

Comparison of Apotex's Petition to Apotex's Expert Declaration (Ex. 1003)¹

Petition Text	Text of Cited Exhibit 1003 Paragraphs
<p>A. Ground 1: Claims 1, 8, 9, 14, and 19 Are Anticipated Under 35 U.S.C. § 102 by Sizemore</p> <p>Claims 1, 8, 9, 14, and 19 are anticipated by Sizemore under 35 U.S.C. § 102. Ex. 1003 (Thirman Decl.) ¶ 67. As explained by Sizemore, the reference provides, <i>inter alia</i>, uses for pharmaceutical compositions comprising mitapivat for treating conditions associated with pyruvate kinase. Ex. 1003 (Thirman Decl.) ¶ 67; Ex. 1004 (Sizemore) at ¶¶ 0005-06; <i>see also id.</i> at Abstract.</p> <p>Sizemore qualifies as prior art under 35 U.S.C. § 102(a)(1). It was published on May 31, 2019, Ex. 1004 (Sizemore) at Cover, before the effective filing date of the '049 patent. Ex. 1003 (Thirman Decl.) ¶ 68. Petitioner is not aware of any exception under 35 U.S.C. § 102(b)(1) that would remove Sizemore as prior art. <i>Id.</i> For example, there is no overlap in inventorship between Sizemore and the</p> <p align="center">- 20 -</p> <p>'049 patent. Compare Ex. 1004 (Sizemore) at Cover with Ex. 1001 ('049 patent) at Cover; Ex. 1003 (Thirman Decl.) ¶ 68.</p>	<p>A. Ground 1: Claims 1, 8, 9, 14, and 19 Are Anticipated by Sizemore</p> <p>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</p> <p align="center">- 21 -</p> <p align="right">Apotex Ex. 1003 Page 25</p> <hr/> <p>pharmaceutical compositions comprising mitapivat for treating conditions associated with pyruvate kinase. Ex. 1004 (Sizemore) at ¶¶ 0005-06; <i>see also id.</i> at Abstract.</p> <p>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.</p>

¹ Verbatim language between the Petition and the Expert Declaration (Ex. 1003) is highlighted.

Petition Text	Text of Cited Exhibit 1003 Paragraphs
<p>1. Claim 1</p> <p>Claim 1 recites a method of treating hemolytic anemia by administering about 10, about 40, about 100, or about 200 mg/day of mitapivat and a moderate inducer of CYP3A4/5. Ex. 1001 ('049 patent), Claim 1; Ex. 1003 (Thirman Decl.)</p> <p>¶ 69. Sizemore anticipates Claim 1 for the following reasons. Ex. 1003 (Thirman Decl.) ¶ 69.</p> <p>Sizemore satisfies the method of treatment and mitapivat claim limitations by disclosing “methods for treating hemolytic anemia in a subject in need thereof comprising administering to the subject an effective amount of [mitapivat], or a pharmaceutical composition thereof” Ex. 1003 (Thirman Decl.) ¶ 70; Ex. 1004 (Sizemore) at ¶ 00137; <i>see also id.</i> at ¶ 00125, Claim 35 (similar). As Sizemore notes, “pyruvate kinase deficiency results in life-long hemolytic anemia,” which mitapivat treats because it is a pyruvate kinase activator. Ex. 1003 (Thirman Decl.) ¶ 70; Ex. 1004 (Sizemore) at ¶¶ 0003, 00122; <i>see also id.</i> at ¶ 0002.</p> <p>Sizemore satisfies the dosing claim limitation by disclosing administration of “about 5 mg,” about 20 mg,” about 50 mg,” and “about 100 mg” of mitapivat “twice per day,” i.e., about 10 mg, about 40 mg, about 100 mg, and about 200 mg/day. Ex. 1003 (Thirman Decl.) ¶ 71; Ex. 1004 (Sizemore) at ¶ 00113; <i>see also id.</i> at ¶ 00114 (disclosing tablet compositions containing “about 5 mg,” “about 20 mg,” “about 50 mg,” and “about 100 mg”).</p>	<p>1. Claim 1</p> <p>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.</p> <p>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; <i>see also id.</i> at ¶ 00125, Claim 35 (similar). As Sizemore notes, “pyruvate kinase deficiency results in life-long hemolytic anemia,” which mitapivat treats</p> <p style="text-align: center;">- 22 -</p> <p>because it is a pyruvate kinase activator. <i>Id.</i> at ¶¶ 0003, 00122; <i>see also id.</i> at ¶ 0002.</p> <p>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. <i>Id.</i> at ¶ 00113; <i>see also id.</i> at ¶ 00114 (disclosing tablet compositions containing “about 5 mg,” “about 20 mg,” “about 50 mg,” and “about 100 mg”).</p>

