

## HEALTH TECHNOLOGY BRIEFING NOVEMBER 2020

### Mitapivat for treating pyruvate kinase deficiency

<b>NIHRIO ID</b>	11252	<b>NICE ID</b>	10289
<b>Developer/Company</b>	Agios Pharmaceuticals Inc	<b>UKPS ID</b>	N/A

<b>Licensing and market availability plans</b>	Currently in phase III clinical trials.
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### SUMMARY

Mitapivat is currently in clinical development for the treatment of adult patients with pyruvate kinase deficiency (PKD) who have regular blood transfusions and those who do not have regular blood transfusions. PKD is a genetic blood disorder caused by low levels of the enzyme pyruvate kinase (PK). Low levels of PK result in a deficiency in energy and causes red blood cells to break down too early. This is known as haemolytic anaemia. Symptoms of PKD vary significantly with some patients requiring no treatment and some patients requiring blood transfusions, surgery to remove the spleen or haematopoietic stem cell transplant which are all associated with risks and complications. There are currently no disease modifying treatments approved for the treatment of PKD.

Mitapivat is administered as an oral tablet, twice a day. Mitapivat works by activating normal PK and mutated PK enzymes. Mitapivat has been shown in clinical trials to be safe and to rapidly increase the haemoglobin levels of adults with PKD. If licensed, mitapivat would be the first approved disease modifying therapy for PKD patients and may reduce the need for surgery, transplantation or transfusions.

*This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.*

## PROPOSED INDICATION

Adult patients with transfusion-dependent and transfusion-independent pyruvate kinase deficiency (PKD).<sup>1,2</sup>

## TECHNOLOGY

### DESCRIPTION

Mitapivat (AG-348) is a first in class, oral, small molecule allosteric activator of pyruvate kinase (PK) in red blood cells (RBC) that directly targets the underlying metabolic defect in PK deficiency.<sup>3-5</sup> In vitro experiments have shown that mitapivat activates wild-type and a variety of mutant RBC PK enzymes. Mitapivat increases the activity of mutant PK enzymes ex-vivo in RBC obtained from patients with PK.<sup>3,6</sup>

Mitapivat is currently in phase III development for the treatment of patients with PKD who are regularly transfused (NCT03559699). During the part 1 dose optimization period of the study, all participants will start on a dose of 5mg mitapivat administered twice daily. Over the course of part 1 each participant's dose will be optimized individually, up to a maximum dose of 50mg twice daily, for up to 16 weeks. During the part 2 fixed-dose period, participants will receive mitapivat at their optimized dose from part 1.<sup>7</sup>

Mitapivat is also in phase III development for the treatment of patients with PKD who are not regularly transfused (NCT03548220). During the part 1 dose optimisation period participants will receive mitapivat for 12 weeks, with investigators assessing the need for dose increases every 4 weeks. Participants will start on a dose of 5mg taken twice daily and the dose may be increased to 20mg twice daily or 50mg twice daily depending on response and tolerance. During the part 2 fixed dose period, participants will receive the last dose they received in part 1, twice daily.<sup>2</sup>

### INNOVATION AND/OR ADVANTAGES

Current management strategies for PKD, including blood transfusion and splenectomy are supportive only and introduce both short- and long-term risks. Haematopoietic stem-cell transplantation (HSCT) has been described in a small number of patients but has been associated with substantial risks of graft-versus-host disease and death. No specific disease-modifying therapy currently exists.<sup>3</sup> Therefore there is a need for development of a disease modifying therapy to reduce the need for current treatment options which are associated with the risks described above.

In-vitro experiments have shown that mitapivat activates wild-type and a variety of mutant RBC PK enzymes.<sup>3</sup> In a dose escalation study involving healthy volunteers, investigators reported an acceptable safety profile and changes in glycolytic intermediates that were consistent with glycolytic pathway activation, supporting the use of mitapivat as a potential targeted treatment option for PKD.<sup>3,8</sup> Results from the phase II study NCT02476916 showed that administration of mitapivat was associated with a rapid increase in the haemoglobin level in 50% of adults with PKD.<sup>3</sup>

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Mitapivat does not currently have Marketing Authorisation in the EU/UK for any indication.

