

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
PETITIONER

v.

AGIOS PHARMACEUTICALS, INC.,
PATENT OWNER

CASE IPR2026-00351
U.S. PATENT NO. 11,878,049
ISSUED: JANUARY 23, 2024

TITLE:
MITAPIVAT THERAPY AND MODULATORS OF CYTOCHROME P450

DECLARATION OF MICHAEL J. THIRMAN, M.D.

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I, Michael J. Thirman, M.D., declare as follows:

I. INTRODUCTION

1. I have been asked by counsel for Petitioner to investigate and provide opinions relating to the above-captioned *inter partes* review (“IPR”).

2. I understand that Petitioner is filing an IPR petition requesting that the United States Patent and Trademark Office cancel Claims 1, 8, 9, 14, and 19 (the “challenged claims”) of U.S. Patent No. 11,878,049 (the “’049 patent,” Ex.1001). I further understand that Agios Pharmaceuticals, Inc. (“Agios” or “Patent Owner”) purports to own the ’049 patent.

3. Specifically, I have been asked to evaluate whether the challenged claims of the ’049 patent would have been obvious to a person of ordinary skill in the art (POSA) as of the effective filing date or were anticipated by the prior art.

4. This declaration identifies my opinions to date. I reserve the right to amend or supplement this declaration, if allowed under the relevant rules, to address any issues raised by Agios’s expert(s) or resulting from further discovery relating to any of the opinions stated herein.

II. QUALIFICATIONS

5. I am currently an Associate Professor and Director of Leukemia Biology of the Section of Hematology/Oncology at University of Chicago.

6. I earned a Bachelor of Arts degree from the University of Michigan, College of Literature, Science, and the Arts in 1982 and my medical degree (MD) from the University of Michigan Medical School in 1986. After an internship and residency at the University of Minnesota Hospitals, Department of Internal Medicine (1986-1989), I was a fellow in the Section of Clinical Pharmacology at the Minneapolis VA Medical Center (1989-1990) and subsequently was a fellow in the Section of Hematology/Oncology at the University of Chicago (1991-1996).

7. I joined the faculty of the University of Chicago Medicine in 1996. From 1996-2003, I held the position of Assistant Professor at the University of Chicago, Section of Hematology/Oncology. From 2003 onward, I have held the position of Associate Professor at the University of Chicago, Section of Hematology/Oncology.

8. Throughout my career, I have developed expertise in the diagnosis and treatment of blood disorders, including hemolytic anemia. I provide comprehensive hematological care to patients including management and treatment of patients with hemolytic anemia.

9. I have authored or co-authored at least 89 peer-reviewed publications and 5 book chapters in hematology/oncology and have delivered at least 40 invited talks. I have served on the Editorial Boards of *Cancer Biology and Therapy*,

Leukemia and Lymphoma, and *Blood Advances*. I am a recipient of the American Society of Hematology Junior Faculty Award.

10. A detailed record of my education and professional accomplishments is contained in my curriculum vitae, attached as Exhibit 1018, which is incorporated by reference herein.

III. BACKGROUND AND STATE OF THE ART

A. Technical Background and State of the Art

11. In my experience, a POSA would have known the following information as of the effective filing date of the '049 patent. Section III.B, *infra*.

12. Hemolytic anemia is a disorder characterized by excessive breakdown of red blood cells. Ex. 1005 (Agresta) at 2. Pyruvate kinase deficiency (“PKD”) is “a congenital hemolytic anemia caused by mutations in the PKLR gene.” Ex. 1009 (Grace Abstract) at 2; *see also* Ex. 1005 (Agresta) at 3-4. Mitapivat, known in the prior art as N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide, Compound 1, formula (I), or AG-348, was taught to be a treatment for both hemolytic anemia generally and PKD specifically. Ex. 1005 (Agresta) at 25, 37-38, 51 (disclosing treatment); *see also id.* at 37 (identifying the compound), 44 (referring to the compound as AG-348); Ex. 1004 (Sizemore) at ¶ 0003 (same); Section VIII, *infra* (defining mitapivat).

13. In this declaration, I use “mitapivat” to refer to this compound.

14. Mitapivat was one of many drugs known to be metabolized by CYP3A4, a type of cytochrome P450 enzyme. Ex. 1005 (Agresta) at 42; Ex. 1010 (Mutalik) at 12. There are several types of cytochrome P450 enzymes, divided into families and subfamilies. Ex. 1010 (Mutalik) at 12. In the name “CYP3A4,” the “3” identifies the family, the “A” identifies the subfamily, and the “4” identifies the specific enzyme. *Id.*

15. Drug interactions between co-administered drugs were known to commonly arise where one drug is metabolized by a cytochrome P450 enzyme, while another drug modulates the enzyme’s activity. Ex. 1010 (Mutalik) at 12-13. Such interactions were a “known factor” in how patients respond to drugs. *Id.* at 2, 12-13.

16. A drug that increases a CYP450 enzyme’s activity, and thus reduces drug exposure, was known as an inducer. *Id.* at 12. Inducers known to decrease exposure of a reference drug by 50-80% (as measured by AUC, area under the plasma concentration time curve) were categorized as “moderate.” *Id.* at 13-14. A common way to combat decreased drug exposure resulting from co-administration with an inducer was to simply increase the drug’s dose. *Id.* at 19, 24; Ex. 1012 (Clark) at 1, 2, 4-6.

17. Several examples of cytochrome P450 modulators were known and in clinical use, including moderate CYP3A4 inducers. Ex. 1010 (Mutalik) at 13-14;

Ex. 1015 (van Giersbergen) at 7. These examples included inducers that complemented mitapivat treatment for hemolytic anemia by treating co-morbidities such as hyperbilirubinemia and pulmonary arterial hypertension. Ex. 1006 (Gordon-Smith) at 9-10; Ex. 1013 (Hackman) at 1, 3; Ex. 1016 (Bachmeyer) at 2-3; Ex. 1015 (van Giersbergen) at 1.

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

18. The '049 patent is titled "Mitapivat Therapy and Modulators of Cytochrome P450." Ex. 1001 ('049 patent) at Cover. The '049 patent was filed on June 12, 2020, as Application No. 16/900,610 and claims priority to U.S. Provisional Application No. 62/861,600 (filed June 14, 2019). Ex. 1001 ('049 patent) at Cover.

