

Filed on behalf of: Agios Pharmaceuticals, Inc.

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

**DECLARATION OF KEVIN H.M. KUO, M.D.
IN SUPPORT OF
PATENT OWNER'S PRELIMINARY RESPONSE**

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I, Kevin H.M. Kuo, declare and state as follows:

I. INTRODUCTION

1. I am a hematologist and clinician-investigator, and I currently hold the positions of Vice President of Research and Innovation at Scarborough Health Network and Associate Professor in the Division of Hematology, Department of Medicine, Faculty of Medicine, at the University of Toronto. I also lead the Adult Sickle Cell Disease Clinic at the Scarborough Health Network and am part of the Division of Medical Oncology and Hematology at University Health Network in Toronto, Canada.

2. I have been retained by Agios Pharmaceuticals, Inc. (“Patent Owner”) as an independent expert consultant to provide my opinion concerning the patentability of U.S. Patent No. 11,878,049 (the “’049 Patent,” Ex.1001).

3. I am receiving compensation for my time spent in connection with this matter at my standard consulting rate of \$850 per hour, plus reimbursement for reasonable expenses. My fee is not dependent on my opinions or on the outcome of this matter.

II. QUALIFICATIONS

4. My qualifications and professional experience, including a list of my publications and my expertise and professional activities, are described in my curriculum vitae, a copy of which is provided with this Declaration as

Exhibit 2014. The following is a summary of some of the relevant aspects in relation to the issues in this proceeding. This summary is not intended to be exhaustive.

5. I have over 15 years of clinical experience in the treatment of patients with congenital hemolytic anemias, including pyruvate kinase deficiency (“PKD”), thalassemias, and sickle cell disease. I have extensive experience in the diagnosis and treatment of patients with these conditions throughout the course of their disease. As part of my practice as a clinician, I routinely examine potential drug-drug interactions (“DDIs”) for my patients.

6. I am an internationally recognized clinical researcher in congenital hemolytic anemias, including PKD, thalassemias, and sickle cell disease. As part of my ordinary course in clinical research, I routinely examine potential DDIs between study medications and concomitant medications in patients in clinical trials. I was involved in the design and execution of the clinical development of mitapivat (formerly AG-348), including its Phase II and III studies in PKD and Phase II and III studies in thalassemias and sickle cell disease.

7. As a key opinion leader in the field of congenital hemolytic anemias, I am frequently consulted for the design of clinical trials in rare anemias and am asked to evaluate draft protocols, including doses and inclusion/exclusion criteria. I have been invited to speak to the FDA about designing clinical trials in rare

anemias. I also frequently review manuscripts for publications and abstract presentations at major conferences based on the results of clinical trials, requiring me to carefully assess all aspects of the trial. In these capacities, I must consider how co-administration of drugs will impact clinical results.

8. Of particular relevance to this proceeding, I served as a Site Principal Investigator for the DRIVE-PK Phase II clinical trial of mitapivat (AG-348) in patients with PKD from 2015 to 2018. The DRIVE-PK study is the same Phase II clinical trial that is the focus of the obviousness arguments by Petitioner's expert, Dr. Thirman. Ex.1003 (Thirman Decl.) ¶¶80–174 (citing Agresta (Ex.1005), Grace Presentation (Ex.1008), Grace Abstract (Ex.1009)).¹ I am a named author on both the Grace Presentation and the Grace Abstract.

9. I received my Bachelor of Science degree in Molecular Genetics and Molecular Biology, graduating with High Distinction, from the University of St. Michael's College at the University of Toronto in 2001. I then obtained my Doctor of Medicine (M.D.) degree from Western University in London, Ontario, Canada in 2005. I subsequently earned my Master of Science (M.Sc.) degree in Health Research Methodology, with a focus on Clinical Epidemiology and Biostatistics,

¹ Except for cites to certain patent documents (Ex.1001, Ex.1004) and Dr. Thirman's Declaration (Ex.1003), all cites are to the stamped pagination.

from McMaster University in 2014. I also completed the Clinical Research Methodology program at the American Society of Hematology (“ASH”) Clinical Research Training Institute from 2014 to 2015.

10. Following my medical degree, I completed my Core General Internal Medicine residency training at the University of Toronto (2005–2008), followed by subspecialty training in Adult Hematology at the University of Toronto (2008–2010). I then completed a Clinical Fellowship in the Canadian Adult Comprehensive Hemoglobinopathy Fellowship program at the University of Toronto (2010–2012), where I received specialized training in the diagnosis and management of hemoglobinopathies and other congenital red blood cell disorders. I was a Clinical Fellow at the Royal London Hospital, Barts Health NHS Trust, in London, UK, in the field of Hemoglobinopathy. I am a Fellow of the Royal College of Physicians of Canada, and I hold sub-specialty certification in Hematology from the Royal College of Physicians and Surgeons of Canada, as well as a Certificate of Clinical Fellowship in Benign Hematology and Hemoglobinopathies from the University of Toronto.

11. I currently serve as Vice President of Research and Innovation at Scarborough Health Network (since January 2025) and as Associate Professor in the Division of Hematology, Department of Medicine, Faculty of Medicine, at the University of Toronto (since July 2022). I am the lead for the Adult Sickle Cell

Disease Clinic at the Scarborough Health Network. I have also held a position as Active Staff in the Division of Medical Oncology and Hematology at University Health Network in Toronto since January 2014. Prior to my current appointments, I served as Assistant Professor in the Division of Hematology at the University of Toronto from 2014 to 2022.

12. I have authored or co-authored more than 100 peer-reviewed publications in the fields of hematology, hemolytic anemias, and related disciplines. My publications have appeared in leading medical journals, including The Lancet, the New England Journal of Medicine, Blood, and the British Journal of Haematology. I am an editor for the journal Hematology, which is the official Journal of the International Society of Hematology (ISH).

13. I have been a member of ASH and have served on ASH's Education Program Advisory Panel (2023–2024) and Annual Meeting Accredited Education Committee. I am a member of the European Hematology Association ("EHA") and a member of the EHA specialized working group on red cells and iron. I am a member of the Trial Steering Committee for the International Pyruvate Kinase Deficiency Registry (Peak Registry) (since 2019). I was also a member of the working group that developed the First International Guidelines for the Diagnosis and Management of Pyruvate Kinase Deficiency (2023–2024).

14. Throughout my career, my work has been recognized with various awards and honors, including the Hour Glass Award from the Thalassemia Foundation of Canada (2023) and the John H. Crookston Award from the Canadian Hematology Society (2008).

III. SUMMARY OF MATERIALS REVIEWED AND CONSIDERED

15. All of the opinions contained in this Declaration are based on the documents I reviewed and my knowledge and professional judgment. In forming the opinions expressed in this Declaration, while drawing on my over 15 years of experience in treating hemolytic anemia and designing clinical trials for hemolytic anemia, I reviewed the following documents:

Ex.	Description
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 Patent 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, <i>Pyruvate kinase deficiency</i> , 27 J. Clin. Path. 128 (1974) (“Gordon-Smith”)
1007	Affidavit of Mina Ching, March 21, 2026 & Exhibit A (Dana-Farber Cancer Institute, <i>A Study of AG-348 in Adult Patients With Pyruvate Kinase Deficiency</i> , Aug. 23, 2016) (“Dana-Farber”)

Ex.	Description
1008	Affidavit of Mina Ching, March 21, 2026, Exhibit B (Rachael F. Grace et al., <i>Results Update from the DRIVE PK Study: Effects of AG-348, a Pyruvate Kinase Activator, in Patients with Pyruvate Kinase Deficiency</i> , (presentation at the 22nd Congress of the European Hematology Association, Madrid, Spain, June 22–25, 2017)) (“Grace Presentation”)
1009	Rachael F. Grace et al., <i>Results Update from the DRIVE PK Study: Effects of AG-348, a Pyruvate Kinase Activator, in Patients with Pyruvate Kinase Deficiency</i> , 30 Blood 2194 (2017) (“Grace Abstract”)
1010	Madhav Mutalik & Dhara Sanghavi, <i>Review of Drug Interactions: A Comprehensive Update</i> , 4 Brit. J. Pharm. Rsch. 954 (2014) (“Mutalik”)
1011	U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., <i>Integrated Review: NDA 216916, Pyrukynd (mitapivat)</i> (2021) (“FDA 2022”)
1012	Nathan P. Clark, <i>Warfarin Interaction With Hepatic Cytochrome P-450 Enzyme-Inducing Anticonvulsants</i> , 24 Clin. & Applied Thrombosis/Hemostasis 172 (2018) (“Clark”)
1013	Pamela S. Hackman, “ <i>Spleen Baby</i> ”: <i>A Case Presentation of Pyruvate Kinase Deficiency in an Amish Neonate</i> , 35 Neonatal Network 375 (2016) (“Hackman”)
1014	Neshan B. Ilangaratne et al., <i>Phenobarbital: missing in action</i> , 90 Bull World Health Organ 871 (2012) (“Ilangaratne”)
1015	Paul L. M. van Giersbergen et al., <i>In vivo and in vitro studies exploring the pharmacokinetic interaction between bosentan, a dual endothelin receptor antagonist, and glyburide</i> , 71 Clin. Pharmacol. & Therapeutics 253 (2002) (“van Giersbergen”)

Ex.	Description
1016	C. Bachmeyer et al., <i>Idiopathic pulmonary arterial hypertension in a patient with pyruvate kinase deficiency and paravertebral extramedullary hematopoiesis</i> , 88 Annals of Hematology 603 (2008) (“Bachmeyer”)
1017	Kha Le et al., <i>Population Pharmacokinetics and Pharmacodynamics of AG-348 in Healthy Human Volunteers Guide Dose Selection for the Treatment of Pyruvate Kinase Deficiency</i> , 126 Blood 3336 (2015) (“Le”)
1018	CV of Michael J. Thirman
2011	Yonggoo Kim et al., <i>Diagnostic Approaches for Inherited Hemolytic Anemia in the Genetic Era</i> , 52 BLOOD RSCH. 84 (2017) (“Kim 2017”)
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”)
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”)

Ex.	Description
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”)
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)

Ex.	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)

16. My opinions are additionally guided by my appreciation of how a person of ordinary skill in the art (“POSA”) would have understood the claims of the ’049 Patent at the time of the alleged invention, which I have been asked to assume is June 14, 2019. I refer to this date as the “priority date” below.