Mitapivat was granted an orphan drug designation by the EMA in April 2020 for the treatment of PKD.<sup>9</sup>

Mitapivat received fast track designation by the FDA in April 2017, for the treatment of PKD.<sup>10</sup>

Mitapivat is not currently in development for any other indication.<sup>11</sup>

## PATIENT GROUP

### DISEASE BACKGROUND

PKD is a genetic blood disorder characterised by low levels of an enzyme called PK.<sup>12</sup> PK is needed to help cells turn glucose into energy in the form of adenosine triphosphate (ATP), in a process called glycolysis.<sup>13</sup> Without PK, there is a deficiency in energy which leads to premature red blood cell (RBC) destruction (haemolytic anaemia).<sup>12,13</sup> Instead of lasting 120 days, RBCs with PKD last only a few days to weeks.<sup>13</sup> PKD is caused by mutations in the PKLR gene which encodes PK and is inherited in an autosomal recessive manner.<sup>12,13</sup>

Symptoms of PKD can be highly variable and how much it affects an individual varies significantly. In some patients, the disease can be life-threatening at birth, other patients may have mild or no symptoms and some patients may develop symptoms during childhood or as adults.<sup>13</sup> Some of the signs and symptoms include chronic haemolytic anaemia, reticulocytosis, increased spleen size, a yellowing of the whites of the eyes (icterus), fatigue, lethargy, recurrent gallstones, jaundice and pale skin. In more severe cases, the first signs and symptoms may appear in utero in the form of hydrops fetalis, a condition which abnormal amounts of fluid build-up in two or more body areas of the foetus. Although the anaemia tends to stabilize in adulthood, episodes of anaemia may occur with acute infections, stress and pregnancy.<sup>13</sup>

PKD can have a negative impact on a patient's activities of daily living. Patients report difficulty with exercise or sports, susceptibility to illness, negative impact on appearance and also on social activities.<sup>14</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

The prevalence of PKD reported varies significantly due to the extreme rarity of the disorder, its similarity to other RBC disorders which leads to misdiagnosis, heterogeneous clinical presentation, ethnic and geographic variability and different methods used in published reports of prevalence. The prevalence of diagnosed PKD in a general Western population is estimated to be in the range of 3.2-8.5 per million population.<sup>15</sup> Applying this estimate to the 2019 mid-year population estimates for England this would equate to between 180 and 478 cases per year.<sup>16</sup>

In England in 2019-20, there were 203 finished consultant episodes (FCE) for anaemia due to disorders of glycolytic enzymes (ICD code D55.2), resulting in 202 admissions, 158 day cases and 15 FCE bed days.<sup>17</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

Symptoms of PKD vary between patients so an individualised treatment plan should be developed.<sup>13</sup> Mild cases require no treatment and people with severe anaemia may need blood transfusions.<sup>12</sup> The decision to transfuse is based on how an individual is tolerating haemolytic anaemia and not based on their levels of haemoglobin.<sup>13</sup> Surgical removal of the spleen (splenectomy) may also be necessary to help reduce the destruction of RBC, however, this does not help in all cases.<sup>12</sup>

Allogeneic HSCT can cure PKD. However, this is a major medical procedure that carries significant risk, including dying from complications related to the transplant.<sup>13</sup>

### CURRENT TREATMENT OPTIONS

There are currently no therapies with Marketing Authorisation approval in the EU for the treatment of PKD.<sup>9</sup>

There are currently no therapies recommended by NICE for the treatment of PKD.

### PLACE OF TECHNOLOGY

If licenced, mitapivat will offer a new treatment option both for PKD patients who regularly receive blood transfusions and for those who do not regularly receive blood transfusions, where there are currently no approved treatment options.<sup>2,7</sup>

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	<b>ACTIVATE-T, <a href="#">NCT03559699</a>, AG348-C-007;</b> An Open-Label Study to Evaluate the Efficacy and Safety of AG-348 in Regularly Transfused Adult Subjects With Pyruvate Kinase (PK) Deficiency <b>Phase III</b> – Active, not recruiting <b>Locations:</b> 6 EU countries (incl UK), USA, Canada and other countries <b>Estimated primary completion date:</b> 11 November 2020	<b><a href="#">NCT03853798</a>, <a href="#">EudraCT 2018-003459-39</a>, AG348-C-011;</b> An Open-Label, Multicenter, Extension Study of AG-348 in Adult Subjects With Pyruvate Kinase Deficiency Previously Enrolled in AG-348 Studies <b>Phase III</b> – Recruiting <b>Locations:</b> 10 EU countries (incl UK), USA, Canada and other countries <b>Estimated primary completion date:</b> September 2024
<b>Trial design</b>	Open-label, single-group assignment	Non-randomised, parallel assignment, open-label
<b>Population</b>	N=27; adults aged 18 years and older; presence of at least 2 mutant alleles in the PK Liver and RBC (PKLR) gene, of which at least	N=100 (planned); adults aged 18 years and older; participants who have completed either antecedent study AG348-C-006 or AG348-C-