19. For the purpose of this IPR only, I have been asked to assume that June 14, 2019 is the effective filing date.

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

21. The first 35 columns, i.e., three quarters, of the '049 patent's specification address the patent's Background, Summary, Brief Description of the Figures, and Detailed Description, which are largely in the form of lengthy laundry lists. *Id.* at 1:1-35:61. After providing nine columns of introductory material,

including a brief description of PKD and mitapivat's development to treat that disorder, the specification provides a generalized description of pharmaceutical compositions. *Id.* at 1:12-8:67, 9:1-10:28. The latter section, in turn, is followed by eighteen laundry-list heavy columns relating to dosing of mitapivat and administration of concomitant medications that may yield drug-drug interactions. *Id.* at 10:29-28:51. Two columns alone are devoted to a vast laundry list of daily doses and dosage ranges, with options broadly ranging from 2 to 3000 mg per day. *Id.* at 12:31-14:17. This laundry list includes dosing ranges, including from about 5 mg to about 500 mg, about 5 mg to about 200 mg, about 300-360 mg, and about 5 mg to about 10 mg. *Id.* at 12:31-14:17. This list also includes individual daily doses from about 5 mg to 60 mg in 5 mg intervals, along with individual daily doses from about 60 to about 300 mg in 10 mg intervals. *Id.* The subsequent seven columns list types of diseases to be treated using mitapivat. *Id.* at 28:52-35:61.

22. Following those portions of the specification are three examples. *Id.* at 35:61-45:22. Example 1 indicates that mitapivat is primarily metabolized by CYP3A4/5. *Id.* at 36:5-12. Example 2 provides a drug-drug interaction clinical study testing the effects of a strong CYP3A4/5 inhibitor (itraconazole) and a strong CYP3A4/5 inducer (rifampicin) on mitapivat, with the specification's figures reporting results from the study. *Id.* at 36:42-67, 37:18-29. The specification's

conclusions drawn from this example are limited to a strong inhibitor and a strong inducer, and thus do **not** address the moderate inducers recited in the challenged claims. *Id.* at 43:36-40.

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

24. While the specification instructs that when a drug-drug interaction occurs, “the amount of mitapivat . . . should be adjusted,” *id.* at 7:33-39, it does not explain how to make that adjustment when mitapivat is co-administered with a moderate CYP3A4/5 inducer. At the same time, nowhere in the specification’s laundry list of doses do the inventors explain how to select a dose from that list. *Id.* at 12:31-14:17. Rather, the list is agnostic as to whether the doses are co-administered with a CYP3A4/5 inducer, inhibitor, or neither, let alone whether the CYP3A4/5 inducer is weak, moderate, or strong. *Id.* Further, the specification provides no experimental data involving co-administration of a moderate CYP3A4/5 inducer and mitapivat. *Id.* at 35:61-45:22. The disclosed studies

regarding that scenario were “being developed,” *id.* at 43:41-50, 44:22-25, while the studies that were actually performed address different scenarios involving a strong inducer or inhibitor, *id.* at 36:42-67.

C. FDA Review Relating to Mitapivat

25. After filing for the challenged patent, on June 17, 2021, Patent Owner filed a New Drug Application (NDA) with the FDA for a mitapivat drug called Pyrukynd[®]. Ex. 1011 (FDA) at 2. In response to a request from the FDA—seemingly after filing the NDA, and thus after filing for the ’049 patent, too—Patent Owner finally performed modeling of the effect of a moderate CYP3A inducer on mitapivat doses of 5 mg, 20 mg, and 50 mg twice daily. *Id.* at 217 (Table 108 and caption).

26. In its February 17, 2022 review of the NDA, the FDA provided its analysis of that modeling and its recommendations. *Id.* at 119; *see also id.* at 2 (listing date). The FDA stated as follows:

Effects of CYP3A Inducers on Mitapivat

...

The review team agrees with the Applicant that the use of mitapivat with strong CYP3A inducers should be avoided due to the large decrease in mitapivat exposure. ***For use with moderate CYP3A inhibitors, the team recommends monitoring of Hb levels for reduced activity of mitapivat and further recommends titration beyond 50 mg twice daily dose if necessary but not to exceed 100 mg twice daily.*** For patients on stable moderate CYP3A inducers, the review team recommends

initiating mitapivat at 10 mg twice daily. These recommendations are supported by PB-pharmacokinetic simulations, which show that mitapivat exposures at 100 mg and 10 mg twice daily concomitantly with a CYP3A inducer is similar to 50 mg and 5 mg twice daily administered alone, respectively.

Id. at 119 (emphasis and underlining added). In my opinion, in the emphasized language, the underlined word “inhibitor” is a typographic error, and should instead be read as “inducer.” That is because (1) the section title and surrounding text addresses inducers, not inhibitors, and (2) applying this recommendation to an inhibitor would conflict with the FDA’s recommendation in a separate section that specifically addresses inhibitors (capping the dose at 20 mg). *Id.* at 118-119.

27. Notably, in my review of the specification, I did not observe a recommendation to dose mitapivat beyond 50 mg twice per day when administering a moderate CYP3A inducer. Section III.B, *supra*.

D. The Prosecution History

28. From my review of the prosecution history, I observe that the initial claims, filed on June 12, 2020, recited methods of treatment by administering an “effective amount” of mitapivat together with a CYP3A4/5 inducer. Ex. 1002 (’049 prosecution history, Jun. 12, 2020 Originally Filed Claims) at 84-89. A subsequent preliminary amendment on August 19, 2020, presented claims reciting administering an “effective amount” of mitapivat either (1) together with a CYP3A4/5 inducer or inhibitor or (2) in the absence of an inhibitor or inducer. Ex.

1002 ('049 prosecution history, Aug. 19, 2020 preliminary amendment) at 99-102. Then-pending Claim 36, depending from Claim 1, recited co-administration of mitapivat and a moderate CYP3A4/5 inducer. *Id.* at 101. But that claim did not specify which doses would be effective. *Id.*

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

30. On November 18, 2022, Applicants cancelled every pending claim and submitted new claims directed to methods of treating hemolytic anemia by administering mitapivat with a moderate CYP3A4/5 inducer, which was narrower than the prior claims that encompassed any CYP3A4/5 inducer (or inhibitor). Ex. 1002 ('049 prosecution history, Nov. 18, 2022 Claims) at 127-28. Those new claims introduced numerical doses for the first time: about 10, about 40, and about 50 mg/day. *Id.*

31. Applicants further argued that the Examiner's prior art was inapplicable to the new claims. Ex. 1002 ('049 prosecution history, Nov. 18, 2022 Response to Non-Final Office Action) at 129-33. Applicants distinguished the boceprevir prior art by arguing that it taught co-administration of a CYP inhibitor, not an inducer. *Id.* at 129-31. Applicants distinguished the dexamethasone prior art by arguing that the drug is a strong inducer, not a moderate inducer. *Id.* at 132-33.