IV. SUMMARY OF OPINIONS

17. I understand that Apotex Inc. (“Apotex”) has challenged the patentability of claims 1, 8, 9, 14, 19 (“Challenged Claims”) of the ’049 Patent, based on the following four grounds:

- Ground 1: Anticipation of all Challenged Claims by Sizemore (Ex.1004);
- Ground 2: Obviousness of Challenged Claims 1, 8, 9, 14 over Agresta (Ex.1005), Dana-Farber (Ex.1007), Grace Presentation (Ex.1008), and the knowledge of a POSA;

- Ground 3: Obviousness of Challenged Claims 1, 8, 9, 14 over Agresta (Ex.1005), Dana-Farber (Ex.1007), Grace Abstract (Ex.1009), and the knowledge of a POSA; and
- Ground 4: Obviousness of Challenged Claim 19 over Agresta (Ex.1005), Dana-Farber (Ex.1007), Grace Presentation (Ex.1008) or Grace Abstract (Ex.1009), Sizemore (Ex.1004), and the knowledge of a POSA.

18. In my opinion, Sizemore does not anticipate the Challenged Claims (Ground 1), because Sizemore does not teach “administering . . . mitapivat or a pharmaceutically acceptable salt thereof and a moderate inducer of cytochrome P450 3A4/5 (CYP3A4/5),” which is required by the Challenged Claims. Instead, Sizemore is a patent publication dealing with crystalline forms of mitapivat alone. Sizemore does not mention using any moderate CYP3A4/5 inducers for any purpose. A POSA would not have understood Sizemore’s single reference to a subject that is not taking a strong CYP3A4 inducer as a teaching to affirmatively co-administer mitapivat with moderate CYP3A4/5 inducers.

19. Additionally, in my opinion, the Challenged Claims would not have been obvious to a POSA as of June 14, 2019. The cited references for Grounds 2 and 3—Agresta, Dana-Farber, Grace Presentation, and Grace Abstract, alone or in combination—would not have motivated a POSA with a reasonable expectation of success to practice the claimed method, including “administering . . . mitapivat or

a pharmaceutically acceptable salt thereof and a moderate inducer of cytochrome P450 3A4/5 (CYP3A4/5).” Those references all relate to clinical trials of mitapivat alone. None include the prospective clinical DDI trials and pharmacokinetic modeling supporting co-administration of mitapivat and moderate CYP3A4/5 inducers, which was first described by Agios in the '049 Patent.

20. In Ground 4, Apotex and Dr. Thirman only challenge claim 19, which depends from claims 1, 8, 9 and 14. Dr. Thirman relies on the same references as Grounds 2–3, but adds Sizemore to address the limitations of claim 19; he argues that Sizemore teaches a tablet composition for mitapivat including specific inactive ingredients (i.e., microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate). For the same reasons as Grounds 2–3, claim 19 - which also requires co-administration of mitapivat and moderate CYP3A4/5 inducers - would not have been obvious.

V. LEGAL STANDARDS

21. I am not a lawyer. In forming my opinions, I have applied the legal standards below that counsel provided to me.

A. Claim Construction

22. I understand that claim terms must be construed (interpreted) as they would be understood by a POSA, following review of the claim language, the specification, and the prosecution history. I also understand that, unless a patentee

provides a different definition in the patent specification, a claim term should be given its plain and ordinary meaning as it would be understood by a POSA at the time of the invention, considering the teachings of the claims themselves, the patent's specification, and the prosecution history. Accordingly, unless a claim term has been defined in the patent specification, either explicitly or by clear implication, I have applied the term's plain and ordinary meaning.

B. Anticipation

23. I understand that a prior art reference anticipates a claim only if it discloses all of the claim limitations combined in the same way as recited in the claim.

24. I understand that anticipation requires that the prior art reference disclose every limitation of the claimed invention either expressly or inherently. I understand that inherent disclosure requires that the missing element is “necessarily” present in the prior art—and inherency may not be established by probabilities or possibilities.

25. I understand that anticipation is a strict standard. A reference that discloses some, but not all, elements of a claim does not anticipate that claim, even if POSA would be able to immediately envisage the missing limitation or the limitation would be obvious to include based on general knowledge in the art.

C. Obviousness

26. I understand that a patent claim is unpatentable as obvious only if the differences between the claimed invention and the prior art are such that the subject matter as a whole would have been obvious to a POSA at the time the invention was made (which I have been asked to assume is June 14, 2019 in this case). I understand that obviousness is evaluated with consideration of the following four factors: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) objective indicia of nonobviousness.

27. I understand that a finding of obviousness requires that a POSA would have been motivated to combine or modify the prior art references to arrive at the claimed invention, and that the POSA would have had a reasonable expectation of success in doing so.

28. I have also been informed that the reason to combine or modify analysis must account for “reasons not to combine or modify.” For example, a motivation to combine or modify may not exist where the combination or modification would be inoperable, would have undesirable properties, or would be unlikely to be productive of the result sought by the inventor.

29. I have been informed that the use of hindsight must be avoided in the obviousness analysis, and one must be cautious to avoid reading into the prior art

the teachings of the claimed invention at issue. In other words, obviousness cannot be established by starting from the claimed invention and working backward to identify each limitation in the prior art. I have also been informed that obviousness must be assessed based on the prior art as a whole and that it is improper to pick and choose from any reference only so much as will support a given position, to the exclusion of other parts necessary for the full appreciation of what the reference suggests to one of skill in the art.

VI. A PERSON OF ORDINARY SKILL IN THE ART

30. I understand that patents are to be read from the perspective of a hypothetical person of ordinary skill in the art (again, a “POSA”) in the relevant field at the time of the invention. I have been informed by counsel that this hypothetical person is a person of ordinary creativity capable of understanding the scientific principles applicable to the pertinent field.

31. I have been informed by counsel that, for the purpose of this proceeding, the undisputed priority date of the ’049 Patent is June 14, 2019. Based on guidance from counsel, I have considered the POSA’s perspective to be from the point of view of June 14, 2019.

32. Dr. Thirman’s proposed POSA definition is the following (Ex.1003 (Thirman Decl.) ¶60):

It is my view 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. A POSA may be part of a team that includes other scientists in related fields, for example a pharmacologist or pharmaceutical formulator.

33. For the purposes of this declaration only, I have applied this definition in my analysis.

34. As of June 14, 2019, I had at least the background and qualifications of a POSA under Dr. Thirman's POSA definition.

VII. CLAIM CONSTRUCTION

35. Counsel has informed me that Apotex has proposed two terms for construction: "mitapivat" and "CYP3A4/5."

36. Counsel has informed me that Apotex proposes that "mitapivat" should be construed as "N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide." I agree with this definition and have applied it in my analysis.

37. Counsel has informed me that Apotex proposes that "CYP3A4/5" be defined as "cytochrome P450 3A4 (CYP3A4) or 3A5 (CYP3A5)," as described in the '049 Patent specification at 2:22–23. I agree with this definition and have applied it in my analysis.

38. I otherwise give the words of the claims their plain and ordinary meaning.

VIII. SCIENTIFIC BACKGROUND AND STATE OF THE ART

A. Treatment of Rare Hemolytic Anemias With Mitapivat

39. Inherited hemolytic anemias are a class of rare genetic diseases that result in increased destruction of red blood cells (“hemolysis”). Ex.2011 (Kim 2017) at 001. The anemia in severe cases can be life-threatening if the heart does not get enough oxygen (angina) and cannot pump enough blood to meet the body’s needs (cardiopulmonary decompensation). *Id.* Chronic hemolytic anemia damages multiple organs. Ex.2017 (Taher 2018) at 001–2; Ex.2016 (Grace 2018) at 009.

40. These anemias can have different causes, such as (1) defects in red blood cell enzymes or (2) defects affecting hemoglobin (the oxygen-carrying protein in red blood cells). Ex.2011 (Kim 2017) at 001, 005–7.

41. Pyruvate kinase deficiency (“PKD”) is an example of an inherited hemolytic anemia caused by an enzyme defect. Ex.2011 (Kim 2017) at 006; Ex.2018 (Grace 2015) at 001. Pyruvate kinase is an enzyme critical for red blood cell metabolism; when defective, red blood cells are prematurely destroyed. Ex.2018 (Grace 2015) at 001. PKD is rare, with only 3.2 to 8.5 cases per million people in Western populations. Ex.2015 (Foy 2025) at 001. But patients that have

PKD have many different serious complications in addition to anemia: iron overload, gallstones, low bone density (increasing fracture risk), as well as pulmonary hypertension and leg ulcers. Ex.2016 (Grace 2018) at 009. They also have a shorter overall survival and a risk of death that is about five times that of matched controls. Ex.2015 (Foy 2025) at 002. For example, at 55 years of age, the estimated probability of survival for patients with PKD has been reported as 92% as compared to 99% for age-matched controls. *Id.*

42. Thalassemia syndromes are examples of inherited hemolytic anemia caused by defects in hemoglobin. Ex.2011 (Kim 2017) at 006. There are two main types of thalassemia, alpha and beta thalassemia, in which different parts of the hemoglobin protein are affected. *Id.*; Ex.2012 (Modell 2008) at 001–2. Alpha thalassemia involves mutated or deleted alpha-globin genes, while beta thalassemia involves mutated or deleted beta-globin genes. Ex.2011 (Kim 2017) at 006; Ex.2012 (Modell 2008) at 001–2. Severe thalassemia is often fatal without treatment. Ex.2012 (Modell 2008) at 002. Like patients with PKD, patients with thalassemia suffer from a variety of complications including iron overload, gallstones, low bone density (increasing fracture risk), as well as heart problems. *Id.*; Ex.2017 (Taher 2018) at 001–3, 005.

43. Mitapivat treatment is transformative for patients with PKD or thalassemia. It is the first and only approved drug in its therapeutic class and the

first and only drug to be approved to treat PKD. Ex.1011 (FDA 2022) at 2, 21–22, 27, 29. Prior PKD treatments were merely supportive therapies that treated clinical symptoms without addressing the underlying deficiency. Ex.2018 (Grace 2015) at 001; Ex.1011 (FDA 2022) at 27, 29. By activating the pyruvate kinase enzyme that provides energy in red blood cells, it directly treats the underlying deficiency that causes disease in patients with PKD and stops their red blood cells from breaking down. Ex.1011 (FDA 2022) at 29. Mitapivat provides a substantial improvement in hemoglobin response in non-transfusion-dependent patients with PKD. *Id.* at 21. It also improves key quality of life metrics including fatigue, shortness of breath, and jaundice and reduces the need for transfusions in patients who are on regular transfusions. *Id.* Moreover, unlike mitapivat, a twice-a-day oral treatment, prior PKD therapies were often invasive, e.g., regular transfusions or splenectomy. Ex.2018 (Grace 2015) at 002–3.

44. Mitapivat is just as life-changing for patients with thalassemia. Mitapivat is the first FDA-approved oral treatment for beta thalassemia and the first drug approval for patients with alpha thalassemia. Ex.2019 (FDA Aqvesme™ Approval) at 001. Mitapivat substantially improves hemoglobin response in patients who are not transfusion-dependent, and reduces transfusions in patients who regularly receive them; it also reduces fatigue-related symptoms as measured by a patient-reported outcome instrument, and patients taking mitapivat

demonstrate clinically meaningful improvements in cardiopulmonary functional capacity (6-minute walk test). *Id.* at 001–2; Ex.2020 (ENERGIZE Press Release) at 003–4. Mitapivat provides these benefits over more invasive prior art treatments for thalassemia, e.g., regular transfusions. Ex.2012 (Modell 2008) at 002.

