



Clinical trial results:

An Open-Label, Multicenter, Extension Study of AG-348 in Adult Subjects With Pyruvate Kinase Deficiency Previously Enrolled in AG-348 Studies

Summary

EudraCT number	2018-003459-39
Trial protocol	DK GB ES FR IE NL DE IT
Global end of trial date	03 July 2024

Results information

Result version number	v1
This version publication date	18 July 2025
First version publication date	18 July 2025

Trial information

Trial identification

Sponsor protocol code	AG348-C-011
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03853798
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Agios Pharmaceuticals, Inc.
Sponsor organisation address	88 Sidney Street, Cambridge, United States, MA 02139-4169
Public contact	Director, Scientific Communications, Agios Pharmaceuticals, Inc., +1 844633 2332, medinfo@agios.com
Scientific contact	Director, Scientific Communications, Agios Pharmaceuticals, Inc., +1 844633 2332, medinfo@agios.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 July 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an open-label, multicentre, extension study to evaluate the long-term safety, tolerability, and efficacy of treatment with mitapivat in subjects who were previously enrolled in Study AG348-C-006 or Study AG348-C-007.

Protection of trial subjects:

Each subject was required to sign an informed consent form (ICF) to participate in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Türkiye: 1
Worldwide total number of subjects	90
EEA total number of subjects	44

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	85
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 42 investigative sites in Denmark, France, Italy, Spain, Germany, United Kingdom, Netherlands, Ireland, Switzerland, United States, Canada, Japan, Korea, Thailand, Brazil and Turkey from 21 March 2019 to 03 July 2024.

Pre-assignment

Screening details:

A total of 90 subjects who had completed Study AG348-C-006 (NCT03548220) or AG348-C-007 (NCT03559699), were enrolled in this extension study to receive mitapivat treatment. Subjects were assigned to Cohorts 1, 2 or 3 depending on the previous treatment received in the antecedent studies.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Subjects who received placebo in Study AG348-C-006 and met the eligibility criteria of this extension study were enrolled to receive mitapivat tablets, 5 milligrams (mg), twice daily (BID), administered orally, for 4 weeks as a starting dose, followed by two potential sequential dose level increases to 20 mg and 50 mg BID at Weeks 4 and 8 respectively as determined by the investigator based on safety and efficacy. The optimized dose for each subject was determined at Week 12, and subjects then received that optimized dose for a period of 12 weeks (Weeks 13-24) as a fixed dose and from Week 25 to Week 193, until study withdrawal, or the study was closed.

Arm type	Experimental
Investigational medicinal product name	Mitapivat
Investigational medicinal product code	AG-348
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received mitapivat 5 mg, 20 mg, or 50 mg tablets, orally, BID, for up to 193 weeks or until study withdrawal, or the study was closed.

Arm title	Cohort 2
------------------	----------

Arm description:

Subjects who received mitapivat at a dose of 5 mg, 20 mg, or 50 mg, BID, in the fixed dose period of Study AG348-C-006 and met the eligibility criteria of this extension study continued to receive the same mitapivat dose up to Week 193 or until study withdrawal, or the study was closed.

Arm type	Experimental
Investigational medicinal product name	Mitapivat
Investigational medicinal product code	AG-348
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received mitapivat 5 mg, 20 mg or 50 mg tablets, orally, BID, for up to 193 weeks or until study withdrawal, or the study was closed.

Arm title	Cohort 3
<p>Arm description:</p> <p>Subjects who received mitapivat at a dose of 5 mg, 20 mg, or 50 mg, BID, in the fixed dose period of Study AG348-C-007 and met the eligibility criteria of this extension study continued to receive the same mitapivat up to Week 193 or until study withdrawal, or the study was closed.</p>	
Arm type	Experimental
Investigational medicinal product name	Mitapivat
Investigational medicinal product code	AG-348
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received mitapivat 5 mg, 20 mg, or 50 mg tablets, orally, BID, for up to 193 weeks or until study withdrawal, or the study was closed.

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	38	35	17
Completed	25	27	11
Not completed	13	8	6
Physician decision	1	-	1
Adverse Event	2	-	-
Death	-	1	-
Withdrawal by Subject	5	5	4
Approved Drug Available for Indication	1	1	-
Reason Unspecified	2	1	-
Lack of efficacy	2	-	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1
-----------------------	----------

Reporting group description:

Subjects who received placebo in Study AG348-C-006 and met the eligibility criteria of this extension study were enrolled to receive mitapivat tablets, 5 milligrams (mg), twice daily (BID), administered orally, for 4 weeks as a starting dose, followed by two potential sequential dose level increases to 20 mg and 50 mg BID at Weeks 4 and 8 respectively as determined by the investigator based on safety and efficacy. The optimized dose for each subject was determined at Week 12, and subjects then received that optimized dose for a period of 12 weeks (Weeks 13-24) as a fixed dose and from Week 25 to Week 193, until study withdrawal, or the study was closed.