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

33. On April 7, 2023, Applicants responded by arguing that rifampicin is a strong inducer and therefore does not satisfy the moderate-inducer claim limitation, nor did the Examiner explain how it does. Ex. 1002 ('049 prosecution history, Apr. 7, 2023 Applicant Arguments and Remarks to Final) at 154. Nor was the Examiner later able to identify prior art that provided teachings relating to a moderate inducer, as evident from the remainder of the prosecution history. However, the prior art does so, as explained in both the anticipation and obviousness grounds below. Sections IX.A.1, (anticipation opinion relying upon Ex. 1004 (Sizemore) utilizing teachings not relied upon by the Examiner); IX.B.1,

IX.C.1 (obviousness opinions relying upon references not cited to or utilized by the Examiner in an office action including Ex. 1007 (Dana-Farber), Ex. 1010 (Mutalik), Ex. 1006 (Gordon-Smith), Ex. 1013 (Hackman), Ex. 1015 (van Giersbergen), Ex. 1016 (Bachmeyer)), *infra*; Ex. 1001 ('049 patent) References Cited; Ex. 1002 ('049 prosecution history).

34. Applicants also cancelled the pending claims and submitted amended Claims 59-77. Ex. 1002 ('049 prosecution history, Apr. 7, 2023 Claims) at 150-52. Notably, the amendment modified the claimed dosing. Ex. 1002 ('049 prosecution history, Apr. 7, 2023 Applicant Arguments and Remarks to Final) at 153. While the earlier November 2022 claims recited doses of about 10, about 40, or about 50 mg/day, the new claim set removed about 50 mg/day and added about 100 or about 200 mg/day. *Id.*; *compare* Ex. 1002 ('049 prosecution history, Apr. 7, 2023 Claims) at 150-52 *with* Ex. 1002 ('049 prosecution history, Nov. 18, 2022 Claims) at 127-28.

35. I note that the addition of the about 100 mg/day and the about 200 mg/day dosing limitations followed the FDA's recommendation of that dose in its review of the Pyrukynd[®] NDA. Section III.C, *supra*. However, the April 2023 response did not mention the FDA reviewers' recommendation. Ex. 1002 ('049 prosecution history, Apr. 7, 2023 Applicant Arguments and Remarks to Final) at

153-55. Nor, in my review of the patent's references cited, do I observe a citation to the FDA review. Ex. 1001 ('049 patent) References Cited.

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

E. The Issued Claims

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

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

Ex. 1001 ('049 patent), Claim 1. Claim 8 depends from Claim 1 and specifies that the subject is administered about 200 mg/day of mitapivat. *Id.*, Claim 8. Claim 9 depends from Claim 8 and further specifies that the subject is administered about 100 mg of mitapivat twice per day. *Id.*, Claim 9; Ex. 1002 ('049 prosecution history, Certificate of Correction) at 459. Claim 14 depends from Claim 9 and

further specifies that the mitapivat is orally administered as part of a tablet composition. *Id.*, Claim 14. Claim 19 depends from Claim 14 and further specifies that the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate. *Id.*, Claim 19.

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

IV. DOCUMENTS

39. In preparing this declaration, I reviewed and considered the documents identified in the below table:

Exhibits	Description
Ex.1001	U.S. Patent No. 11,878,049 to Iyer et al. (the “’049 patent”).
Ex.1002	Prosecution History for U.S. Patent No. 11,878,049 (“’049 prosecution history”).
Ex.1004	International Publication No. WO 2019/104134 A1 to Sizemore et al. (“Sizemore”).
Ex.1005	International Publication No. WO 2016/201227 A1 to Agresta et al. (“Agresta”).
Ex.1006	E.C. Gordon-Smith, <i>Pyruvate kinase deficiency</i> , 27 J. Clin. Path. 128 (1974) (“Gordon-Smith”).
Ex.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”).

Exhibits	Description
Ex.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”).
Ex.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”).
Ex.1010	Madhav Mutalik & Dhara Sanghavi, <i>Review of Drug Interactions: A Comprehensive Update</i> , 4 Brit. J. Pharm. Rsch. 954 (2014) (“Mutalik”).
Ex.1011	U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Rsch., <i>Integrated Review: NDA 216916, Pyrukynd (mitapivat)</i> (2021) (“FDA”).
Ex.1012	Nathan P. Clark, <i>Warfarin Interaction With Hepatic Cytochrome P-450 Enzyme-Inducing Anticonvulsants</i> , 24 Clin. & Applied Thrombosis/Hemostasis 172 (2018) (“Clark”).
Ex.1013	Pamela S. Hackman, <i>“Spleen Baby”: A Case Presentation of Pyruvate Kinase Deficiency in an Amish Neonate</i> , 35 Neonatal Network 375 (2016) (“Hackman”).
Ex.1014	Neshan B. Ilangaratne et al., <i>Phenobarbital: missing in action</i> , 90 Bull World Health Organ 871 (2012) (“Ilangaratne”).
Ex.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.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”).

Exhibits	Description
Ex.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”).
Ex.1018	CV of Michael J. Thirman, M.D.

40. In addition to these documents, I relied upon my education, knowledge, and experience, including in the field of hematology. I further considered the level of ordinary skill in the art, as well as the general knowledge in the relevant art, as of the effective filing date of the '049 patent.

V. SUMMARY OF OPINIONS

41. Based on my work in this case, it is my opinion that Claims 1, 8, 9, 14, and 19 of the '049 patent are unpatentable in view of the prior art. The challenged claims are anticipated by Sizemore. Claims 1, 8, 9, and 14 would also have been obvious over both (1) Agresta, Dana-Farber, Grace Presentation, and the knowledge of a POSA, and (2) Agresta, Dana-Farber, Grace Abstract, and the knowledge of a POSA. Claim 19 would have been obvious over Agresta, Dana-Farber, Grace Presentation or Grace Abstract, Sizemore, and the knowledge of a POSA.

VI. LEGAL STANDARDS

42. I have been asked to provide opinions according to the applicable legal standards below.

A. Person of Ordinary Skill in the Art

43. I understand that a POSA is a hypothetical person who is presumed to be aware of pertinent art, including knowledge in the art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. I understand that this hypothetical POSA is considered to have the normal skills and knowledge of a person in the technical field.

44. I understand that factors assessed in determining the level of skill of a POSA include the educational level of the inventor, type of problems encountered in the art, prior art solutions to those problems, rapidity with which innovations are made, sophistication of the technology, and educational level of active workers in the field.