B. Drug-Drug Interactions

45. Patients frequently use more than one medication at a time. The performance of one drug can be altered by the presence of another drug, causing drug-drug interactions (“DDIs”).

46. DDIs pose a serious risk for complications, and threaten the efficacy and safety of the target medication. Ex.2023 (FDA, Clinical Drug Interaction Studies) at 005 (“Unanticipated, unrecognized, or mismanaged DDIs are an important cause of morbidity and mortality associated with prescription drug use”). Because of DDI risks, before prescribing any drug, clinicians must consider the other drugs a patient is taking. Ex.2021 (Rowland & Tozer) at 004–7. And to ensure DDIs are managed effectively, regulatory agencies like the FDA require them to be “defined during drug development” and “understood via nonclinical and clinical assessment at the time of the investigational drug’s approval.” Ex.2023 (FDA, Clinical Drug Interaction Studies) at 005.

47. DDIs must be identified and characterized empirically. The FDA generally requires “[p]rospective clinical DDI studies” which are “specifically

designed to detect DDIs.” Ex.2023 (FDA, Clinical Drug Interaction Studies) at 006.

48. DDIs have diverse underlying causes. DDIs can result from two drugs having additive or opposing direct effects on the same site of action or system, without necessarily altering drug concentrations. An example is that two blood pressure medications can work in different ways to reduce blood pressure more than either drug would alone. Ex.2021 (Rowland & Tozer) at 004. For example, the combination of a drug that blocks the tightening of blood vessels (i.e., beta blocker) and a diuretic, which lowers fluid volume in the bloodstream, lowers blood pressure more than either alone because the reduced fluid can more easily flow through the widened vessels. *Id.*

49. DDIs can also occur when one drug changes the concentration or availability of another drug by changing how the body processes the second drug—i.e., how the drug is taken up into the body (absorption), carried through the body and bloodstream (distribution), broken down (metabolism), or removed from the body (elimination). These are referred to as “pharmacokinetic” DDIs. Ex.2021 (Rowland & Tozer) at 005, 007. For example, two drugs can bind together in the gut to form a complex that cannot be absorbed into the blood. *Id.* at 005. This can happen with antacids containing calcium and antibiotics or chloroquine. *Id.* Or a

drug can change how blood flows through the liver and thus how fast a second drug is cleared from the body. *Id.* at 032.

50. DDIs can also happen when one drug changes how fast or slow another drug is broken down in the body (metabolized). Ex.2021 (Rowland & Tozer) at 014–32.

51. Cytochrome P450 (CYP) enzymes are a large group of enzymes that metabolize drugs and toxins in the body. Multiple distinct types of cytochrome P450 (CYP) exist in the body (e.g., CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2). Depending on the drug, it can be metabolized by one 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).

52. A CYP inducer is a drug that increases the level of a given CYP enzyme; that in turn can decrease the levels of a second drug (e.g., mitapivat) that is metabolized by that CYP enzyme. Ex.2021 (Rowland & Tozer) at 030; Ex.2024 (Hakkola 2020) at 021–23.

53. A CYP inhibitor decreases the activity of a CYP. Inhibition generally occurs in one of two ways. Ex.2021 (Rowland & Tozer) at 015–16. In competitive inhibition, the CYP inhibitor binds to the CYP enzyme's active site, which is used to break down drugs, and blocks the second drug from binding and being metabolized. *Id.* However, the block is not permanent. *Id.* This is the most

common type of inhibition. *Id.* Alternatively, a CYP inhibitor may bind to the CYP enzyme active site and undergo a chemical change to permanently bind to and inactivate the CYP enzyme in “mechanism-based inhibition.” *Id.* at 016. This results in elevated levels of the second drug in the body, which can lead to toxic side effects or overdose-like symptoms—even when the second drug is taken at its normal dose. *Id.* at 014–29.

54. Identification and characterization of interactions between CYP inducers/inhibitors and a second drug (like mitapivat) is critical for proper dosing; the second drug’s safety and efficacy depends on how much of that drug is present in the body and for how long. Clinicians commonly describe the drug exposure for the second drug using two basic measurements. The area under the plasma concentration-time curve (“AUC”) captures the total amount of the second drug the body is exposed to over time. The maximum plasma concentration (“C_{max}”) is the highest level of the second drug reached in the blood after a dose. Together AUC and C_{max} are the standard measures used to assess how much of the second drug is present in the bloodstream, and they are important measurements to understand if there is a clinically meaningful change in the amount of the second drug available to treat the patient.

55. CYP inducers are classified by potency based on their ability to reduce the AUC of a sensitive index substrate—drugs with well-characterized

sensitivity to CYP induction. The FDA defines a “strong” inducer as one that decreases the AUC of a sensitive substrate by $\geq 80\%$, a “moderate” inducer as one causing a ≥ 50 to $< 80\%$ decrease, and a “weak” inducer as one causing a ≥ 20 to $< 50\%$ decrease. Ex.2023 (FDA, Clinical Drug Interaction Studies) at 024, 031–32; Ex.2024 (Hakkola 2020) at 003; *see also* Ex.1001 (’049 Patent) at 5:44–53. This classification characterizes the potency of an inducer only in relation to sensitive index substrates. Ex.2024 (Hakkola 2020) at 003. The sensitivity of any new drug must be empirically determined.

56. There are many different CYP enzymes and the potency of a “CYP inducer” or “CYP inhibitor” is defined in relation to specific CYP enzymes, e.g., CYP2B6, CYP3A4, or other CYP enzymes. Ex.2021 (Rowland & Tozer) at 014–15. CYP3A4 and CYP3A5 are closely related and overlap heavily in the drugs that induce them and the drugs that are metabolized by them; inducers of these CYPs may be referenced collectively as CYP3A4/5 inducers. Ex.2024 (Hakkola 2020) at 030; Ex.2021 (Rowland & Tozer) at 015.

57. As an illustration of how CYP induction sensitivity varies by drug and must be empirically determined, the table below shows how a strong inducer for a given CYP can have widely varying effects on different drugs each metabolized by these CYPs (CYP3A4/5). This table shows how rifampin, a strong inducer of CYP3A4/5, can have widely varying effects on different drugs metabolized by

CYP3A4/5. Notably, this table also shows how AUC and $C_{\max}$ can be differently impacted by that same strong CYP3A4/5 inducer (rifampin). For everolimus and dasatinib, the reductions of AUC and $C_{\max}$ by rifampin are roughly equivalent. There is an about 80% reduction for AUC and $C_{\max}$ for dasatinib and about a 60% reduction for AUC and $C_{\max}$ for everolimus. But for venetoclax and vandetanib, the AUC and $C_{\max}$ reductions are quite different. AUC is reduced by rifampin by about 70% for venetoclax but $C_{\max}$ is reduced by only half that. For vandetanib, AUC is reduced by 40% by rifampin and $C_{\max}$ is unchanged.

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

Drug	AUC Reduction	$C_{\max}$ Reduction	Reference²
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))

58. The drug-specific effect of rifampin and its unpredictable impact on AUC and $C_{\max}$ highlight the need for clinical DDI data and accompanying sophisticated modeling to characterize DDIs. Dosing to compensate for DDIs

² Each of the references is the current label as of the priority date of June 14, 2019.

cannot be predicted without empirical DDI clinical data or by back-of-the-envelope arithmetic. This is all the more true because it is unpredictable whether DDIs will impact AUC and $C_{\max}$ in the same way; each of these metrics affects safety and efficacy, and a POSA would have needed to consider them independently. Any attempt to compensate for DDIs with dose adjustments must be shown to provide both AUC and $C_{\max}$ levels that are within the therapeutic window (i.e., high enough to be effective, but not so high as to be toxic); that can only be established through clinical DDI data and physiologically based pharmacokinetic (“PBPK”) modeling. Ex.2022 (FDA, In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies) at 006; Ex.2023 (FDA, Clinical Drug Interaction Studies) at 006, 008–9, 013–14.

59. The impact of a CYP inducer on a co-administered drug depends on a variety of factors including basic biochemistry of the interaction between the co-administered drug and the CYP enzyme (e.g., affinity of the co-administered drug to the CYP and catalytic efficiency of the reaction between the CYP enzyme and co-administered drug), relative contribution of a specific enzyme to overall metabolism or pharmacokinetic behavior of a co-administered drug, and alternative enzymatic and excretory clearance routes. Ex.2024 (Hakkola 2020) at 003. It is unpredictable whether and to what extent any CYP inducer will have clinically significant effects.

60. At the time of the invention in 2019, clinical DDI testing was necessary to characterize and manage DDIs for a new drug and required by the FDA. According to the FDA, when preclinical and early pharmacokinetic data suggest that a specific metabolizing enzyme contributes $\geq 25\%$ of the drug's elimination, then "the sponsor *should* conduct *clinical DDI studies* using strong index inhibitors and/or inducers of the enzyme." Ex.2022 (FDA, In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies) at 006–7 (emphases added); Ex.2023 (FDA, Clinical Drug Interaction Studies) at 006 ("Proper and thorough DDI evaluations that can inform regulatory decision-making generally require studies specifically designed for this purpose.").

61. The FDA accepted evidence-based PBPK modeling as of June 14, 2019 "to predict the effects of enzyme modulators on the PK [pharmacokinetics] of an investigational substrate" but only after this clinical DDI testing using strong inhibitors and inducers of the metabolizing enzyme, and "*if* the models *can describe the available data on DDIs for a strong enzyme inhibitor or inducer.*" Ex.2022 (FDA, In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies) at 038 (emphases added); *see also* Ex.2023 (FDA, Clinical Drug Interaction Studies) at 008–9 ("Before using a PBPK modeling approach . . . the sponsor should verify the models using human pharmacokinetic data and information from DDI studies that used strong index perpetrators [i.e., inhibitors

or inducers]”), 013–14 (explaining that “clinical DDI studies should start with a strong index inhibitor and a strong index inducer” and that modeling may be used “to gain a full understanding of the investigational drug’s DDI potential” only after such studies); Ex.2024 (Hakkola 2020) at 032 (“human in vivo DDI studies are still needed to definitively demonstrate the consequences of [CYP] inhibition/induction”); *see also id.* at 001 (“After preclinical studies, there is an ultimate need of human in vivo studies and observations on [CYP] inhibition and induction.”).