Reporting group title	Cohort 2
-----------------------	----------

Reporting group description:

Subjects who received mitapivat at a dose of 5 mg, 20 mg, or 50 mg, BID, in the fixed dose period of Study AG348-C-006 and met the eligibility criteria of this extension study continued to receive the same mitapivat dose up to Week 193 or until study withdrawal, or the study was closed.

Reporting group title	Cohort 3
-----------------------	----------

Reporting group description:

Subjects who received mitapivat at a dose of 5 mg, 20 mg, or 50 mg, BID, in the fixed dose period of Study AG348-C-007 and met the eligibility criteria of this extension study continued to receive the same mitapivat up to Week 193 or until study withdrawal, or the study was closed.

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	38	35	17
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	38.0	36.9	36.9
standard deviation	± 15.95	± 15.77	± 15.09
Gender categorical Units: Subjects			
Female	23	20	12
Male	15	15	5
Ethnicity Units: Subjects			
Hispanic or Latino	1	2	0
Not Hispanic or Latino	33	23	12

Unknown or Not Reported	4	10	5
Race/Ethnicity Units: Subjects			
White	31	23	13
Asian	3	5	2
Native Hawaiian or Other Pacific Islander	0	1	0
Other	1	0	0
Not reported	3	6	2

Reporting group values	Total		
Number of subjects	90		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	55		
Male	35		
Ethnicity Units: Subjects			
Hispanic or Latino	3		
Not Hispanic or Latino	68		
Unknown or Not Reported	19		
Race/Ethnicity Units: Subjects			
White	67		
Asian	10		
Native Hawaiian or Other Pacific Islander	1		
Other	1		
Not reported	11		

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description: Subjects who received placebo in Study AG348-C-006 and met the eligibility criteria of this extension study were enrolled to receive mitapivat tablets, 5 milligrams (mg), twice daily (BID), administered orally, for 4 weeks as a starting dose, followed by two potential sequential dose level increases to 20 mg and 50 mg BID at Weeks 4 and 8 respectively as determined by the investigator based on safety and efficacy. The optimized dose for each subject was determined at Week 12, and subjects then received that optimized dose for a period of 12 weeks (Weeks 13-24) as a fixed dose and from Week 25 to Week 193, until study withdrawal, or the study was closed.	
Reporting group title	Cohort 2
Reporting group description: Subjects who received mitapivat at a dose of 5 mg, 20 mg, or 50 mg, BID, in the fixed dose period of Study AG348-C-006 and met the eligibility criteria of this extension study continued to receive the same mitapivat dose up to Week 193 or until study withdrawal, or the study was closed.	
Reporting group title	Cohort 3
Reporting group description: Subjects who received mitapivat at a dose of 5 mg, 20 mg, or 50 mg, BID, in the fixed dose period of Study AG348-C-007 and met the eligibility criteria of this extension study continued to receive the same mitapivat up to Week 193 or until study withdrawal, or the study was closed.	
Subject analysis set title	MItapivat: 5 mg
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received mitapivat in study AG348-C-003 and AG348-C-007 and who received both mitapivat and placebo in study AG348-C-006 were enrolled to receive mitapivat 5 mg, orally, BID until sequential step of dose increase to 20 mg BID, until withdrawal, or the study was closed. The safety analysis set was defined as all subjects who received at least 1 dose of study drug. The safety exposure-response (E-R) analysis was based on pooled data, consisting of all subjects from Study AG348-C-003 (SAS-003, only core part), Study AG348-C-006 (SAS-006), Study AG348 C-007 (SAS-007), and Study AG348-C-011 (SAS-011, Cohort 1), as well as the placebo-treated subjects from Study AG348-C-006.	
Subject analysis set title	MItapivat: 20 mg
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received mitapivat in study AG348-C-003 and AG348-C-007 and who received both mitapivat and placebo in study AG348-C-006 were enrolled to receive mitapivat starting dose of 5 mg BID with sequential step of dose increase to 20 mg BID. Subjects received 20 mg, orally, BID until sequential step of dose increase to 50 mg BID, study withdrawal, or the study was closed. The safety analysis set was defined as all subjects who received at least 1 dose of study drug. The safety E-R analysis was based on pooled data, consisting of all subjects from Study AG348-C-003 (SAS-003, only core part), Study AG348-C-006 (SAS-006), Study AG348 C-007 (SAS-007), and Study AG348-C-011 (SAS-011, Cohort 1), as well as the placebo-treated subjects from Study AG348-C-006.	
Subject analysis set title	MItapivat: 50 mg
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received mitapivat in study AG348-C-003 and AG348-C-007 and who received both mitapivat and placebo in study AG348-C-006 were enrolled to receive mitapivat starting dose of 5 mg BID with sequential steps of dose increases to 20 mg BID and from 20 mg BID to 50 mg BID. Subjects received 50 mg, orally, BID until study withdrawal, or the study was closed. The safety analysis set was defined as all subjects who received at least 1 dose of study drug. The safety E-R analysis was based on pooled data, consisting of all subjects from Study AG348-C-003 (SAS-003, only core part), Study AG348-C-006 (SAS-006), Study AG348 C-007 (SAS-007), and Study AG348-C-011 (SAS-011, Cohort 1), as well as the placebo-treated subjects from Study AG348-C-006.	