B. Claim Construction

45. I understand that claims terms are generally given their ordinary and customary meaning as would be understood by a POSA as of the effective filing date in view of the claim language, specification, and prosecution history.

46. I understand that extrinsic evidence, which consists of all evidence external to the patent and prosecution history including, for example, dictionaries and technical publications, may also be relevant to claim construction.

47. I further understand that a patent applicant may set forth a special definition of a claim term in the specification, and then when the applicant does so, that definition may apply, rather than the term's ordinary and customary meaning.

C. Prior Art

48. I understand that a printed publication may qualify as prior art if it was published before the effective filing date of the challenged patent.

49. I further understand that to qualify as prior art, printed publications must be publicly accessible. I understand that an affidavit from the Internet Archive demonstrates that a webpage was publicly accessible as of the date and time stamp shown in the Wayback Machine.

50. I understand that certain exceptions may prevent disclosures from qualifying as prior art for printed publications published less than one year before the effective filing date. Those exceptions include when those disclosures were obtained directly or indirectly from an inventor or joint inventor, or when the subject matter of those disclosures was previously disclosed by the inventor, joint inventor, or one who obtained the subject matter from them.

D. Anticipation

51. I understand that anticipation requires a single prior art reference to disclose each and every limitation of the claim, either expressly or inherently. I

further understand that the anticipation analysis takes into account a POSA's understanding of the prior art reference based upon their knowledge.

E. Obviousness

52. I understand that a patent claim is unpatentable if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious to a POSA before the effective filing date of the claimed invention.

53. I understand that the following four factors are considered when determining whether a patent claim would have been obvious: (1) the scope and content of the prior art; (2) differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations of non-obviousness. I understand that a party seeking to invalidate a patent as obvious must demonstrate that a POSA would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the POSA would have had a reasonable expectation of success in doing so.

54. I understand that obviousness may be shown by considering more than one prior art reference.

55. I understand that the use of hindsight must be avoided when considering whether the alleged invention would have been obvious to the POSA.

56. I understand that it would have been obvious to discover an optimum value of a parameter by routine experimentation from general conditions disclosed in the prior art. I understand if the parameter was recognized as affecting a result, i.e., as result effective, that may further support obviousness.

57. I further understand that when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, those solutions would have been obvious to try.

58. I understand that a claimed value would have been obvious where the value falls within a range disclosed by the prior art.

VII. LEVEL OF SKILL

59. I have been asked to provide opinions from the perspective of a person of ordinary skill in the art (“POSA”) as of the effective filing date of the claims of the ’049 patent.

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.

61. I have applied this definition and offer my opinion from the perspective of a POSA herein.

62. Based on my experiences described above, Section II, *supra*, and in my CV, in my opinion, I am qualified to provide opinions from a POSA's perspective regarding the '049 patent.

VIII. CLAIM CONSTRUCTION

63. In my opinion, "mitapivat" should be construed as "N-(4-(4-(cyclopropylmethyl)piperazine-1-carbonyl)phenyl)quinoline-8-sulfonamide." The specification confirms that those two names, as well as AG-348, are synonymous. Ex. 1001 ('049 patent) at 1:33-51.

64. The specification contains several definitions. In my opinion, those definitions should apply. Many of those definitions appear in a part of the specification entitled "Definitions." *Id.* at 4:55-8:67.

65. The specification additionally defines "CYP3A4/5" as "cytochrome P450 3A4 (CYP3A4) **or** 3A5 (CYP3A5)." *Id.* at 2:22-23 (emphasis added).

66. I otherwise give the words of the claims their ordinary and customary meaning or their defined meanings set forth in the patent specification.

IX. DETAILED BASES FOR OPINION

A. Ground 1: Claims 1, 8, 9, 14, and 19 Are Anticipated by Sizemore

67. In my opinion, Claims 1, 8, 9, 14, and 19 are anticipated by Sizemore. As explained by Sizemore, the reference provides, among other things, uses for

pharmaceutical compositions comprising mitapivat for treating conditions associated with pyruvate kinase. Ex. 1004 (Sizemore) at ¶¶ 0005-06; *see also id.* at Abstract.

68. Sizemore qualifies as prior art. It was published on May 31, 2019, Ex. 1004 (Sizemore) at Cover, before the effective filing date of the '049 patent. I am not aware of any exception that would remove Sizemore as prior art. For example, there is no overlap in inventorship between Sizemore and the '049 patent. *Compare* Ex. 1004 (Sizemore) at Cover *with* Ex. 1001 ('049 patent) at Cover.

1. Claim 1

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

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

because it is a pyruvate kinase activator. *Id.* at ¶¶ 0003, 00122; *see also id.* at ¶ 0002.

71. Sizemore satisfies the dosing claim limitation by disclosing administration of “about 5 mg,” about 20 mg,” about 50 mg,” and “about 100 mg” of mitapivat “twice per day,” i.e., about 10 mg, about 40 mg, about 100 mg, and about 200 mg/day. *Id.* at ¶ 00113; *see also id.* at ¶ 00114 (disclosing tablet compositions containing “about 5 mg,” “about 20 mg,” “about 50 mg,” and “about 100 mg”).

72. Sizemore satisfies the moderate CYP3A4/5 inducer limitation based upon its disclosures regarding combination therapy and CYP3A4 modulators viewed with the knowledge and understanding of a POSA.

73. Here, a POSA would read Sizemore as disclosing co-administration of mitapivat with a moderate CYP3A4 inducer. Sizemore discloses administration of a therapeutic agent, i.e., mitapivat, “alone or in combination with other therapies.” Ex. 1004 (Sizemore) at ¶ 0046. Sizemore then limits the other therapies taken by the treated subjects. *Id.* at ¶ 0053. Sizemore discloses that, “[i]n certain embodiments, such subject is not taking inhibitors of cytochrome P450 (CYP)3A4, strong inducers of CYP3A4, strong inhibitors of P-glycoprotein (P-gp), or digoxin.” *Id.* By excluding all inhibitors of CYP3A4 while excluding only strong inducers of CYP3A4, a POSA would have understood Sizemore to contemplate

administration of **moderate** inducers of CYP3A4. That is because a POSA would have viewed Sizemore's disclosure with his or her background knowledge, for example, that mitapivat was a CYP3A4 substrate and that moderate CYP3A4 inducers were publicly available. Section III.A, *supra*.