62. As of June 14, 2019, Agios had reported that the CYP3A4 enzyme breaks down mitapivat in the body. Ex.1005 (Agresta) at 42; Ex.1017 (Le) at 2. This would suggest to a POSA that drugs that induce or inhibit the activity of CYP3A4 (or the related CYP3A5 enzyme) could potentially lead to DDIs with mitapivat. A POSA would have understood that the FDA would require clinical DDI studies with strong index inhibitors and/or inducers of CYP3A4/5 and mitapivat. As of June 14, 2019, no such clinical DDI trials or further modeling had been reported for mitapivat and DDIs between mitapivat and CYP3A4/5 inducers (strong, moderate, or weak) had not been characterized.

63. Agios had also reported as of June 2019 that mitapivat itself was an inducer of CYP3A4, the same enzyme responsible for its metabolism (auto-induction). Ex.1005 (Agresta) at 42; Ex.1017 (Le) at 2. When a drug induces its

own metabolism, it accelerates its own clearance over time, such that its exposure declines with repeated dosing even before any external CYP inducer is introduced (time-varying clearance). Ex.1005 (Agresta) at 42; Ex.1017 (Le) at 2. Moreover, because mitapivat is an inducer of CYP3A4, it could also increase the clearance of other co-administered drugs that are metabolized by CYP3A4, and not merely its own. The additional layer of complexity introduced by mitapivat's auto-induction only made the characterization of DDIs even more unpredictable without the dedicated clinical DDI studies and associated PBPK modeling that Agios was the first to perform and first disclosed in the '049 Patent.

64. In approving mitapivat to treat PKD, the FDA relied on Agios's dedicated clinical DDI studies and associated PBPK analysis to assess CYP3A4/5 DDIs. Ex.1011 (FDA 2022) at 210–224 (Agios PBPK analyses “adequate to predict the interaction effect of CYP3A inducers”); *see also id.* at 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). This is the type of data and analyses that a POSA would have required before co-administering a moderate CYP3A4/5 inducer and mitapivat. Without such data and analyses, a POSA's concern with the potential for a clinical DDI

between a moderate CYP3A4/5 inducer and mitapivat could force patients to discontinue or avoid therapy with mitapivat altogether.

65. Without a basis to understand and manage the potential for a clinical DDI between a moderate CYP3A4/5 inducer and mitapivat, a POSA, as of June 14, 2019, would have avoided co-administration of the two.

C. Clinical Trial Exclusions

66. This avoidance approach is reflected in exclusion criteria in early-phase clinical trials.

67. The exclusion of concomitant medications from a clinical trial reflects a judgment by the trial sponsor about the risks associated with conducting the trial. Among the risks a sponsor must manage in designing an early-phase efficacy or dose selection trial (e.g., Phase II) is the risk that a genuinely effective treatment could appear ineffective—or that its safety and efficacy signals could be confounded—because of an uncharacterized DDI. For example, for drugs that are metabolized by a particular CYP enzyme, it was standard practice to exclude strong inducers of that enzyme, since they are most likely to cause DDIs affecting safety and/or efficacy. This exclusion reflects caution on the part of the sponsor in the absence of clinical DDI data required to understand potential DDIs.

68. The absence of an exclusion for a different category of medications is not a determination that co-administration with that category is safe or clinically appropriate.

IX. THE '049 PATENT (Ex.1001)

69. To characterize DDIs between mitapivat and CYP3A4/5 inducers and inhibitors, the '049 Patent ("Mitapivat Therapy and Modulators of Cytochrome P450"), provides preclinical and clinical trial data, and describes PBPK modeling of such DDIs. Based on those teachings, the '049 Patent claims methods of treating hemolytic anemia with specific doses of mitapivat (about 10, 40, 100, or 200 mg/day), for patients who are taking a moderate inducer of CYP3A4/5.

70. The '049 Patent explains that 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 body, as determined by the measured plasma levels of the compound and its metabolites." Ex.1001 ('049 Patent) at 5:21–26. Such DDIs can also lead to a "decrease in the therapeutic efficacy of the first drug (e.g., mitapivat)." *Id.* at 21:59–22:2; *see also id.* at 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 . . .").

71. In Example 1, the '049 Patent describes *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. Regarding CYP3A4/5, the patent reports:

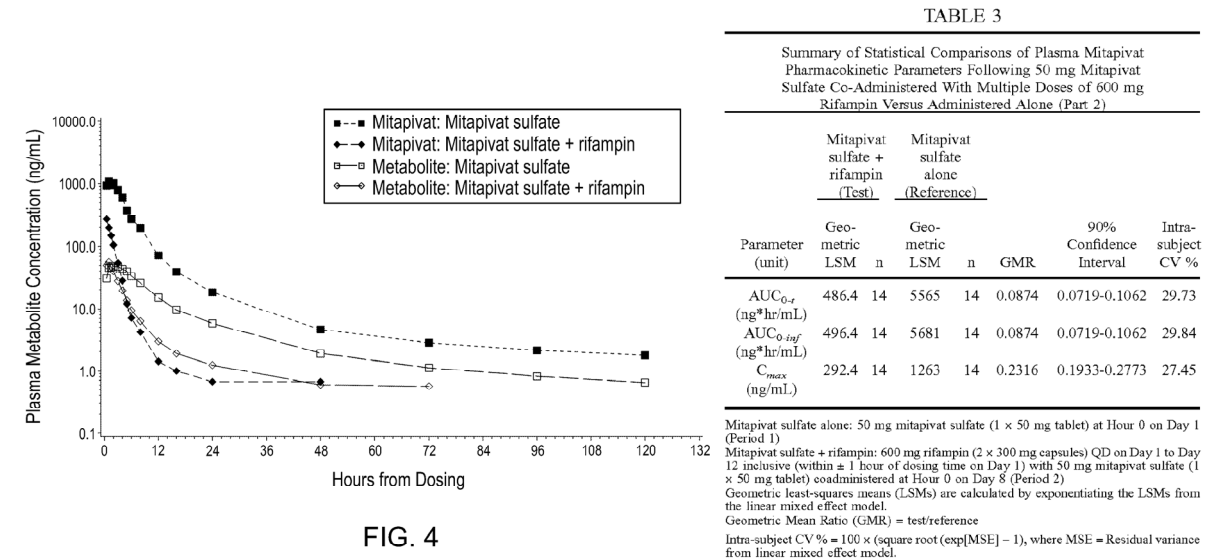
- “mitapivat sulfate was primarily metabolized [broken down] by CYP3A4/5 (>90%)”;
- “minor contributions from CYP2C9, CYP2C8, and CYP1A2” to the breakdown of mitapivat;
- “inhibition of . . . CYP3A4 (largely irreversible)” by mitapivat itself; and
- mitapivat is “a potential inducer of human . . . CYP3A4.”

Ex.1001 ('049 Patent) at 36:8–17.

72. Example 2 of the '049 Patent includes data from 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 presented in Tables 1–4 and Figures 1–4.

73. Data from the clinical DDI studies in the '049 Patent demonstrates that mitapivat levels in the blood are extremely sensitive to co-administration with

rifampin, a standard index strong inducer of CYP3A4/5. 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). Ex.1001 ('049 Patent) at 42:22–62 (“The geometric mean AUC0- t and AUC0-inf ratios of mitapivat in the presence and absence of rifampin were 0.09 [9%]. The geometric mean Cmax ratio of mitapivat in the presence and absence of rifampin was 0.23 [23%].”).



Id. at Fig. 4; *id.* at 42:28–53.

74. Example 3 of the '049 Patent describes the development of a “physiologically based pharmacokinetic model (*hereinafter* “PBPK model”) for mitapivat sulfate based on the currently available in-vitro and clinical PK [pharmacokinetic] data.” Ex.1001 ('049 Patent) at 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 metabolized by a variety of CYP and other enzymes. *Id.* at 44:1–67. For example, “[t]he impact of the co-administration of the moderate CYP3A4 inducer efavirenz on the PK [pharmacokinetic profile] of mitapivat sulfate will be determined following single and multiple dose administration of 5, 20 and 50 mg BID.” *Id.* at 44:22–25. The modeling also characterizes the effects of 5 to 50 mg BID mitapivat sulfate on drugs metabolized or otherwise cleared by the following enzymes: CYP3A4, CYP2B6, CYP2C9, CYP2C8/CYP3A4, CYP2C19, OATP1B1/OATP1B3, P-gp, metformin and OAT3. *Id.* at 44:26–67. The modeling was even designed to account for the effect of an increase in stomach pH. *Id.* at 45:1–11.

75. I understand Apotex is challenging claims 1, 8, 9, 14 and 19 of the ’049 Patent, which are copied below.

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) at 45:25–30.

8. The method of claim 1, wherein the subject is administered about 200 mg/day of mitapivat or a pharmaceutically acceptable salt thereof. *Id.* at 46:7–9.

9. The method of claim 8, wherein the subject is administered about 100 mg of mitapivat or a pharmaceutically acceptable salt thereof twice

per day. *Id.* at 46:10–12; Ex.1002 ('049 Patent prosecution history) at 459.

14. The method of claim 9, wherein the mitapivat or a pharmaceutically acceptable salt thereof is orally administered as part of a tablet composition. Ex.1001 ('049 Patent) at 46:24–26.

19. The method of claim 14, wherein the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate. *Id.* at 46:39–41.

X. ASSERTED PRIOR ART

76. I have reviewed each of the prior art references that Dr. Thirman asserts across four grounds: Sizemore (Grounds 1 and 4), Agresta (Grounds 2–4), Dana-Farber (Grounds 2–4), Grace Presentation (Grounds 2 and 4), and Grace Abstract (Grounds 3–4). As I explain below, none of these references discloses co-administration of mitapivat with a moderate CYP3A4/5 inducer.

A. Sizemore (Ex.1004)

77. I understand from counsel that Sizemore is a patent publication, International Publication No. WO 2019/104134 A1, titled “Crystalline Forms of N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide.” Ex.1004 (Sizemore) at Cover. Sizemore is directed to crystalline forms of mitapivat, not DDIs. *Id.* at [0056]–[0083]. Sizemore states that its purpose was “to develop alternative forms of Compound 1 in an effort to facilitate

isolation, manufacturing, and formulation development, as well as to enhance storage stability.” *Id.* at [0004].

78. Consistent with that purpose, the experimental disclosure in Sizemore is devoted to the preparation and characterization of forms of mitapivat—X-ray powder diffraction patterns, thermal analyses, solubility, and related solid-state properties. Ex.1004 (Sizemore) at [0161]–[0249]. Sizemore evaluated only mitapivat alone; that is the only drug administered (to rats, not humans) and it was solely for the purpose of comparing pharmacokinetic parameters (AUC and C_{max}) of different forms of mitapivat. *Id.* at [0233]–[0249]. No DDIs were evaluated in these experiments. *Id.*

79. Sizemore does not teach co-administering any CYP3A4/5 inducer with mitapivat. Sizemore’s only reference to CYP3A4/5 appears in the definition of a “subject,” which states 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.” Ex.1004 (Sizemore) at [0053] (emphases added). That sentence describes categories of drugs a subject is **not** taking; it does not describe administering anything to the subject. And Sizemore does not mention **moderate** CYP3A4/5 inducers at all.