Petition Text	Text of Cited Exhibit 1003 Paragraphs
<p>Sizemore satisfies the moderate CYP3A4/5 inducer limitation based upon its disclosures regarding combination therapy and CYP3A4 modulators viewed with the knowledge and understanding of a POSA. Ex. 1003 (Thirman Decl.) ¶ 72.</p>	<p>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.</p>
<p>Here, a POSA would read Sizemore as disclosing co-administration of mitapivat with a moderate CYP3A4 inducer. Ex. 1003 (Thirman Decl.) ¶ 73. Sizemore discloses administration of a therapeutic agent, i.e., mitapivat, “alone or in combination with other therapies.” Ex. 1004 (Sizemore) at ¶ 0046; Ex. 1003 (Thirman Decl.) ¶ 73. Sizemore then limits the other therapies taken by the treated subjects. Ex. 1004 (Sizemore) at ¶ 0053; Ex. 1003 (Thirman Decl.) ¶ 73. Sizemore discloses that, “[i]n certain embodiments, such subject is not taking inhibitors of cytochrome P450 (CYP)3A4, strong inducers of CYP3A4, strong inhibitors of P-glycoprotein (P-gp), or digoxin.” <i>Id.</i> By excluding all inhibitors of CYP3A4 while excluding only strong inducers of CYP3A4, a POSA would have understood Sizemore to contemplate administration of <i>moderate</i> inducers of CYP3A4. Ex. 1003 (Thirman Decl.) ¶ 73. That is because a POSA would have viewed Sizemore’s disclosure with his or her background knowledge, for example, that mitapivat was a CYP3A4 substrate and that moderate CYP3A4 inducers were publicly available. <i>Id.</i>; Section IV.A, <i>supra</i>.</p> <p>- 23 -</p>	<p>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. <i>Id.</i> 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.” <i>Id.</i> By excluding all inhibitors of CYP3A4 while excluding only strong inducers of CYP3A4, a POSA would have understood Sizemore to contemplate</p> <p>- 23 -</p> <p>Apotex Ex. 1003 Page 27</p> <hr/> <p>administration of <i>moderate</i> 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, <i>supra</i>.</p>

Petition Text	Text of Cited Exhibit 1003 Paragraphs
<p data-bbox="617 233 674 256" style="text-align: center;">- 23 -</p> <p data-bbox="363 456 579 479">2. Claims 8 and 9</p> <p data-bbox="237 505 1039 919">Claim 8 depends from Claim 1 and further recites that the subject is administered about 200 mg/day of mitapivat. Ex. 1001 ('049 patent), Claim 8; Ex. 1003 (Thirman Decl.) ¶ 74. Claim 9 depends from Claim 8 and further recites that the subject is administered about 100 mg of mitapivat twice per day. Ex. 1001 ('049 patent), Claim 9; Ex. 1002 ('049 prosecution history, Certificate of Correction) at 459; Ex. 1003 (Thirman Decl.) ¶ 74. Sizemore anticipates Claims 8 and 9 for the same reasons as Claim 1 and the further reasons below. Ex. 1003 (Thirman Decl.) ¶ 74; Section V.A.1, <i>supra</i>.</p> <p data-bbox="237 945 1020 1252">As discussed above, Sizemore discloses a dose of “about 100 mg of compound 1 twice per day.” Ex. 1004 (Sizemore) at ¶¶ 00113, 00114; Ex. 1003 (Thirman Decl.) ¶ 75. This disclosure satisfies Claim 9’s limitation of about 100 mg twice per day. Ex. 1003 (Thirman Decl.) ¶ 75. It simultaneously satisfies Claim 8’s limitation of about 200 mg/day because about 100 mg twice per day totals about 200 mg/day. <i>Id.</i></p> <p data-bbox="363 1278 604 1300">3. Claims 14 and 19</p> <p data-bbox="237 1326 1010 1408">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</p>	<p data-bbox="1203 238 1419 261">2. Claims 8 and 9</p> <p data-bbox="1077 287 1887 647">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. <i>Id.</i>, 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, <i>supra</i>.</p> <p data-bbox="1077 673 1887 927">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.</p> <p data-bbox="1203 953 1436 976">3. Claim 14 and 19</p> <p data-bbox="1077 1002 1875 1083">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</p> <p data-bbox="1457 1143 1514 1166" style="text-align: center;">- 24 -</p> <p data-bbox="1703 1203 1900 1226" style="text-align: right;">Apotex Ex. 1003 Pa</p>