2. Claims 8 and 9

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

75. As discussed above, Sizemore discloses a dose of "about 100 mg of compound 1 twice per day." Ex. 1004 (Sizemore) at ¶¶ 00113, 00114. This disclosure satisfies Claim 9's limitation of about 100 mg twice per day. It also satisfies Claim 8's limitation of about 200 mg/day because about 100 mg twice per day totals about 200 mg/day.

3. Claim 14 and 19

76. Claim 14 depends from Claim 9 (and therefore from Claims 8 and 1) and additionally recites that the mitapivat is orally administered as part of a tablet

composition. Ex. 1001 ('049 patent), Claim 14. Claim 19 depends from Claim 14 (and therefore from Claims 9, 8, and 1) and additionally recites that the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate. *Id.*, Claim 19. In my opinion, Sizemore anticipates Claims 14 and 19 for the same reasons as Claims 1, 8, and 9 and the further reasons below. Sections IX.A.1-2, *supra*.

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

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

4. Conclusion

79. For the foregoing reasons, it is my opinion that Claims 1, 8, 9, 14, and 19 are unpatentable as anticipated by Sizemore.

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

80. It is my opinion that Claims 1, 8, 9, and 14 are unpatentable as obvious over Agresta, Dana-Farber, Grace Presentation, and the knowledge of a POSA.

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

82. Dana-Farber and Grace Presentation describe the same Phase 2 study, disclosing the same unique National Clinical Trial ("NCT") identification number: NCT02476916. Ex. 1007 (Dana-Farber) at 5; Ex. 1008 (Grace Presentation) at 19.

A POSA would have understood that Agresta also describes the same Phase 2 study, indicated by the shared key features of the study. *Compare* Ex. 1005 (Agresta) at Cover (applicant Agios), 44 (safety and efficacy study), 45 (Phase 2 study, adult PKD patients, treatment with Compound 1 (mitapivat), 24-week treatment, 50 mg and 300 mg dosing arms, 25 patients per arm), 46 (assessing hemoglobin, ATP, and 2,3-DPG levels) *with* Ex. 1007 (Dana-Farber) at 5 (same study goal, patient type, and treatment compound) *and* Ex. 1008 (Grace Presentation) at 17 (Agios-funded study), 19 (same phase of study, patient type, treatment compound, treatment length, dosing arms, number of patients per arm, and same clinical assessments).

83. As discussed further below, a POSA would have been motivated to combine these references, because the references all address treatment of the same disease (PKD) using the same drug (mitapivat) in the same Phase 2 clinical study. Section IX.B.3, *infra*. And a POSA would have had a reasonable expectation of success given the study's positive results and the routine nature of handling drug-drug interactions. Section IX.B.3, *infra*. And a POSA would have had a reasonable expectation of success given the study's positive results and the routine nature of handling drug-drug interactions. Section IX.B.4, *infra*.

84. Each of Agresta, Dana-Farber, and Grace Presentation qualify as prior art as they were each published before the effective filing date:

Reference	Publication Date
Agresta	Agresta was published on December 15, 2016. Ex. 1005 (Agresta) at Cover.
Dana-Farber	Dana-Farber was published on August 23, 2016. Ex. 1007 (Dana-Farber) at 1-2, 5.
Grace Presentation	Grace Presentation was published on October 7, 2017. Ex. 1008 (Grace Presentation) at 1-2, 15.

85. The public accessibility of the Dana-Farber reference has been verified through an affidavit from the Internet Archive. Ex. 1007 (Dana-Farber) at 1-2. That affidavit shows that the article was captured by the Wayback Machine from the Dana-Farber website on August 23, 2016, before the June 14, 2019, effective filing date. Ex. 1007 (Dana-Farber) at 1-2, 5. Moreover, the affidavit shows that a POSA would have been able to navigate to the article from the website's homepage, by clicking "search clinical trials," followed by navigating to "all blood disorders," and then to the study's title, "A Study of AG-348 in Adult Patients With Pyruvate Kinase Deficiency." Ex. 1007 (Dana-Farber) at 7-18. Additionally, it shows that clinical trials were searchable by keyword. *Id.*

86. Further, a POSA would have recognized that the study's co-principal investigator, scientific advisor, and lead author (Rachael Grace) was affiliated with Dana-Farber. Ex. 1008 (Grace Presentation) at 18-19; Ex. 1009 (Grace Abstract) at 1-2. Indeed, a POSA would have consulted the website of a research and treatment center like Dana-Farber to learn more about the clinical trials they conducted.

87. Likewise, the public accessibility of the Grace presentation has been verified through an affidavit from the Internet Archive. Ex. 1008 (Grace Presentation) at 1-2. That affidavit shows that the article was captured by the Wayback Machine from the Agios website on October 27, 2017, before the June 14, 2019 effective filing date. Ex. 1008 (Grace Presentation) at 1-2, 15. Moreover, the affidavit shows that a POSA would have been able to navigate to the presentation from the website's homepage, via the website's events and presentations page. *Id.* at 5-13.

88. Further, a POSA would have recognized that the study was sponsored by Agios. Ex. 1005 (Agresta) at Cover (listing applicant as Agios), 42-43 (disclosing Phase 2 study protocol). Indeed, a POSA would have consulted the website of a pharmaceutical company like Agios to learn more about the clinical trials they conducted.

1. Claim 1 Would Have Been Obvious

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

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

90. Agresta teaches methods for treating hemolytic anemia by administering mitapivat. Ex. 1005 (Agresta) at 25 (disclosing “a method for treating hemolytic anemia . . . comprising administering to a subject in need thereof a therapeutically effective amount of . . . [mitapivat]”), 51 (Claim 17 reciting same); Section III.A, *supra*. One type of hemolytic anemia that Agresta discloses treating is PKD, including in a Phase 2 clinical study. Ex. 1005 (Agresta) at 37-38; *see also id.* at 19 (disclosing a method of treating PKD); 37-47 (disclosing examples relating to PKD treatment, including Phase 2 clinical study protocol).

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

92. Because, as discussed above, the prior art taught administering mitapivat to treat PKD, a POSA would have understood that logical candidates for

co-administered drugs are those also administered to those suffering from PKD, for example, to treat a comorbidity. A POSA would have been aware of such drugs.

93. One example would have been phenobarbitone (also known as phenobarbital); Ex. 1006 (Gordon-Smith) at 10; Ex. 1013 (Hackman) at 3, which, as discussed below, a POSA would have known to be a moderate CYP3A4 inducer. A POSA would have known that PKD causes not only hemolytic anemia but also hyperbilirubinemia (elevated bilirubin levels in the blood). Ex. 1006 (Gordon-Smith) at 9-10; Ex. 1013 (Hackman) at 375. To manage hyperbilirubinemia, the prior art taught administering phenobarbital. Ex. 1006 (Gordon-Smith) at 10; Ex. 1013 (Hackman) at 3.

