]" potential DDIs and "plan[ning] the appropriate action" is directed to approved drugs—not investigational drugs (like mitapivat at the priority date) that lack clinical DDI data. Ex.1010 (Mutalik), 24; Ex.2013 (Kuo Decl.) ¶141. Indeed, Mutalik recognized that co-administration of certain drugs may not be feasible due to DDIs. Ex.1010 (Mutalik), 24; Ex.2013 (Kuo Decl.) ¶142. Clark (Ex.1012) is directed to DDIs for an entirely different drug (warfarin) than mitapivat and has no bearing on co-administration of mitapivat with moderate CYP3A4/5 inducers. Ex.2013 (Kuo Decl.) at 65 n.3.

Studies), 006 (“[p]roper and thorough DDI evaluations that can inform regulatory decision-making generally require studies specifically designed for this purpose ... [i.e.,] [p]rospective clinical DDI studies”); Ex.2024 (Hakkola 2020), 001 (“human in vivo studies and observations on inhibition and induction ... is absolutely needed for clinical drug treatment to prevent possible adverse outcomes and ensure safety”). The clinical impact of a moderate CYP3A4/5 inducer on mitapivat was unpredictable without mitapivat-specific clinical DDI data. *See supra* Section II.B (same inducer can have widely varying effects on different drugs broken down by CYP3A4/5). In turn, it was unpredictable whether the co-administration of mitapivat with a moderate CYP3A4/5 inducer would be safe and effective. The challenged claims would not have been obvious.

VII. Apotex's Expert's Declaration is Conclusory and Entitled to No Weight

All four Grounds in the Petition are fundamentally flawed, and should be rejected, for an independent reason. Each of Grounds 1-4 relies on the opinion of Apotex's expert (Dr. Thirman) to supply the missing limitation of co-administering mitapivat with a moderate CYP3A4/5 inducer. But Dr. Thirman “merely repeats, *verbatim*, the conclusory assertion [in the Petition] for which it is offered to support,” and is entitled to no weight. *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15-16 (P.T.A.B. Aug. 24, 2022) (precedential) (original emphasis); *see also Tiktok Inc. v. NTECH Props., Inc.*, IPR2024-01339, Paper 9 at 16 (P.T.A.B. Feb. 25, 2025)

(according “little or no weight” to “testimony [that] repeats, almost verbatim, the language in the Petition without any further explanation or supporting reasoning or evidence”); 37 C.F.R. § 42.65(a) (“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”).

Instead of identifying any disclosure of the claimed co-administration in the asserted prior art, Apotex repeatedly and consistently turns to Dr. Thirman's opinion that “a POSA would have understood” the asserted prior art to teach such co-administration. Pet. 23, 31-33, 45. But that opinion “offers only a *verbatim* restatement of the assertion being supported, without any supporting evidence or technical reasoning.”¹⁶ *Xerox*, IPR2022-00624, Paper 9 at 16 (original emphasis).

¹⁶ The Petition and Dr. Thirman's Declaration contains large swaths of identical or nearly identical language, including typographical errors that appear identically in both places. *Compare* Pet. 21, *with* Ex.1003 (Thirman Decl.) ¶71 (missing quotation mark before “about 20 mg” and “about 50 mg”), Pet. 32, *with* Ex.1003 (Thirman Decl.) ¶100 (“while at the same patients”), Pet. 40, *with* Ex.1003 (Thirman Decl.) ¶118 (citing to corresponding nonexistent sections), Pet. 44, *with* Ex.1003 (Thirman Decl.) ¶132 (superfluous “these”), Pet. 54, *with* Ex.1003 (Thirman Decl.) ¶166 (superfluous comma at “Claims, 9”).

Dr. Thirman cites an FDA review document (Ex.1011) for irrelevant arguments,¹⁷ and yet, Dr. Thirman provides no analysis whatsoever of FDA guidance concerning DDIs (Exs.2022, 2023). As discussed above, the FDA guidance reflects the unpredictability in the art with respect to DDIs as of June 14, 2019. Far from FDA accepting a POSA's "understanding" – which would be nothing more than unsupported speculation – FDA requires extensive testing, including clinical trials. Ex.2022 (FDA, In Vitro Metabolism- and Transporter- Mediated DDI Studies), 005-7; Ex.2023 (FDA, Clinical Drug Interaction Studies), 005-9, 013-14; *Roxane*, IPR2016-00690, Paper 8 at 19. It was *Agios* that first characterized mitapivat DDIs, including with clinical trial data reported in the '049 Patent. Dr. Thirman's conclusory opinions – which parrot the same conclusory opinions as the Petition – are not probative; they do not salvage Apotex's fatally flawed Petition.

¹⁷ Dr. Thirman and Apotex try to distract with inventorship and § 112 grounds that cannot be resolved in an IPR. Such allegations are both inaccurate and irrelevant to this proceeding.

VIII. Conclusion

For the reasons set forth above, the Director should deny the Petition for Inter Partes Review.

Respectfully submitted,

Dated: August 26, 2026

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify that this Patent Owner's Preliminary Response complies with the word count limitation of 37 C.F.R. § 42.24(b)(1) because the Patent Owner's Preliminary Response contains 7,231 words using Microsoft Word's counting feature, excluding the cover page, signature block, and the parts of the Patent Owner's Preliminary Response exempted by 37 C.F.R. § 42.24(b)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 26th day of August, 2026, a true and correct copy of the foregoing **Patent Owner's Preliminary Response and all Exhibits** were served by electronic mail on Petitioner's lead and backup counsel at the following email addresses:

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