composition. Ex. 1001 ('049 patent), Claim 14; Ex. 1003 (Thirman Decl.) ¶ 76. Claim 19 depends from Claim 14 (and therefore from Claims 9, 8, and 1) and

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

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

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

4. Conclusion

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

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.

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

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

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

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.

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

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

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

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

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:

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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.

1. Claim 1 Would Have Been Obvious

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

¶ 89. Claim 1 would have been obvious over the combination of Agresta, Dana-Farber, Grace Presentation, and the knowledge of a POSA. Ex. 1003 (Thirman Decl.) ¶ 89.

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

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

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

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.

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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).

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<p>Agresta contemplates administering mitapivat in combination with “one or more additional therapeutic or prophylactic agents” as part of a “multiple dose regimen.” Ex. 1005 (Agresta) at 36; Ex. 1003 (Thirman Decl.) ¶ 91. Indeed, a POSA would have understood that co-administration of multiple drugs is common given the multiple medical conditions that patients may have and the need to treat those conditions. Ex. 1010 (Mutalik) at 2; Ex. 1003 (Thirman Decl.) ¶ 91.</p> <p>Because, as discussed above, the prior art taught administering mitapivat to treat PKD, a POSA would have understood that logical candidates for co-administered drugs are those also administered to those suffering from PKD, for example, to treat a comorbidity. Ex. 1003 (Thirman Decl.) ¶ 92; <i>In re Kerkhoven</i>, 626 F.2d 846, 850 (C.C.P.A. 1980) (holding “<i>prima facie</i> obvious” combining two compositions, reasoning it “flows logically” to combine compositions having the same purpose but taught individually in the prior art). A POSA would have been aware of such drugs. Ex. 1003 (Thirman Decl.) ¶ 92.</p> <p>One example would have been phenobarbitone (also known as phenobarbital), Ex. 1006 (Gordon-Smith) at 10; Ex. 1013 (Hackman) at 3, which, as discussed below, a POSA would have known to be a moderate CYP3A4 inducer. Ex. 1003 (Thirman Decl.) ¶ 93. A POSA would have known that PKD</p> <p>- 29 -</p>	<p>91. Agresta contemplates administering mitapivat in combination with “one or more additional therapeutic or prophylactic agents” as part of a “multiple dose regimen.” <i>Id.</i> 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 (Mutalik) at 2.</p> <p>92. Because, as discussed above, the prior art taught administering mitapivat to treat PKD, a POSA would have understood that logical candidates for</p> <p>- 30 -</p> <p>Apotex Ex. 1003 P.</p> <hr/> <p>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.</p> <p>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</p>

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

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

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

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 (Ilangeratne) 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.

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

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

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. *Id.*

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

Dana-Farber further details the protocol for the Agresta Phase 2 study of mitapivat in PKD patients, including inclusion and exclusion criteria⁷. Ex. 1007 (Dana-Farber) at 5-6; Ex. 1003 (Thirman Decl.) ¶ 99; Section V.B.1.a, *supra*. Dana-Farber teaches that patients taking strong CYP3A4 inducers were excluded from the study, while at the same patients taking moderate inducers were not excluded. Ex. 1007 (Dana-Farber) at 6 (Exclusion Criterion #12); Ex. 1003 (Thirman Decl.) ¶ 100. A POSA would thus have understood PKD patients taking moderate CYP3A4 inducers—such as those receiving phenobarbitone or bosentan—could be enrolled and treated with mitapivat. Ex. 1003 (Thirman Decl.) ¶ 100. That understanding, taken together with the positive results of this study, as discussed below, demonstrates that a POSA would have been able to co-administer