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

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

administering bosentan, including, as in Bachmeyer, to a PKD patient. Ex. 1016 (Bachmeyer) at 3; Ex. 1015 (van Giersbergen) at 1.

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

97. Indeed, a POSA would have been aware of several examples of such inducers. Ex. 1010 (Mutalik) at 13-14. A POSA would have co-administered those inducers with mitapivat when the need for those inducers arose. *Id.* at 2.

98. Agresta thus teaches treating a hemolytic anemia patient by co-administering mitapivat with other drugs. Further, as discussed above, a POSA

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

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

99. Dana-Farber further details the protocol for the Agresta Phase 2 study of mitapivat in PKD patients, including inclusion and exclusion criteria. Ex. 1007 (Dana-Farber) at 5-6; Section IX.B.1.a, *supra*. Inclusion criteria define which patients are permitted to enroll in a clinical trial, while exclusion criteria define which patients are prohibited from enrolling in a clinical trial. Ex. 1007 (Dana-Farber) at 5-6.

100. Dana-Farber teaches that patients taking strong CYP3A4 inducers were excluded from the study, while at the same patients taking moderate inducers were not excluded. Ex. 1007 (Dana-Farber) at 6 (Exclusion Criterion #12). A POSA would thus have understood PKD patients taking moderate CYP3A4 inducers—such as those receiving phenobarbitone or bosentan—could be enrolled and treated with mitapivat. That understanding, taken together with the positive results of this study, as discussed below, demonstrates that a POSA would have been able to co-administer mitapivat and a moderate CYP3A4 inducer. Section IX.B.1.c, *infra*.

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

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

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

103. A POSA would further have known that a key way to manage a drug-drug interaction, when necessary, was to adjust the dose of a drug affected by the

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

104. In my opinion, a POSA would thus have selected a mitapivat dose for co-administration with a moderate CYP3A4 inducer that is sufficient to compensate for the interaction between the drugs. A POSA would have utilized Grace Presentation's disclosures to do so, given that patients in the disclosed study were permitted to receive moderate CYP3A4 inducers. Section IX.B.1.b, *supra*.

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

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

107. Moreover, arriving at doses recited in the claims would have been a matter of routine optimization. Ex. 1017 (Le) at 2 (publication by several Agios authors, including inventor Yang, describing dose selection as “optimiz[ation]”). A POSA would have optimized the mitapivat dose because it was recognized as a result-effective variable. That is because, as discussed above, adjusting dose was recognized as a routine way to manage a drug-drug interaction to ensure adequate drug concentration, and thus efficacy. Ex. 1010 (Mutalik) at 24; *see also id.* at 19; Ex. 1017 (Le) at 2-4; Ex. 1012 (Clark) at 1, 2, 4, 5, 6.

108. A POSA would have been able to arrive at an optimal mitapivat dose by routine adjustment within the dosage options provided by the prior art.

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

110. Moreover, in my opinion, the claimed mitapivat doses would have been obvious to try, as there were a finite number of predictable solutions and a design need to select a dose.

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

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

Id. at 26. As for a design need, for the reasons discussed above, there was a design need to utilize a mitapivat dose to counteract the known interaction with CYP3A4 inducers.

112. As such, it is my opinion that selecting from among seven identified dosing levels in view of the design need would have been obvious to try.

* * *

113. For the foregoing reasons, it is my opinion that Claim 1 would have been obvious.

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

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

114. Claim 8 depends from Claim 1 and further recites that the subject is administered about 200 mg/day of mitapivat. Ex. 1001 ('049 patent), Claim 8. Claim 9 depends from Claim 8 and further recites that the subject is administered about 100 mg of mitapivat twice per day. *Id.*, Claim 9. In my opinion, Claims 8 and 9 would have been obvious over Agresta in view of Dana-Farber, Grace Presentation, and the knowledge of a POSA for the reasons discussed above regarding Claim 1 and the reasons that follow. Section IX.B.1, *supra*.

115. Administering about 100 mg/dose twice daily would have been obvious for each of the same reasons that the claimed doses of Claim 1 would have been obvious. First, Agresta expressly discloses “about 100 mg” as a dose for twice-daily oral administration, totaling 200 mg/day. Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8. Second, Grace Presentation confirms that this dose was safe and effective in PKD patients. Ex. 1008 (Grace Presentation) at 23, 26-31. Third,

it is my opinion that a POSA would have arrived at the dose via routine optimization. See Section IX.B.1.c, *supra*. Fourth, it would have been obvious to try. *Id.*

116. For the foregoing reasons, it is my opinion that Claims 8 and 9 would have been obvious.

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

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

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

119. For the foregoing reasons, it is my opinion that Claim 14 would have been obvious.

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

120. In my opinion, a POSA would have been motivated to combine Agresta, Dana-Farber, and Grace Presentation. That is because those references all address treatment of the same disease (PKD) using the same drug (mitapivat) in the same Phase 2 clinical study. Section IX.B.1, *supra*.

121. In my opinion, a POSA would also have been motivated to combine these references in view of the nature of the problem to be solved, i.e., a drug-drug interaction between mitapivat and CYP3A4 inducers. Agresta teaches co-administration of mitapivat with other drugs, during which a POSA would have recognized a potential drug-drug interaction between mitapivat and CYP3A4 inducers. *Id.* A POSA would thus have been motivated to investigate co-administration of mitapivat and a moderate CYP3A4 inducer when treating PKD, and how to dose mitapivat when doing so. *Id.* A POSA would have looked to Dana-Farber and Grace Presentation, which provide procedures and results from the Phase 2 trial that would have allowed a POSA to confirm that such administration is feasible and to arrive at a mitapivat dose. Sections IX.B.1.b-c, *supra*.

122. For the foregoing reasons, it is my opinion that a POSA would have been motivated to combine Agresta, Dana-Farber, and Grace Presentation.

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

123. In my opinion, a POSA would have had a reasonable expectation of success in arriving at the claimed invention based on the prior art teachings discussed above. Section IX.B.1, *supra*.

124. In particular, the results of the Phase 2 trial would have provided a reasonable expectation of success. Section IX.B.1.c, *supra*. In that trial, patients were treated in a manner that meets the claims: the patients were treated for PKD using mitapivat at two of the claimed dosing alternatives, and were permitted to receive a moderate CYP3A4 inducer. *Id.* And Grace Presentation indicates that the disease was effectively treated without raising any concerns about co-administration of mitapivat with a moderate CYP3A4 inducer. *Id.*

125. A reasonable expectation of success would further have been supported by the fact that POSAs routinely, and successfully, managed drug-drug interactions and would have been able to do so by routine dose adjustment. *Id.*

126. A POSA would also have had a reasonable expectation of success for the reasons that a POSA would have had motivation to combine. Section IX.B.3, *supra*.