	1 is a missense mutation; history of a minimum of 6 transfusion episodes in the 52-week period prior to date of informed consent	007 through the part 2-week 24 visit
<b>Intervention(s)</b>	<p>Part 1 dose optimisation period:</p> <ul style="list-style-type: none"> <li>Participants begin receiving 5mg mitapivat (oral tablet) twice daily. Dose will be increased to 20 mg or 50mg depending on their response and tolerance to mitapivat for up to 16 weeks</li> </ul> <p>Part 2 fixed dose period:</p> <ul style="list-style-type: none"> <li>Participants will receive their optimized dose of mitapivat as determined by participant's transfusion cycle and response to mitapivat in part 1 [from week 16 to week 24]</li> </ul>	Mitapivat (oral tablet). Participants will continue the same dose of mitapivat that they were receiving at the last visit of the AG348-C-007 study, twice daily, for up to 192 weeks.
<b>Comparator(s)</b>	No comparator	No comparator
<b>Outcome(s)</b>	<p>Primary outcome measure:</p> <ul style="list-style-type: none"> <li>Percentage of participants achieving a reduction in transfusion burden in part 2 [Time frame: from part 2, day 1 to the end of the study (part 2, week 24)]</li> </ul> <p>See trial record for full list of outcome measures</p>	<p>Primary outcome measures:</p> <ul style="list-style-type: none"> <li>Number of participants with adverse events (AEs) and serious adverse events (SAEs) [Time frame: from baseline to safety follow-up (up to 198 weeks)]</li> <li>Number of participants with AEs leading to dose reduction, treatment interruption and treatment discontinuation [Time frame: from baseline to safety follow-up (up to 198 weeks)]</li> </ul> <p>See trial record for full list of outcome measures</p>
<b>Results (efficacy)</b>	-	-
<b>Results (safety)</b>	-	-

<b>Trial</b>	<p><b>ACTIVATE</b>, <a href="#">NCT03548220</a>, <b>AG348-C-006</b>; A Phase III, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AG-348 in Not Regularly Transfused Adult Subjects With Pyruvate Kinase Deficiency  <b>Phase III</b> – Active, not recruiting  <b>Locations</b>: 9 EU countries (incl UK), USA, Canada and other countries</p>	<p><a href="#">NCT03853798</a>; An Open-Label, Multicenter, Extension Study of AG-348 in Adult Subjects With Pyruvate Kinase Deficiency Previously Enrolled in AG-348 Studies  <b>Phase III</b> – Recruiting  <b>Locations</b>: 10 EU countries (incl UK), USA, Canada and other countries</p>
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	<b>Estimated primary completion date:</b> October 2020	<b>Estimated primary completion date:</b> September 2024
<b>Trial design</b>	Randomized, double-blind, placebo-controlled, parallel assignment	Non-randomised, parallel assignment, open-label
<b>Population</b>	N = 80; adults aged 18 years and older; documented clinical laboratory confirmation of PKD, defined as documented presence of at least 2 mutant alleles in the PKLR gene, of which at least 1 is a missense mutation; haemoglobin (Hb) concentration less than or equal to 10.0g/dL; considered not regularly transfused, defined as having had no more than 4 transfusion episodes in the 12-month period up to the first day of study treatment and no transfusions in the 3 months prior to the first day of study treatment	N=100 (planned); adults aged 18 years and older; participants who have completed either antecedent study AG348-C-006 or AG348-C-007 through the part 2 week 24 visit
<b>Intervention(s)</b>	<p>Part 1 dose optimisation period:</p> <ul style="list-style-type: none"> <li>Participants receive mitapivat orally, twice a day for 12 weeks. Participants begin by receiving 5mg mitapivat. Investigators will assess the need for dose increases every 4 weeks and dose may be increased to 20mg twice a day or 50mg twice a day depending on their response to mitapivat and their tolerance [Time Frame: 12 weeks ]</li> </ul> <p>Part 2 fixed dose period:</p> <ul style="list-style-type: none"> <li>Participants receive the lase dose of mitapivat received in Part 1, twice daily. [Time Frame: 12 weeks ]</li> </ul>	Mitapivat (oral tablet). Participants will continue the same dose of mitapivat that they were receiving at the last visit of the AG348-C-006 study, twice daily, for up to 192 weeks.
<b>Comparator(s)</b>	Placebo Participants will receive placebo, orally, twice a day matching the dose of mitapivat given in part 1 and part 2	No comparator
<b>Outcome(s)</b>	<p>Primary outcome measure: Percentage of participants achieving a haemoglobin response (HR) in part 2 [Time frame: baseline, part 2: weeks 16, 20, 24]</p> <p>See trial record for full list of outcome measures</p>	<p>Primary outcome measures:</p> <ul style="list-style-type: none"> <li>Number of participants with adverse events (AEs) and serious adverse events (SAEs) [Time frame: from baseline to safety follow-up (up to 198 weeks)]</li> </ul>