80. Dr. Thirman relies on the statement that a “therapeutically effective amount of a compound described herein” (i.e., form of mitapivat), is an amount

“alone or in combination with other therapies.” Ex.1003 (Thirman Decl.) ¶73 (citing Ex.1004 (Sizemore) at [0046]). But that statement does not identify any CYP3A4/5 inducers. In my opinion, and as I explain further in Section XI below, a POSA would have understood that Sizemore is directed to forms of mitapivat and how to make and formulate them. A POSA would not have understood Sizemore to provide instructions about which concomitant medications may be safely and effectively co-administered with mitapivat, and certainly not as teaching co-administration of mitapivat with a moderate CYP3A4/5 inducer.

B. Agresta (Ex.1005)

81. I understand from counsel that Agresta is a patent publication, International Publication No. WO 2016/201227 A1. Ex.1005 (Agresta) at Cover. Agresta is directed to methods of treating PKD and other hemolytic anemias by administering mitapivat alone. *E.g., id.* at 25. Every study described in Agresta evaluates mitapivat as a standalone therapy and does not disclose co-administration of any other drugs, much less moderate CYP3A4/5 inducers.

82. Agresta’s Example 3 reports the first-in-human Phase I studies of mitapivat alone in healthy volunteers. Ex.1005 (Agresta) at 39–44. Example 4 sets out a prospective protocol for the Phase II DRIVE-PK study of mitapivat alone in adults with PKD. *Id.* at 44–47. Neither the Phase I studies nor the Phase II protocol was designed to evaluate DDIs, and neither reports any DDI data. *Id.* at

37–47. Agresta identifies no concomitant medication of any kind that was administered with mitapivat in these studies. *Id.*

83. Agresta does not teach co-administering any CYP3A4/5 inducer with mitapivat. Agresta’s only reference to a CYP enzyme is in the context of identifying a complicating factor in the dosing of mitapivat alone, i.e., it is itself an inducer of the CYP3A4 enzyme responsible for its own clearance—auto-induction. Agresta observed that mitapivat pharmacokinetic parameters “were lower on Day 14 compared with that on Day 1, suggesting that multiple doses of Compound 1 [mitapivat] may result in an increase in the rate of drug metabolism,” and explained that “[t]he decrease in exposure on Day 14 is consistent with pre-clinical data suggesting that Compound 1 is a moderate inducer of cytochrome P450 3A4 (CYP3A4), which is the major route of the oxidative metabolism of Compound 1 [mitapivat].” Ex.1005 (Agresta) at 42.

C. Dana-Farber (Ex.1007)

84. Dana-Farber is purportedly an archived Dana-Farber/Boston Children’s Cancer and Blood Disorders Center webpage for the clinical trial, “A Study of AG-348 in Adult Patients With Pyruvate Kinase Deficiency” (Study AG348-C-003, NCT02476916)—that is, DRIVE-PK. Ex.1007 (Dana-Farber) at 5. The page is a patient-facing recruitment listing for a study of mitapivat alone, and contains no data. It provides a two-sentence description of the study, gives its

status, phase, diagnosis category, conducting institutions, overall principal investigator, and contact information, and then lists fourteen inclusion criteria and sixteen exclusion criteria. *Id.* at 5–6.

85. Dana-Farber does not mention moderate inducers and does not teach co-administering any CYP3A4/5 inducer with mitapivat. Dr. Thirman relies on one of the exclusion criteria (#12) that excludes patients taking “restricted products known to strongly inhibit cytochrome P450 (CYP) 3A4 metabolism within 5 days prior to . . . Day 1 dosing, or to strongly induce cytochrome P450 3A4 (CYP3A4) metabolism within 28 days prior to Day 1 dosing, or to strongly inhibit P-glycoprotein transporter within 5 days prior to Day 1 dosing, or digoxin within 5 days prior to Day 1 dosing.” Ex.1007 (Dana-Farber) at 6.

86. Read as a whole, these criteria reflect the clinical trial sponsor, Agios, managing uncertainty about potential DDIs by excluding strong inducers and inhibitors that are most likely to cause any such DDIs. Nothing in Dana-Farber states that any patient taking a moderate CYP3A4/5 inducer was enrolled or that co-administration of mitapivat with a moderate CYP3A4/5 inducer is safe, effective, or clinically appropriate.

D. Grace Presentation (Ex.1008)

87. Grace Presentation is a slide presentation titled, “Effects of AG-348, a pyruvate kinase activator, in patients with pyruvate kinase deficiency: Updated

results from the DRIVE PK study.” Ex.1008 (Grace Presentation) at 16–32. I am one of its named authors and was a Site Principal Investigator for the study it reports. *Id.* at 17. The presentation reports interim safety, tolerability, pharmacodynamic, and hemoglobin data for mitapivat alone. *Id.* at 19–31.

88. DRIVE-PK was a Phase 2 study testing mitapivat therapy alone in non-transfusion-dependent adults with PK deficiency. Ex.1008 (Grace Presentation) at 19.

89. Grace Presentation does not teach co-administering any CYP3A4/5 inducer with mitapivat; it reports nothing about any concomitant medications. It does not list the concomitant medications taken by enrolled patients or identify any patient as taking any CYP3A4/5 inducer and does not state that information regarding concomitant-medications data was collected or evaluated. Ex.1008 (Grace Presentation) at 18–32. It does not mention any CYP enzymes, inducers, inhibitors, or DDIs. *Id.*

90. Two features of the reported data are important to note. First, not all patients in the trial responded to mitapivat. Ex.1008 (Grace Presentation) at 26. Second, of the six drug-related serious adverse events reported, the first listed is “[w]ithdrawal hemolysis followed by anemia.” *Id.* at 21. A POSA would have understood withdrawal hemolysis to be a risk associated with the loss of mitapivat exposure. Far from reassuring a POSA about co-administration with a moderate

CYP3A4/5 inducer, these data would have reinforced the unpredictable effects of changing levels of mitapivat in the blood.

E. Grace Abstract (Ex.1009)

91. Grace Abstract is a conference abstract regarding the DRIVE-PK study, “Results Update from the DRIVE PK Study: Effects of AG-348, a Pyruvate Kinase Activator, in Patients with Pyruvate Kinase Deficiency.” I am one of its named authors as well.

92. Similar to the Grace Presentation, the Grace Abstract reports DRIVE-PK interim data for mitapivat alone in substantially more condensed form. Ex.1009 (Grace Abstract) at 2–3.

93. The Grace Abstract likewise contains no information regarding concomitant medications. It does not report the concomitant medications taken by enrolled patients, identify any enrolled patient as taking a CYP3A4/5 inducer, or state whether concomitant-medication data were collected or analyzed. Ex.1009 (Grace Abstract) at 2–3. It does not mention any CYP enzymes, inducers, inhibitors, or DDIs anywhere. *Id.* In my opinion, the Grace Abstract is an abbreviated report of the same monotherapy dose-ranging data reported in the Grace Presentation, and it similarly provides a POSA with no information about co-administration of mitapivat with a moderate CYP3A4/5 inducer.

XI. GROUND 1: SIZEMORE DOES NOT ANTICIPATE CLAIMS 1, 8, 9, 14 AND 19

94. In my opinion, Sizemore does not anticipate claims 1, 8, 9, 14 and 19. Claims 1, 8, 9, 14 and 19 of the '049 Patent each require “administering to the subject . . . a moderate inducer of cytochrome P450 3A4/5 (CYP3A4/5).” A POSA would not have understood Sizemore to teach such co-administration.

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

95. Dr. Thirman argues “a POSA would have understood Sizemore to contemplate administration of *moderate* inducers of CYP3A4.” Ex.1003 (Thirman Decl.) ¶73 (original emphasis). I understand from counsel that co-administration of mitapivat with moderate CYP3A4/5 inducers needs to be disclosed and that Apotex cannot rely on expert testimony to fill in a missing limitation. In my opinion, this co-administration is a missing limitation. There is nothing in Sizemore that teaches co-administering mitapivat with a moderate CYP3A4/5 inducer expressly. Additionally, nothing in Sizemore indicates that co-administration is necessarily present in Sizemore even if unstated.

96. Sizemore does not teach co-administering any CYP3A4/5 inducer with mitapivat. Nothing in Sizemore’s experimental disclosure teaches co-administration of mitapivat and moderate CYP3A4/5 inducers. Sizemore is a patent publication directed to crystalline forms of mitapivat. Ex.1004 (Sizemore)

at [0056]–[0083]. Sizemore is not directed to DDIs. Sizemore’s experimental disclosure is devoted to the preparation and characterization of forms of mitapivat. *Id.* at [0161]–[0249]. Sizemore evaluated only mitapivat alone; that is the only drug administered (to rats, not humans) and it was solely for the purpose of comparing pharmacokinetic parameters (AUC and Cmax) of different forms of mitapivat. *Id.* at [0233]–[0249]. No DDIs were evaluated in these experiments. *Id.*

97. Dr. Thirman relies on Sizemore’s only reference to CYP3A4/5, which appears in the definition of a “subject” and states 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” to argue that “a POSA would read Sizemore as disclosing co-administration of mitapivat with a moderate CYP3A4 inducer.” Ex.1003 (Thirman Decl.) ¶73 (citing Ex.1004 (Sizemore) at [0053]). That sentence describes categories of drugs a subject is **not** taking; it does not describe administering anything to the subject. And Sizemore does not mention **moderate** CYP3A4/5 inducers. A POSA would have considered mitapivat DDI interactions with CYP3A4/5 modulators to merit serious concern and would have required DDI data (or guidance from regulatory authorities based on that data) before co-administering mitapivat with a moderate CYP3A4/5 inducer.

98. Dr. Thirman additionally relies on Sizemore's statement that a "therapeutically effective amount of a compound described herein" (i.e., form of mitapivat) is an amount "alone or in combination with other therapies." Ex.1003 (Thirman Decl.) ¶73 (citing Ex.1004 (Sizemore) at [0046]). But that statement does not identify any CYP3A4/5 inducers. There is nothing in this statement that would lead a POSA to conclude that these "other therapies" necessarily included moderate CYP3A4/5 inducers.

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

99. I understand from counsel that the mere suggestion of a claim limitation does not satisfy the anticipation standard. In any event, it is my opinion that Sizemore would not have even suggested co-administration of mitapivat with moderate CYP3A4/5 inducers to a POSA.

100. Dr. Thirman argues that "[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." Ex.1003 (Thirman Decl.) ¶73 (original emphasis). I do not agree. Dr. Thirman is using hindsight, starting from the claimed co-administration of moderate CYP3A4/5 inducers and working backwards to argue that Sizemore teaches that element.