127. For the foregoing reasons, it is my opinion that a POSA would have had a reasonable expectation of success in arriving at the claimed invention.

5. Lack of Secondary Considerations

128. Based on my review of the prosecution history, I am not aware of any evidence of secondary considerations of nonobviousness. Ex. 1002 ('049 prosecution history). Specifically, I observe that Patent Owner made no assertion of secondary considerations during the prosecution of the '049 patent. *Id.*

6. Conclusion

129. For the foregoing reasons, the combination of Agresta, Dana-Farber, Grace Presentation, and the knowledge of a POSA satisfy each of the limitations of the challenged claims. Further, it is my opinion that a POSA would have been motivated to combine those references and had a reasonable expectation of success at arriving at the claimed invention.

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

130. It is my opinion that Claims 1, 8, 9, and 14 are unpatentable as obvious over Agresta, Dana-Farber, Grace Abstract, and the knowledge of a POSA.

131. Agresta and Dana-Farber were each references that served as part of the obviousness combination in Ground 2, along with Grace Presentation. Section IX.B, *supra*. In Ground 3, Grace Abstract replaces Grace Presentation. Grace

Abstract provides similar teachings to Grace Presentation, though in the form of an abstract. Ex. 1009 (Grace Abstract) at 1; Section IX.B.1.c, *supra*; Section IX.C.1, *infra*. Together, these references satisfy all the limitations of Claims 1, 8, 9, and 14.

132. A POSA would have thus been motivated to combine these Agresta, Dana-Farber, and Grace Abstract, for the same reasons that a POSA would have been motivated to combine the references of Ground 2. Section IX.C.3, *infra*. And a POSA would have had a reasonable expectation of success for the same reasons set forth in Ground 2. Section IX.C.4, *infra*.

133. Each of Agresta and Dana-Farber qualify as prior art for the reasons discussed above. Section IX.B, *supra*. Further, Grace Abstract qualifies as prior art as it was published before the effective filing date:

Reference	Publication Date
Grace Abstract	Grace was published on December 7, 2017. Ex. 1009 (Grace Abstract) at 1.

1. Claim 1 Would Have Been Obvious

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

135. As discussed above, Agresta discloses treatment of hemolytic anemia using mitapivat, including in a Phase 2 clinical trial, and further discloses co-administering mitapivat with other drugs. Section IX.B.1.a, *supra*. Further, a POSA would have understood such drugs to include moderate CYP3A4 inducers, such as phenobarbitone and bosentan, and that such drugs may give rise to a drug-drug interaction with mitapivat. *Id.*

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

137. Grace Abstract teaches positive results from the same Phase 2 study discussed in Agresta and Dana-Farber. Ex. 1009 (Grace Abstract) at 1-3; *id.* at 2 (disclosing the same NCT identification number as in Dana-Farber: NCT02476916); Section IX.B, *supra*. Specifically, Grace Abstract teaches that Phase 2 study patients were effectively treated for PKD and does not report any difficulty with treating patients receiving both mitapivat and moderate CYP3A4 inducers as permitted by Dana-Farber. Ex. 1009 (Grace Abstract) at 1-3; Ex. 1007 (Dana-Farber) at 5-6. In my opinion, a POSA would thus have understood that he

or she would have been able to co-administer mitapivat and a moderate CYP3A4 inducer.

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

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

140. In my opinion, a POSA would thus have selected a mitapivat dose for co-administration with a moderate CYP3A4 inducer that is sufficient to compensate for the interaction between the drugs. A POSA would have utilized Grace Abstract's disclosures to do so, given that patients in the disclosed study

were permitted to receive moderate CYP3A4 inducers, as discussed above.

Section IX.B.1.b, *supra*.

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

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

143. Each dose recited in the challenged claims—about 10 mg/day, about 40 mg/day, about 100 mg/day, or about 200 mg/day—thus falls within the range of safe and effective doses reported by Grace Abstract. Ex. 1009 (Grace Abstract) at 2-3.

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

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

146. A POSA would have been able to arrive at an optimal mitapivat dose by routine adjustment within the dosage options provided by the prior art.

147. Indeed, in the Phase 2 study, the investigators performed such adjustment when dosing the subjects, Ex. 1009 (Grace Abstract) at 2-3, illustrating the routine nature of dose adjustment. As taught by Grace Abstract, safety and efficacy results were assessed at regular intervals, permitting selection of a dose that appropriately balanced those results. *Id.*

148. Moreover, in my opinion, the claimed mitapivat doses would have been obvious to try, as there were a finite number of predictable solutions and a design need to select a dose.

149. As for a finite number of predictable solutions, a POSA would have understood from Agresta that there were eleven possible twice-daily dosing options within Grace Abstract’s effective range: about 50–300 mg at 25 mg

increments. Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8 (disclosing “. . . about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg”); *see also id.* at 45 (disclosing 25 mg dosage form size for use in Phase 2 study).

150. Even considering a 5 mg dose option, as well as an additional option or options between 5 mg and 50 mg, the number of options would remain finite.

151. As for a design need, for the reasons discussed above, there was a design need to utilize a mitapivat dose to counteract the known interaction between mitapivat and CYP3A4 inducers. Selecting from among eleven identified dosing levels in view of the design need, in my opinion, would have been obvious to try.

152. For the foregoing reasons, it is my opinion that Claim 1 would have been obvious.

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

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

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

knowledge of a POSA for the reasons discussed above regarding Claim 1 and the reasons that follow. Section IX.C.1, *supra*.

154. In my opinion, administering about 100 mg/dose twice daily would have been obvious for each of the same reasons that the claimed doses of Claim 1 would have been obvious. First, Agresta expressly discloses “about 100 mg” as a dose for twice-daily oral administration, totaling 200 mg/day. Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8. Second, Grace Abstract confirms that this dose fell within the range of safe and effective doses in PKD patients. Ex. 1009 (Grace Abstract) at 2-3.