		<ul style="list-style-type: none"> <li>Number of participants with AEs leading to dose reduction, treatment interruption and treatment discontinuation [Time frame: from baseline to safety follow-up (up to 198 weeks)]</li> </ul> <p>See trial record for full list of outcome measures</p>
Results (efficacy)	-	-
Results (safety)	-	-

<b>Trial</b>	<b>DRIVE PK</b> , <a href="#">NCT02476916</a> , <a href="#">EudraCT 2015-000484-13</a> ; A Phase 2, Open Label, Randomized, Dose Ranging, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study of AG-348 in Adult Patients With Pyruvate Kinase Deficiency <b>Phase II – Active, not recruiting</b> <b>Locations:</b> 4 EU (incl UK), USA and Canada <b>Primary completion date:</b> 08 May 2017
<b>Trial design</b>	Randomised, parallel assignment, open-label
<b>Population</b>	N=52; adults aged 18 years and older; PKD deficiency confirmed by enzymatic assay at screening; transfusion independent, defined as no more than 3 units of RBC transfused in 12 months prior to the first day of study dosing and no transfusions within 4 months of first day of study dosing
<b>Intervention(s)</b>	Mitapivat Participants assigned to receive either 50mg or 300mg of mitapivat taken twice daily. Doses were changed throughout the study period due to treatment emergent adverse events (AEs) and haemoglobin (Hb) levels exceeding mid-point of sex-adjusted ranges.
<b>Comparator(s)</b>	No comparator
<b>Outcome(s)</b>	Primary outcome measure: Percentage of participants experiencing at least one AE in the core period [Time frame: up to week 24]  See trial record for full list of outcome measures
<b>Results (efficacy)</b>	See trial record
<b>Results (safety)</b>	See trial record

## ESTIMATED COST

The estimated cost of mitapivat is not yet known.

## RELEVANT GUIDANCE

### NICE GUIDANCE

No relevant guidance identified.

### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Adult). E06/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Services for Haemoglobinopathy Care (All Ages). B08/S/a.

### OTHER GUIDANCE

- Grace RF, Layton MD and Barcellini W. How we manage patients with pyruvate kinase deficiency. 2019.<sup>18</sup>
- National Organization for Rare Disorders (NORD). Rare disease database: Pyruvate kinase deficiency. 2019.<sup>13</sup>
- Genetic and Rare Diseases Information Center. Pyruvate kinase deficiency. 2016.<sup>12</sup>

## ADDITIONAL INFORMATION

Agios Pharmaceuticals Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

## REFERENCES

- 1 Clinicaltrials.gov. A Phase 2, Open-label, Randomized, Dose Ranging, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study of AG-348 in Adult Patients With Pyruvate Kinase Deficiency. Trial ID NCT02476916. 2015. Status: Active, not recruiting. Available from: <https://clinicaltrials.gov/ct2/show/NCT02476916> [Accessed 05 October 2020].
- 2 Clinicaltrials.gov. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AG-348 in Not Regularly Transfused Adult Subjects With Pyruvate Kinase Deficiency. Trial ID NCT03548220. 2018. Status: Completed. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT03548220> [Accessed 05 October 2020].
- 3 Grace, R. F., Rose C., Layton D. M., Galactéros F., Barcellini W., Morton D. H., et al. *Safety and Efficacy of Mitapivat in Pyruvate Kinase Deficiency*. *New England Journal of Medicine*. 2019;381(10):933-44. Available from: <https://doi.org/10.1056/NEJMoa1902678>
- 4 Specialist Pharmacy Service. *Mitapivat*. 2019. Available from: <https://www.sps.nhs.uk/medicines/mitapivat/> [Accessed 09 October 2020].
- 5 Agios Pharmaceuticals. *Agios Announces Publication of Data for Mitapivat from Core and Extension Phases of the DRIVE PK Study in Patients with Pyruvate Kinase Deficiency in the New England Journal of Medicine*. 2019. Available from: <https://investor.agios.com/news-releases/news-release-details/agios-announces-publication-data-mitapivat-core-and->