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

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

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**

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

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

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

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

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Petition Text	Text of Cited Exhibit 1003 Paragraphs
<p>A POSA would further have known that a key way to manage a drug-drug interaction, when necessary, was to adjust the dose of a drug affected by the interaction. Ex. 1003 (Thirman Decl.) ¶ 103; Ex. 1010 (Mutalik) at 24; <i>see also id.</i> at 19. That is because a POSA would have recognized that administration of a cytochrome P450 inducer reduced the concentration of the affected drug in the body, Ex. 1010 (Mutalik) at 12-13, which could be counteracted by an increased dose to increase that concentration, Ex. 1017 (Le) at 2-4 (disclosing that increasing mitapivat dose increases drug concentration, as well as the drug's effects); Ex. 1012 (Clark) at 1, 2, 4, 5, 6 (disclosing increasing dose of the drug warfarin to counteract reduced concentration resulting from administering a cytochrome P450 inducer). Ex. 1003 (Thirman Decl.) ¶ 103.</p> <p>A POSA would thus have selected a mitapivat dose for co-administration with a moderate CYP3A4 inducer that is sufficient to compensate for the interaction between the drugs. Ex. 1003 (Thirman Decl.) ¶ 104. A POSA would have utilized Grace Presentation's disclosures to do so, given that patients in the disclosed study were permitted to receive moderate CYP3A4 inducers. <i>Id.</i>; Section V.B.1.b, <i>supra</i>.</p> <p>- 34 -</p>	<p>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</p> <p>- 34 -</p> <p>Apotex Ex. 1003 P</p> <hr/> <p>interaction. Ex. 1010 (Mutalik) at 24; <i>see also id.</i> 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).</p> <p>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, <i>supra</i>.</p>

Petition Text	Text of Cited Exhibit 1003 Paragraphs
<p data-bbox="598 233 661 256" style="text-align: center;">- 34 -</p> <hr/> <p data-bbox="210 459 1037 773">Regarding dosing, Grace Presentation taught that the Phase 2 study protocol provided 50 mg and 300 mg twice daily of mitapivat as starting doses, and further permitted dose adjustment. Ex. 1003 (Thirman Decl.) ¶ 105; Ex. 1008 (Grace Presentation) at 23; <i>see also</i> 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. <i>Id.</i></p> <p data-bbox="210 803 1037 1349">Grace Presentation further taught that doses of < 25, 25, 50, 100, 150, 200, and 300 mg twice daily were effective, as indicated by hemoglobin increases, and were “well tolerated.” Ex. 1008 (Grace Presentation) at 19 (disclosing that hemoglobin changes are “indicators of clinical activity”), 21, 26-31 (reporting results); Ex. 1003 (Thirman Decl.) ¶ 106; <i>see also</i> Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8 (disclosing dosage amounts); <i>id.</i> at 46 (disclosing that hemoglobin changes are “indicators of clinical activity”). Significantly, 50 and 100 mg twice daily total 100 mg and 200 mg per day, respectively, thus meeting the “about 100 mg” and “about 200 mg” doses recited in Claim 1. Ex. 1003 (Thirman Decl.) ¶ 106.</p>	<p data-bbox="1071 241 1898 555">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; <i>see also</i> 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. <i>Id.</i></p> <p data-bbox="1455 656 1518 678" style="text-align: center;">- 35 -</p> <p data-bbox="1707 716 1898 738" style="text-align: right;">Apotex Ex. 1003 P</p> <hr/> <p data-bbox="1071 914 1898 1393">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); <i>see also</i> Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8 (disclosing dosage amounts); <i>id.</i> 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.</p>