101. Because mitapivat was reported to be metabolized by CYP3A4, strong CYP3A4/5 inducers would be most likely to cause DDIs, and it would have been reasonable for a POSA to have avoided co-administering mitapivat with them. Such avoidance would have also been consistent with standard practice in early clinical trials. *See supra* Section VIII.C. But avoidance of strong CYP3A4/5 inducers would not teach a POSA which inducers cause DDIs – strong, moderate, or weak. CYP3A4/5 inducers are classified by their potency in relation to sensitive index substrates: the same inducer can have widely varying effects on different drugs metabolized by CYP3A4/5 and the impact of inducers on a new drug must be empirically determined. *See supra* Section VIII.B. Avoidance of strong inducers tells a POSA nothing about the clinical impact of moderate inducers, and whether or how these impacts can be overcome. If anything, given Sizemore’s disclosure regarding the avoidance of co-administration of strong CYP3A4/5 inducers with mitapivat, a POSA would have avoided co-administering moderate CYP3A4/5 inducers absent the clinical DDI data and analyses necessary to characterize potential DDIs.

102. A POSA would not have assumed that Sizemore’s single sentence regarding a “subject” not taking a strong inducer reflected clinical DDI studies. But even if a POSA had assumed—without reason—that Sizemore’s “subject” reflected DDI studies in some way, a POSA would have known that it is standard

practice to study DDIs with strong CYP inducers *before* conducting such studies with moderate inducers. As of June 14, 2019, under the 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) at 013. And if DDIs were found with a strong CYP inhibitor or inducer, then the FDA required further clinical DDI studies or specific modeling and simulation approaches such as pharmacologically based pharmacokinetic modeling with a verified inhibitor or inducer. *Id.* at 014. Even if Sizemore’s “subject” sentence somehow were assumed to reflect clinical DDI studies, a POSA would not have considered Sizemore to suggest co-administration of mitapivat and a moderate CYP3A4/5 inducer because Sizemore is missing the clinical DDI data and subsequent analysis regarding moderate CYP3A4/5 inducers that a POSA would have required to substantiate that mitapivat could be co-administered with moderate CYP3A4/5 inducers.

103. Moreover, a POSA would have been even more likely to exercise caution here, where mitapivat itself was known to induce CYP3A4. *See supra* Section VIII.B. The combined effect of mitapivat’s own induction and that of an external CYP3A4/5 inducer provided an additional layer of complexity that only made the characterization of DDIs even more unpredictable without the dedicated clinical DDI studies and associated PBPK modeling that Agios was the first to

perform and disclosed in the '049 Patent. *Id.* Without such characterization, a POSA would not have assumed that safe and effective co-administration of mitapivat with moderate CYP3A4/5 inducers was possible.

104. Finally, Dr. Thirman argues that a POSA would consider Sizemore's exclusion of "all inhibitors" while "excluding only strong inducers" to be part of why "a POSA would have understood Sizemore to contemplate administration of *moderate* inducers of CYP3A4." Ex.1003 (Thirman Decl.) ¶73 (original emphasis). I understand from counsel that, for purposes of these proceedings, I am to assume a POSA would have been aware of the Dana-Farber reference, which excludes patients taking "products known to *strongly* inhibit cytochrome P450 (CYP) 3A4 metabolism." Ex.1007 (Dana-Farber) at 6 (emphasis added). Dr. Thirman agrees that Dana-Farber reflects which patients were actually excluded in Agios's Phase II DRIVE-PK study. Ex.1003 (Thirman Decl.) ¶¶81–82, 99–100.

XII. GROUNDS 2–4: CLAIMS 1, 8, 9, 14 AND 19 WOULD NOT HAVE BEEN OBVIOUS OVER THE ASSERTED PRIOR ART

105. Dr. Thirman argues that claims 1, 8, 9 and 14 would have been obvious over Agresta, Dana-Farber, Grace Presentation (or alternatively Grace Abstract), and the knowledge of a POSA. Ex.1003 (Thirman Decl.) ¶¶80, 130. In particular, Ground 2 relies on Agresta, Dana-Farber, and Grace Presentation, as well as the knowledge of a POSA. *Id.* ¶¶80–129. Ground 3 applies the same combination, substituting Grace Abstract for Grace Presentation. *Id.* ¶¶130–163.

106. In Ground 4, Dr. Thirman adds Sizemore to the combinations of Grounds 2 and 3 to address excipients in dependent claim 19; he does not rely on Sizemore with respect to claims 1, 8, 9 or 14. Ex.1003 (Thirman Decl.) ¶¶164–173.

107. In my opinion, none of these combinations of references make claims 1, 8, 9, 14 and 19 of the '049 Patent obvious. Each of these references is directed to treating hemolytic anemia or PKD with mitapivat alone and does not teach co-administration of mitapivat with moderate CYP3A4/5 inducers. Even when looking at the references together, a POSA would not have been motivated with a reasonable expectation of success to co-administer moderate CYP3A4/5 inducers with mitapivat.

A. The Asserted Prior Art References Are Directed to Treatment With Mitapivat Alone and Do Not Teach Co-Administration of Mitapivat With a Moderate CYP3A4/5 Inducer

108. Dr. Thirman relies on disclosures from Agresta, Dana-Farber, Grace Presentation, and Grace Abstract that are directed to clinical trials of *mitapivat alone*, and not to characterizing DDIs or the co-administration of mitapivat with moderate CYP3A4/5 inducers.

1. Agresta Does Not Teach Co-Administration of Mitapivat With a Moderate CYP3A4/5 Inducer

109. I understand from counsel that Agresta is a PCT publication. It teaches treating hemolytic anemia using mitapivat alone. *See, e.g.*, Ex.1005

(Agresta) at 10, 13, 22, 25, 39–48. Agresta provides the results of the first studies of mitapivat in humans (Phase I clinical trials), as well as a protocol for a Phase II clinical study for treating PKD with mitapivat. Ex.1005 (Agresta) at 39–44 (Phase I studies and results), 44–47 (Phase II protocol for DRIVE-PK). Neither of these were DDI studies.

110. Agresta contains no discussion of mitapivat DDIs or how to address them. Agresta has a single mention of CYP enzymes in its 70 pages. Ex.1005 (Agresta) at 42. Agresta identifies a non-linear dose response for mitapivat alone in the Phase I clinical trials, whereby levels of mitapivat were lower after multiple ascending doses than after a single dose. *Id.* Agresta suggests the lowered levels of mitapivat can be explained because mitapivat itself is an inducer of CYP3A4, the same enzyme responsible for its metabolism (auto-induction). *Id.* Nowhere does Agresta refer to co-administration of mitapivat with any CYP3A4/5 modulators.

111. In my opinion, far from teaching co-administration of mitapivat with a moderate CYP3A4/5 inducer, Agresta's identification of CYP3A4 as a route for mitapivat metabolism would lead a POSA to avoid co-administration of a moderate CYP3A4/5 inducer. As explained above, such co-administration would unpredictably impact mitapivat PK, efficacy, and safety. *See supra* Section VIII.B. Understanding the impact of co-administration of CYP3A4/5 inducers on

mitapivat pharmacokinetics required the dedicated clinical DDI studies and associated pharmacokinetic modeling conducted by Agios and first disclosed in the '049 Patent. *Id.* Such information was not publicly available before June 14, 2019.

112. Moreover, a POSA would have faced even greater uncertainty with co-administration considering Agresta's disclosure that mitapivat *itself* is an inducer of CYP3A4. Ex.1005 (Agresta) at 42. Under such circumstances, a POSA would have been even more cautious about the unpredictability of the effects of co-administering moderate CYP3A4/5 inducers with mitapivat.

2. Dana-Farber Does Not Teach Co-Administration of Mitapivat With a Moderate CYP3A4/5 Inducer

113. In Dana-Farber, Dr. Thirman relies on the exclusion criteria of the Phase II study of mitapivat in patients with PKD (DRIVE-PK). Ex.1007 (Dana-Farber) at 5–6. Exclusion criteria define which patients are prohibited from enrolling in a clinical trial.

114. Dana-Farber *prohibits* the enrollment of patients taking *strong* CYP3A4 inducers. Ex.1007 (Dana-Farber) at 6. Dana-Farber related to the DRIVE-PK study, which was a study of mitapivat alone. Dana-Farber does not mention moderate CYP3A4/5 inducers. And Dana-Farber does not teach co-administration (as opposed to avoidance) of mitapivat and CYP3A4/5 inducers. As described in further detail below, a POSA would not have interpreted the

absence of an exclusion criteria for moderate CYP3A4/5 inducers to be a teaching that co-administration of mitapivat with moderate CYP3A4/5 inducers is safe, effective, or clinically appropriate.

3. Grace Presentation and Grace Abstract Do Not Teach Co-Administration of Mitapivat With a Moderate CYP3A4/5 Inducer

115. Grace Presentation and Grace Abstract (“the Grace References”) report the design and interim results of DRIVE-PK—an open-label, randomized Phase II study in patients with PKD—and describe outcomes relating to safety and tolerability and indicators of clinical activity such as a change in hemoglobin levels. Ex.1008 (Grace Presentation) at 21–31; Ex.1009 (Grace Abstract) at 2–3. But the Grace References do not report any concomitant medications taken by enrolled patients. Ex.1008 (Grace Presentation) at 21–31; Ex.1009 (Grace Abstract) at 2–3. They do not identify any patients taking CYP inducers. Ex.1008 (Grace Presentation) at 21–31; Ex.1009 (Grace Abstract) at 2–3. Neither reference states that information regarding concomitant medications was collected or evaluated. Ex.1008 (Grace Presentation); Ex.1009 (Grace Abstract).

116. In fact, because DRIVE-PK was not a prospective DDI study nor was it designed to assess DDIs, these references do not mention CYP enzymes, inducers, or DDIs. Ex.1008 (Grace Presentation); Ex.1009 (Grace Abstract). And as the relevant FDA guidance explained as of the priority date, “[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.2023 (FDA, Clinical Drug Interaction Studies) at 006.

B. The Asserted Prior Art References – Alone or in Combination – Do Not Provide Motivation to Co-Administer Mitapivat With a Moderate CYP3A4/5 Inducer

117. The asserted prior art would not have motivated a POSA to co-administer mitapivat with a moderate CYP3A4/5 inducer. None of the asserted prior art references were directed to characterizing mitapivat DDIs or co-administered mitapivat with moderate CYP3A4/5 inducers; they were all focused on investigating mitapivat alone. Instead, Agresta and Dana-Farber would have alerted a POSA to avoid co-administering mitapivat with a moderate CYP3A4/5 inducer, because of the potential for clinically meaningful and unpredictable DDIs.