155. Third, it is my opinion that a POSA would have arrived at the dose via routine optimization. See Section IX.C.1, *supra*. Fourth, it would have been obvious to try. *Id.*

156. For the foregoing reasons, it is my opinion that Claims 8 and 9 would have been obvious.

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

157. Claim 14 depends from Claim 9 (and therefore from Claims 8 and 1) and additionally recites that the mitapivat is orally administered as part of a tablet composition. Ex. 1001 ('049 patent), Claim 14. In my opinion, Claim 14 would have been obvious over Agresta in view of Dana-Farber, Grace Abstract, and the

knowledge of a POSA for the reasons discussed above regarding Claims 1, 8, and 9 and the reasons that follow. Sections IX.C.1, IX.C.2.a, *supra*.

158. Agresta expressly discloses that mitapivat may be formulated as “tablets” and administered “orally.” Ex. 1005 (Agresta) at 35. Further, the Phase 2 clinical study described in Agresta specifically administered mitapivat to PKD patients using oral capsules. *Id.* at 45. The positive results of the study support use of tablets, because tablets, like capsules, are solid oral dosage forms. *Id.* at 35 (explaining that “any orally acceptable dosage form,” including tablets and capsules, may be used); Section IX.C.1, *supra*.

159. For the foregoing reasons, it is my opinion that Claim 14 would have been obvious.

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

160. Given the similar disclosures of the references of Grounds 2 and 3, a POSA would have been motivated to combine the references of Ground 3, the same reasons that a POSA would have been motivated to combine the references of Ground 2. Section IX.B.3, *supra*.

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

161. Given the similar disclosures of the references of Grounds 2 and 3, a POSA would have had a reasonable expectation of success as to Ground 3 for the

same reasons that a POSA would have had a reasonable expectation of success as to Ground 2. Section IX.B.4, *supra*.

5. Lack of Secondary Considerations

162. Based on my review of the prosecution history, I am not aware of any evidence of secondary considerations of nonobviousness. Ex. 1002 ('049 prosecution history). Specifically, I observe that Patent Owner made no assertion of secondary considerations during the prosecution of the '049 patent. *Id.*

6. Conclusion

163. For the foregoing reasons, the combination of Agresta, Dana-Farber, Grace Abstract, and the knowledge of a POSA satisfy each of the limitations of the challenged claims. Further, it is my opinion that a POSA would have been motivated to combine those references and had a reasonable expectation of success at arriving at the claimed invention. *Id.*

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

164. In my opinion, Claim 19 is unpatentable over Agresta, Dana-Farber, Grace Presentation or Grace Abstract, Sizemore, and the knowledge of a POSA. Claim 19 depends from claims previously addressed in Grounds 2 and 3 (Claims 1, 8, 9, and 14). Sections IX.B-C, *supra*. As discussed above, those claims would have been obvious over Agresta, Dana-Farber, Grace Presentation, and the knowledge of a POSA (Ground 2), or, alternatively, Agresta, Dana-Farber, Grace

Abstract, and the knowledge of a POSA (Ground 3). *Id.* In Ground 4, I rely upon those arguments and add Sizemore to address Claim 19. Together, these references satisfy all the limitations of Claim 19. *Id.*

165. As discussed further below, a POSA would have been motivated to combine these references, because the references all address treatment of the same disease (PKD) using the same drug (mitapivat) and address the same clinical study. Section IX.D.2, *infra*. A POSA would further have been motivated to combine these references in view of the nature of the problem to be solved, i.e., a drug-drug interaction between mitapivat and CYP3A4 inducers. *Id.* And a POSA would have had a reasonable expectation of success for the same reasons discussed in Grounds 2 and 3, as well as based upon Sizemore's disclosures. Section IX.D.3, *infra*.

1. Claim 19 Would Have Been Obvious

166. Claim 19 depends from Claim 14 (and therefore from Claims, 9, 8, and 1) and additionally recites that the tablet composition further comprises microcrystalline cellulose, mannitol, croscarmellose sodium, and sodium stearyl fumarate. Ex. 1001 ('049 patent), Claim 19. In my opinion, Claim 19 would have been obvious over Agresta in view of Dana-Farber, Grace Presentation or Grace Abstract, Sizemore and the knowledge of a POSA for the reasons discussed above

regarding Claims 1, 8, 9, and 14 in Grounds 2 or 3 and the reasons that follow.

Sections IX.B-C, *supra*.

167. As explained above in Ground 1, Sizemore discloses, among other things, uses for pharmaceutical compositions comprising mitapivat for treating conditions associated with pyruvate kinase. Section IX.A, *supra*. Sizemore specifically discloses that scientists developed mitapivat to treat PKD and investigated mitapivat in the same Phase 2 trial as in Agresta, Dana-Farber, Grace Presentation, and Grace Abstract. Ex. 1004 (Sizemore) at ¶¶ 0003, 0004 (citing the same NCT identification number: NCT02476916 as in Dana-Farber, Grace Presentation, and Grace); Sections IX.B, IX.C.1, *supra*. As pertinent here, Sizemore discloses pharmaceutical compositions comprising mitapivat for treating PKD. Ex. 1004 (Sizemore) at ¶ 0006; *see also id.* at Abstract.

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

00116, Claim 30 (disclosing ingredient amounts and percentages), 00219 (disclosing tablet formulation, methods of making, and that other excipients can be added to “aid” its properties); *see also id.* at ¶¶ 0093-110 (disclosing additional exemplary ingredients).

169. For the foregoing reasons, it is my opinion that Claim 19 would have been obvious.

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

170. In my opinion, a POSA would have been motivated to combine Agresta, Dana-Farber, and Grace Presentation or Grace Abstract, and Sizemore.

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

172. For the foregoing reasons, it is my opinion that a POSA would have been motivated to combine Agresta, Dana-Farber, Grace Presentation or Grace Abstract, and Sizemore.

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

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

4. Lack of Secondary Considerations

174. Based on my review of the prosecution history, I am not aware of any evidence of secondary considerations of nonobviousness. Ex. 1002 ('049 prosecution history). Specifically, I observe that Patent Owner made no assertion of secondary considerations during the prosecution of the '049 patent. *Id.*

5. Conclusion

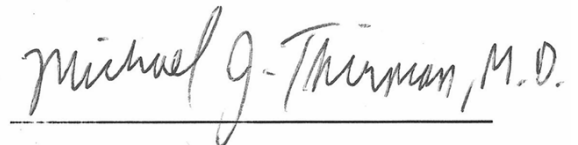
175. For the foregoing reasons, the combination of Agresta, Dana-Farber, Grace Presentation or Grace Abstract, Sizemore, and the knowledge of a POSA satisfy each of the limitations of the challenged claims. Further, it is my opinion

that a POSA would have been motivated to combine those references and had a reasonable expectation of success at arriving at the claimed invention.

X. CONCLUSION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: May 17, 2026



Michael J. Thirman, M.D.