- [extension#:~:text=Mitapivat%20is%20an%20investigational%2C%20first,%2C%20potentially%20debilitating%2C%20hemolytic%20anemia](#). [Accessed 12 November 2020].
- 6 Kung, C., Hixon J., Kosinski P. A., Cianchetta G., Histen G., Chen Y., et al. AG-348 enhances pyruvate kinase activity in red blood cells from patients with pyruvate kinase deficiency. *Blood*. 2017;130(11):1347-56. Available from: <https://doi.org/10.1182/blood-2016-11-753525>
- 7 Clinicaltrials.gov. An Open-Label Study to Evaluate the Efficacy and Safety of AG-348 in Regularly Transfused Subjects with Pyruvate Kinase (PK) Deficiency. Trial ID NCT03559699. 2018. Status: Active, not recruiting. Available from: <https://clinicaltrials.gov/ct2/show/NCT03559699> [Accessed 07 October 2020].
- 8 Yang, H., Merica E., Chen Y., Cohen M., Goldwater R., Kosinski P. A., et al. Phase 1 Single- and Multiple-Ascending-Dose Randomized Studies of the Safety, Pharmacokinetics, and Pharmacodynamics of AG-348, a First-in-Class Allosteric Activator of Pyruvate Kinase R, in Healthy Volunteers. *Clinical Pharmacology in Drug Development*. 2019;8(2):246-59. Available from: <https://doi.org/10.1002/cpdd.604>
- 9 European Medicines Agency (EMA). *Public summary of opinion on orphan designation: Mitapivat sulfate for the treatment of pyruvate kinase deficiency*. 2020. Available from: [https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/20/2270-public-summary-positive-opinion-orphan-designation-mitapivat-sulfate-treatment-pyruvate-kinase\\_en.pdf](https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/20/2270-public-summary-positive-opinion-orphan-designation-mitapivat-sulfate-treatment-pyruvate-kinase_en.pdf) [Accessed 08 October 2020].
- 10 New Drug Approvals. *Mitapivat*. 2020. Available from: <https://newdrugapprovals.org/2019/06/08/mitapivat/> [Accessed 09 October 2020].
- 11 Clinicaltrials.gov. *Search for Mitapivat clinical studies*. 2020. Available from: [https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age\\_v=&gndr=&intr=mitapivat&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd\\_s=&strd\\_e=&prcd\\_s=&prcd\\_e=&sfpd\\_s=&sfpd\\_e=&rfpd\\_s=&rfpd\\_e=&lupd\\_s=&lupd\\_e=&sort=](https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=mitapivat&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=) [Accessed 27 October 2020].
- 12 National Center for Advancing Translational Sciences. *Pyruvate Kinase Deficiency*. 2016. Available from: <https://rarediseases.info.nih.gov/diseases/7514/pyruvate-kinase-deficiency> [Accessed 06 October 2020].
- 13 National Organisation for Rare Diseases (NORD). *Pyruvate Kinase Deficiency*. 2019. Available from: <https://rarediseases.org/rare-diseases/pyruvate-kinase-deficiency/> [Accessed 07 October 2020].
- 14 Grace, R. F., Cohen J., Egan S., Wells T., Witherspoon B., Ryan A., et al. *The burden of disease in pyruvate kinase deficiency: Patients' perception of the impact on health-related quality of life*. *European Journal of Haematology*. 2018;101(6):758-65. Available from: <https://doi.org/10.1111/ejh.13128>
- 15 Agios Pharmaceuticals. *Prevalence of Red Cell Pyruvate Kinase Deficiency: A systematic Literature Review*. 2019. Available from: <https://investor.agios.com/static-files/19d3bd38-ccc0-4864-9bd7-ff038442ecd8> [Accessed 09 October 2020].
- 16 Office for National statistics (ONS). *Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2019*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2019estimates> [Downloaded 24 June 2020].
- 17 NHS Digital. *Hospital Admitted Patient Care Activity, 2019-20: Diagnosis*. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20> [Downloaded 17 September 2020].
- 18 Grace, R. F., Mark Layton D., Barcellini W. *How we manage patients with pyruvate kinase deficiency*. *British Journal of Haematology*. 2019 2019/03/01;184(5):721-34. Available from: <https://doi.org/10.1111/bjh.15758>

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