1. A POSA Would Have Avoided Co-Administration of Mitapivat With Moderate CYP3A4/5 Inducers Based on Agresta’s Disclosures Regarding Mitapivat Metabolism and Auto-Induction

118. Dr. Thirman argues that Agresta “teaches treating a hemolytic anemia patient by co-administering mitapivat with other drugs” by pointing to Agresta’s disclosure of a possible “combination of Compound 1 [mitapivat] and one or more additional therapeutic or prophylactic agents.” Ex.1003 (Thirman Decl.) ¶¶91, 98 (citing Ex.1005 (Agresta) at 36). He further argues that “a POSA would have understood such [additional] drugs to include moderate CYP3A4 inducers and that

such drugs may give rise to a drug-drug interaction with mitapivat.” *Id.* ¶98. I do not agree.

119. Agresta’s suggestion that a patient may require “one or more additional therapeutic or prophylactic agents” does not teach co-administration of moderate CYP3A4/5 inducers specifically. Ex.1005 (Agresta) at 36.

120. Moreover, Agresta’s identification of CYP3A4 as a route for mitapivat metabolism would have led a POSA to avoid co-administration of a moderate CYP3A4/5 inducer. As explained above, such co-administration would unpredictably impact mitapivat pharmacokinetics and a POSA would have faced even greater uncertainty with co-administration considering Agresta’s disclosure that mitapivat *itself* is an inducer of CYP3A4. *See supra* Section VIII.B. In the absence of the dedicated clinical DDI studies and associated pharmacokinetic modeling conducted by Agios and first disclosed in the ’049 Patent, a POSA would have avoided co-administration of moderate CYP3A4/5 inducers and mitapivat.

2. A POSA Would Have Avoided Co-Administration of Mitapivat With Moderate CYP3A4/5 Inducers Based on Dana-Farber’s Disclosure of Avoiding Strong CYP3A4/5 Inducers

121. Dr. Thirman argues that Dana-Farber, which sets out the exclusion criteria for the DRIVE-PK trial, teaches that patients with PKD taking moderate CYP3A4/5 inducers “could be enrolled and treated with mitapivat.” Ex.1003 (Thirman Decl.) ¶¶99–100. Dr. Thirman reasons that because Dana-Farber

prohibited enrollment of patients taking strong CYP3A4 inducers but did not prohibit enrollment of patients taking moderate CYP3A4 inducers, a POSA “would thus have understood” that co-administration of mitapivat with moderate inducers was feasible and that the doses effective in DRIVE-PK as taught by Grace Presentation could be administered to patients taking moderate inducers. *Id.* ¶100. In my opinion, for the reasons below, this reasoning is flawed. Again, Dr. Thirman is using hindsight, starting with the claimed co-administration with moderate CYP3A4/5 inducers and reading that into Dana-Farber.

122. First, Dr. Thirman’s analysis equates the absence of an exclusion with an affirmative teaching. Dana-Farber is silent regarding moderate CYP3A4/5 inducers. Without clinical DDI data or related analyses regarding CYP3A4/5 inducers, a POSA would not have interpreted Dana-Farber’s silence regarding moderate inducers in the exclusion criteria to teach that co-administration of mitapivat with moderate CYP3A4/5 inducers is safe, effective, or clinically appropriate.

123. Second, Dr. Thirman’s logic misconstrues the purpose and meaning of clinical trial exclusion criteria. Exclusion criteria in early-phase clinical trials (like the one in Dana-Farber) manage known variables that are most likely to confound the investigation in the trial or impact safety. *See supra* Section VIII.C. A POSA would not have relied on exclusion criteria as a substitute for clinical DDI

data in clinical decision-making regarding DDI risks; the FDA requires clinical DDI data. *See supra* Section VIII.B, C. Clinical trials—especially in earlier phases—can and often do have exclusion criteria and testing parameters that are inconsistent with what is ultimately determined by ***clinical data*** to be efficacious or required. For example, a wider range of doses may be tested in Phase II clinical trials than what is ultimately determined to be safe and efficacious and approved. A POSA would not have assumed, without data, that the absence of an exclusion for co-administration of moderate CYP3A4/5 inducers meant that such inducers could be successfully co-administered with mitapivat.

124. Third, a POSA would have understood that Dana-Farber’s exclusion of strong CYP3A4 inducers followed standard practice for a drug that was understood to be metabolized by a particular CYP enzyme and would not have conveyed anything to a POSA about moderate CYP3A4/5 inducers. *See supra* Section VIII.C. A POSA would have understood that when a drug was known or suspected to have significant metabolism by a given enzyme, it would be standard practice to avoid concomitant use of strong inducers and inhibitors of that enzyme in clinical trials, because strong inducers and inhibitors would be most likely to cause DDIs affecting safety and/or efficacy. But, as described above, the magnitude of the effect of a strong, moderate, or weak CYP3A4/5 inducer on a drug metabolized by CYP3A4/5 varies widely by drug and cannot be predicted

without empirical testing. *See supra* Section VIII.B. The impact of a moderate CYP3A4/5 inducer can still be quite significant. If anything, if presented with the clinical trial exclusion criteria excluding strong CYP3A4/5 inducers, a POSA would have likewise avoided co-administering moderate CYP3A4/5 inducers until presented with the evidence otherwise, i.e., the clinical data and PBPK modeling considered by the FDA. *See* Ex.1011 (FDA 2022) at 210–224 (Agiros PBPK analyses “adequate to predict the interaction effect of CYP3A inducers”); *see also id.* at 184–185 (clinical DDI study), 215.

3. A POSA Would Not Have Assumed Patients in the Grace References Were Successfully Co-Administered Mitapivat and Moderate CYP3A4/5 Inducers

125. Dr. Thirman argues that because the Grace References “teach[] that Phase 2 study patients were effectively treated for PKD and do[] not report any difficulty with treating patients receiving both mitapivat and moderate CYP3A4 inducers as permitted by Dana-Farber,” 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, 137. For the reasons below, I do not agree.

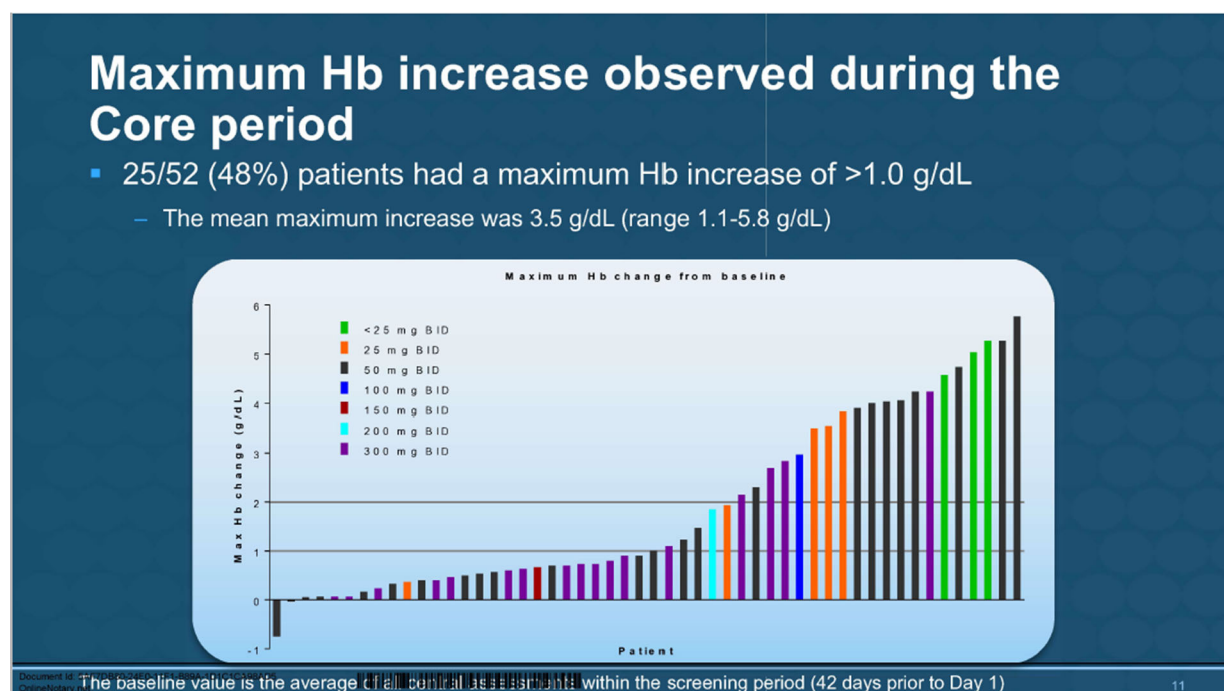
126. First, as explained above, in light of Agresta’s disclosure of CYP3A4 as a metabolic pathway for mitapivat and additionally because of mitapivat’s own auto-induction of CYP3A4, a POSA would have avoided co-administration of

moderate CYP3A4/5 inducers with mitapivat and not believed that he or she would have been able to co-administer mitapivat and a moderate CYP3A4 inducer. *See supra* Section VIII.B. Dana-Farber’s exclusion criteria likewise would have suggested to a POSA to avoid co-administration of mitapivat and a moderate CYP3A4 inducer. *See supra* Section VIII.B, C.

127. Second, the Grace References are silent on DDIs and do not state whether any data relevant to DDIs was collected or evaluated. The Grace References do not report the concomitant medications taken by enrolled patients, nor identify any enrolled patients taking CYP inducers, and thus cannot establish that patients taking moderate CYP3A4/5 inducers and mitapivat were effectively treated for PKD. Ex.1008 (Grace Presentation) at 21–31; Ex.1009 (Grace Abstract) at 2–3. Even assuming that Dana-Farber’s exclusion criteria permitted patients taking moderate CYP3A4/5 inducers to enroll in DRIVE-PK, the fact that such patients “could be enrolled” does not establish that any such patient actually was enrolled, and Dr. Thirman provides no such evidence. Even considering that a patient taking a moderate CYP3A4/5 inducer was able to enroll, without concomitant medication data during treatment, a POSA has no basis to conclude that any patient in DRIVE-PK actually received mitapivat while concurrently taking a moderate CYP3A4/5 inducer.

128. Third, that the Grace References “do not report any difficulty” with co-administration is not evidence of safe and effective treatment. From a scientific standpoint, the absence of a reported problem in a reference that does not analyze co-administration outcomes is simply silence—it is not affirmative evidence of success. A POSA would not have reasonably inferred that co-administration at the claimed doses was safe and effective based on data from a trial that did not identify co-administered patients, track their concomitant medications during treatment, or analyze their outcomes separately.

129. The DRIVE-PK results reported in the Grace Presentation in fact underscore the point.



Ex.1008 (Grace Presentation) at 26.