Petition Text	Text of Cited Exhibit 1003 Paragraphs
<p>Moreover, arriving at doses recited in the claims would have been a matter of routine optimization. Ex. 1017 (Le) at 2 (publication by several Agios authors, including inventor Yang, describing dose selection as “optimiz[ation]”); Ex. 1003 (Thirman Decl.) ¶ 107. A POSA would have optimized the mitapivat dose because</p> <p style="text-align: center;">- 35 -</p> <hr/> <p>it was recognized as a result-effective variable. <i>Pfizer Inc. v. Sanofi Pasteur Inc.</i>, 94 F.4th 1341, 1348 (Fed. Cir. 2024) (holding that routine optimization of a parameter recognized as result-effective by the prior art is “normally obvious”); Ex. 1003 (Thirman Decl.) ¶ 107. That is because, as discussed above, adjusting dose was recognized as a routine way to manage a drug-drug interaction to ensure adequate drug concentration, and thus efficacy. Ex. 1003 (Thirman Decl.) ¶ 107; Ex. 1010 (Mutalik) at 24; <i>see also id.</i> at 19; Ex. 1017 (Le) at 2-4; Ex. 1012 (Clark) at 1, 2, 4, 5, 6.</p> <p>Here, a POSA would have been able to arrive at an optimal mitapivat dose by routine adjustment within the dosage options provided by the prior art. Ex.</p>	<p>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; <i>see also id.</i> at 19; Ex. 1017 (Le) at 2-4; Ex. 1012 (Clark) at 1, 2, 4, 5, 6.</p> <p>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.</p> <p style="text-align: center;">- 36 -</p> <p style="text-align: right;">Apotex Ex. 1003 Pa</p>

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

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

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

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

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

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

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

* * *

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

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

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

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

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

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.

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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*.

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

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

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

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

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

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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*.

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

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

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

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

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

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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*.

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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-

between mitapivat and CYP3A4 inducers. Ex. 1003 (Thirman Decl.) ¶ 121. Agresta teaches co-administration of mitapivat with other drugs, during which a POSA would have recognized a potential drug-drug interaction between mitapivat and CYP3A4 inducers. Ex. 1003 (Thirman Decl.) ¶ 121; Section V.B.1.a, *supra*. A POSA would thus have been motivated to investigate co-administration of mitapivat and a moderate CYP3A4 inducer when treating PKD, and how to dose mitapivat when doing so. Ex. 1003 (Thirman Decl.) ¶ 121; Section V.B.1.a, *supra*. A POSA would have looked to Dana-Farber and Grace Presentation, which provide procedures and results from the Phase 2 trial that would have allowed a POSA to confirm that such administration is feasible and to arrive at a mitapivat dose. Ex. 1003 (Thirman Decl.) ¶ 121; Sections V.B.1.b-c, *supra*.

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

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

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

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

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

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

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

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

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

5. Lack of Secondary Considerations

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

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

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

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

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

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

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

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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.

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

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

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

1. Claim 1 Would Have Been Obvious

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

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

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

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

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

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

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.

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

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

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

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

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

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

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

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

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.

Further, claimed doses do not merely appear in the prior art within a range; two of them (about 100 mg and about 200 mg) are expressly disclosed by Agresta.

Ex. 1003 (Thirman Decl.) ¶ 144; Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8.

Moreover, arriving at the claimed doses would have been a matter of routine optimization. Ex. 1017 (Le) at 2 (describing dose selection as “optimiz[ation]”);

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

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

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

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selection of a dose that appropriately balanced those results. Ex. 1009 (Grace

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.

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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.*

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

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

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

would have been obvious to try. *Id.*; *Amgen*, 66 F.4th at 967-68 (holding dosing

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.

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

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

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

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

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

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Ex. 1005 (Agresta) at 15, 20, 25-26, 35, Claim 8; Ex. 1003 (Thirman Decl.) ¶ 154. Second, Grace Abstract confirms that this dose fell within the range of safe and effective doses in PKD patients. Ex. 1009 (Grace Abstract) at 2-3; Ex. 1003

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

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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.

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

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

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

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

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

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

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

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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*.

For the foregoing reasons, Claim 14 would have been obvious. Ex. 1003

(Thirman Decl.) ¶ 159.

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

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

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

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

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5. Lack of Secondary Considerations

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

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

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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

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

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

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

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

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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.*

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

1. Claim 19 Would Have Been Obvious

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

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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

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regarding Claims 1, 8, 9, and 14 in Grounds 2 or 3 and the reasons that follow. Sections IX.B-C, *supra*.

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

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

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,

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

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

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

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

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

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

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

4. Lack of Secondary Considerations

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

5. Conclusion

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

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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

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