130. Despite 25/52 (48%) of patients experiencing a maximum hemoglobin increase greater than 1.0 g/dL, there are still individual variations in response, with some patients failing to achieve those hemoglobin levels, even at the highest doses studied. Ex.1008 (Grace Presentation) at 26. Even assuming that some patients in the trial were taking moderate CYP3A4/5 inducers, a POSA would have no indication that the patients taking moderate CYP3A4/5 inducers were among the patients successfully treated, as opposed to being among the patients with minimal hemoglobin change (less than 1.0 g/dL). *Id.* Any assumption that the successfully treated patients in Grace Presentation included patients with co-administered moderate CYP3A4/5 inducers is based on hindsight reasoning, assuming without a basis in the disclosures that the facts align with the conclusion that Dr. Thirman seeks to prove.

4. Combining the Asserted Prior Art Does Not Provide Motivation to Co-Administer Mitapivat With a Moderate CYP3A4/5 Inducer

131. Dr. Thirman argues that a POSA would have been motivated to combine the Agresta, Dana-Farber, and Grace 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, 160. Dr. Thirman argues that Agresta “teaches co-administration of mitapivat with other drugs, during which a POSA would have recognized a potential drug-drug interaction,” the

Dana-Farber and Grace References “provide procedures and results from the Phase 2 trial that would have allowed a POSA to confirm that such administration is feasible.” *Id.* I disagree for the following reasons and in my opinion, combining the asserted prior art does not provide motivation to co-administer mitapivat with a moderate CYP3A4/5 inducer.

132. First, Agresta and Dana-Farber each point to the potential for DDIs between mitapivat and inducers of CYP3A4/5—but neither provides any data characterizing any such DDIs or supporting the co-administration of mitapivat and moderate inducers of CYP3A4/5. Agresta’s disclosure of CYP3A4 as a metabolic pathway for mitapivat and additionally mitapivat’s own auto-induction of CYP3A4 underscores the complexity and unpredictability of DDIs between mitapivat and moderate CYP3A4/5 inducers. *See supra* Section VIII.B. Dana-Farber’s exclusion criteria suggest avoiding co-administration until DDI studies are conducted. *See supra* Section VIII.B, C.

133. Second, adding the Grace References does not motivate a POSA to co-administer mitapivat and a moderate CYP3A4/5. Even assuming that patients taking moderate CYP3A4/5 inducers were enrolled in DRIVE-PK (and Dr. Thirman provides no evidence this is the case), the Grace References are silent regarding DDIs. The Grace References do not report the concomitant medications taken by enrolled patients, nor identify any enrolled patients taking CYP inducers;

nor do they state that such information was collected or analyzed. The Grace References do not (and could not) establish that patients taking moderate CYP3A4/5 inducers and mitapivat were effectively treated for PKD. Ex.1008 (Grace Presentation) at 21–31; Ex.1009 (Grace Abstract) at 2–3.

134. Third, the Grace References themselves report safety data that emphasized the unpredictability of changing mitapivat blood levels. Of the six drug-related serious adverse events reported in the Grace References, the first listed is “[w]ithdrawal hemolysis followed by anemia.” Ex.1008 (Grace Presentation) at 21; Ex.1009 (Grace Abstract) at 2. Withdrawal hemolysis occurs when mitapivat exposure is abruptly reduced or discontinued, causing activated red blood cells to rapidly hemolyze. The reporting of withdrawal hemolysis as a serious adverse event thus would have reinforced the unpredictable effects of changing levels of mitapivat in the blood.

C. A POSA Would Not Have Had a Reasonable Expectation of Success for Co-Administration of Mitapivat With a Moderate CYP3A4/5 Inducer

135. Dr. Thirman argues that a POSA would have had a reasonable expectation of success in arriving at the claimed invention based on the asserted prior art references because of (1) the successful results of the DRIVE-PK Phase II trial, as disclosed in Grace Presentation, (2) because “POSAs routinely, and successfully, managed drug-drug interactions,” and (3) for the reasons that a POSA

would have been motivated to combine the references. Ex.1003 (Thirman Decl.) ¶¶123–126. I disagree for the reasons below. Dr. Thirman’s expectation of success is based on hindsight knowledge of Agios’s DDI clinical trial data and pharmacologically based pharmacokinetic modeling, not what a POSA would have expected at the priority date.

136. First, a POSA would have had no reasonable expectation of success for the co-administration of moderate CYP3A4/5 inducers with mitapivat because none of the asserted references includes any clinical DDI data, or any discussion or rationale to support co-administration. As described above, a POSA would have required evidence—including clinical DDI data—to reasonably expect success for co-administration of moderate CYP3A4/5 inducers with mitapivat. As of June 14, 2019, the clinical significance of DDIs with mitapivat was unknown because there had not been any clinical DDI testing for mitapivat. *See supra* Section VIII.B. Because of the unpredictability of clinical DDI effects, as of June 14, 2019, regulatory authorities like the FDA required clinical DDI studies when preclinical and early pharmacokinetic data suggest a metabolizing enzyme (like CYP3A4) contributes to a drug’s metabolism and elimination. *See supra* Section VIII.B; Ex.2022 (FDA, In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies) at 006; *see also* Ex.2024 (Hakkola 2020) at 001, 032. As of June 14, 2019, Agios had reported that the CYP3A4 enzyme breaks down

mitapivat in the body, but no clinical data or evidence-based PBPK modeling regarding CYP3A4/5 DDIs had been reported. Under such circumstances—and especially in light of the additional data suggesting that mitapivat itself was an inducer of CYP3A4—a POSA would have required evidence teaching co-administration to reasonably expect its success.

137. Second, the results of the DRIVE-PK Phase II trial would not have provided a POSA with a reasonable expectation of success for co-administration of mitapivat with a moderate CYP3A4/5 inducer. Dr. Thirman is only able to point to disclosures regarding exclusion criteria in support of his suggestion that patients in the DRIVE-PK study “were *permitted* to receive a moderate CYP3A4 inducer.” Ex.1003 (Thirman Decl.) ¶124 (emphasis added). But no asserted reference discloses that any patients in the Phase II DRIVE-PK study were in fact taking a moderate CYP3A4 inducer or that such information was collected or analyzed. Moreover, even if some patients in DRIVE-PK were concurrently taking moderate CYP3A4/5 inducers (which a POSA would not have assumed to be the case), some patients did not respond. Ex.1008 (Grace Presentation) at 26; Ex.1009 (Grace Abstract) at 3. A POSA would not have known if those patients failed to respond because of DDIs.

138. Moreover, the safety data in the Grace References would have further prevented a POSA from having a reasonable expectation of success. The Grace

References report withdrawal hemolysis followed by anemia as one of the six drug-related serious adverse events observed in DRIVE-PK. Ex.1008 (Grace Presentation) at 21; Ex.1009 (Grace Abstract) at 2. Withdrawal hemolysis is a clinically significant event in which red blood cells undergo rapid destruction when mitapivat exposure is reduced and these data would have reinforced the unpredictable effects of changing levels of mitapivat in the blood.

139. Third, a POSA would not have had a reasonable expectation of success based on prior management of other DDIs. The FDA's draft guidance as of June 14, 2019, required independent DDI evaluation of new drugs like mitapivat. *See supra* Section VIII.B. For mitapivat, there was no clinical DDI data or other evidence available prior to the data of the '049 Patent, and so, a POSA would not reasonably expect co-administration of moderate CYP3A4/5 inducers with mitapivat would be efficacious and/or safe. *Id.*

140. Dr. Thirman relies on Mutalik (Ex.1010) to argue that DDIs can be routinely managed, and suggests this supports that a POSA would have expected that mitapivat and a moderate CYP3A4/5 inducer could be co-administered. *See* Ex.1003 (Thirman Decl.) ¶¶103, 107, 138–139 (citing Mutalik (Ex.1010) at 19,

24).³ Dr. Thirman cites Mutalik’s instructions to “prescribers” to “know all the medications that the patient is receiving in order to understand, prevent or manage the possible drug interactions.” But, Mutalik does not support a reasonable expectation of success in co-administering mitapivat and a moderate CYP3A4/5 inducer for two reasons.

141. First, Mutalik’s discussion is limited to prescribers, i.e., clinicians that are directing the administration of approved drugs, not investigational drugs, and Mutalik supports the need for clinical DDI investigations to give prescribers the correct information for DDI management at the time of drug approval. Ex.1010

³ Dr. Thirman also argues that Clark (Ex.1012) supports that a “POSA would have recognized that administration of a cytochrome P450 inducer reduced the concentration of the affected drug in the body, . . . which could be counteracted by an increased dose to increase that concentration.” Ex.1003 (Thirman Decl.) ¶103. But Clark (Ex.1012) is entirely devoted to post-hoc analysis related to DDIs for an entirely different drug, warfarin, and contains no disclosures regarding mitapivat. As discussed above, the impact of CYP3A4/5 inducers on drugs that are metabolized by CYP3A4/5 is drug-specific and must be determined empirically. A POSA would not consider Clark to teach or suggest successful dose adjustment and co-administration of mitapivat.

(Mutalik) at 24. In other passages, Mutalik details the many types of “experimental methods to study or detect drug interactions” for investigational drugs and emphasizes a requirement for clinical DDI studies. *Id.* at 21–23. Because the observations from preclinical studies “may not necessarily occur in human beings,” such preclinical studies are used “to decide if and which future drug interaction studies should be performed in man.” *Id.* at 21. As for clinical studies, Mutalik states that individual clinical studies should be performed per interacting drug pair, i.e., for clinical studies in humans, “[p]air-wise drug interaction studies to cover as many medications as can be identified for a drug candidate are done.” *Id.* at 23.

142. Second, Mutalik explains that DDIs can cause patients to discontinue or avoid therapy. When discussing the various methodologies to “[a]void or minimise the impact of a drug interaction”—for prescribers, i.e., clinicians providing approved drugs—Mutalik observes that “discontinuation and/or change in the modality of an intervention” may be required, emphasizing that for some drugs and DDIs, co-administration may not be possible. Ex.1010 (Mutalik) at 24. Mutalik does not provide any reasons why co-administration, as opposed to discontinuation, would be the outcome of DDI management for mitapivat and moderate CYP3A4/5 inducers.

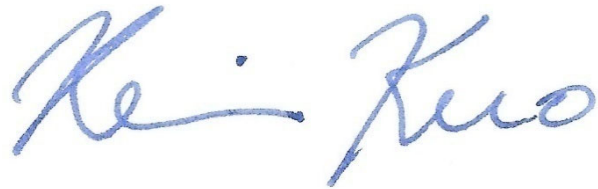
143. For all of these reasons, a POSA would not have had a reasonable expectation of success in co-administering moderate CYP3A4/5 inducers and

mitapivat absent the clinical DDI data and analyses necessary to characterize potential DDIs, and Dr. Thirman's arguments do not prove otherwise.

XIII. CONCLUSION

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true. Further, I am aware that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001. I declare under penalty of perjury that the foregoing is true and correct.

Executed on August 25, 2026 (date), in Toronto, Ontario, Canada (city, state).



Kevin H.M. Kuo