Primary: All Cohorts: Number of Subjects With at Least One Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, Related TEAEs and TEAEs With Severity Greater Than or Equal to Grade 3

End point title	All Cohorts: Number of Subjects With at Least One Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, Related TEAEs and TEAEs With Severity Greater Than or Equal to Grade 3 ^[1]
-----------------	---

End point description:

TEAEs are adverse events (AEs) with initial onset date during on-treatment period/worsening from baseline & includes both serious & non-serious TEAEs. Severity of AEs was evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.03): grade 1:mild;grade 2:moderate;grade 3:severe or medically significant but not immediately life-threatening;grade 4:life threatening or disabling;grade 5:death related to AE. Safety analysis set included all subjects who received at least 1 dose of study drug.

End point type	Primary
----------------	---------

End point timeframe:

Up to 197 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this end point.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	35	17	
Units: count of subjects				
Subjects with TEAEs	37	33	15	
Subjects with Serious TEAEs	11	8	4	
Subjects with TEAEs related to study drug	22	14	4	
Subjects with any TEAE of Grade ≥ 3	18	10	5	

Statistical analyses

No statistical analyses for this end point

Primary: All Cohorts: Number of Subjects With TEAEs Leading to Dose Reduction, Treatment Interruption and Treatment Discontinuation

End point title	All Cohorts: Number of Subjects With TEAEs Leading to Dose Reduction, Treatment Interruption and Treatment Discontinuation ^[2]
-----------------	---

End point description:

A clinical AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the study drug. TEAE is defined as any AE that increased in severity or newly developed during the treatment-emergent period. The safety analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Primary
----------------	---------

End point timeframe:

Up to 197 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this end point.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	35	17	
Units: count of subjects				
Subjects with TEAEs Leading to Dose Reduction	2	2	1	
Subjects with TEAEs Leading to Interruption	3	4	0	
Subjects with TEAEs Leading to Discontinuation	2	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: All Cohorts: Number of Subjects With Clinically Significant Abnormalities in Laboratory Parameters Reported as TEAEs

End point title	All Cohorts: Number of Subjects With Clinically Significant Abnormalities in Laboratory Parameters Reported as TEAEs ^[3]
-----------------	---

End point description:

Clinical laboratory assessments including hematology, clinical chemistry, triglycerides, urate, coagulation, urinalysis, and liver function tests were performed in the study. Number of subjects with clinically significant abnormalities graded ≥ 3 in laboratory parameters were reported as TEAEs. Clinically significant treatment-emergent laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.03): grade 1: mild; grade 2: moderate; grade 3: severe or medically significant but not immediately life-threatening; grade 4: life threatening or disabling; grade 5: death related to AE. Clinical significance was determined based on the judgment of the Investigator. The safety analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Primary
----------------	---------

End point timeframe:

Up to 197 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this end point.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	35	17	
Units: count of subjects				
Anaemia	3	1	0	
Haemolysis	1	2	0	
Alanine aminotransferase increased	0	0	1	
Aspartate aminotransferase increased	2	1	1	
Blood bilirubin increased	0	0	1	
Blood triglycerides increased	1	0	0	
Hypertriglyceridaemia	1	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: All Cohorts: Number of Subjects With Clinically Significant Abnormalities in Vital Signs Measurements and Physical Examinations Reported as TEAEs

End point title	All Cohorts: Number of Subjects With Clinically Significant Abnormalities in Vital Signs Measurements and Physical Examinations Reported as TEAEs ^[4]
-----------------	--

End point description:

Vital signs and physical examinations including height, weight, body mass index (BMI), systolic blood pressure, diastolic blood pressure, pulse rate, temperature were assessed. Number of subjects who experienced clinically significant abnormalities in vital signs and physical examinations as TEAEs were reported. Clinical significance was determined based on the judgment of the Investigator. The safety analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Primary
----------------	---------

End point timeframe:

Up to 197 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this end point.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	35	17	
Units: count of subjects				
Weight decreased	0	1	1	
Hot flush	2	0	2	
Hypotension	1	0	0	
Hypertension	1	2	0	

Statistical analyses

No statistical analyses for this end point

Primary: All Cohorts: Number of Subjects With Clinically Significant Abnormalities in Electrocardiogram (ECG) Parameters Reported as TEAEs

End point title	All Cohorts: Number of Subjects With Clinically Significant Abnormalities in Electrocardiogram (ECG) Parameters Reported as TEAEs ^[5]
-----------------	--

End point description:

The following ECG parameters including RR, PR, heart rate-corrected QT interval using the Fridericia's formula [QRS], QT, and QTc were assessed during the study. Number of subjects with clinically

significant abnormalities in ECG parameters as TEAEs were reported. Clinical significance was determined based on the judgment of the Investigator. The safety analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Primary
End point timeframe:	
Up to 197 weeks	

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not planned for this end point.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	35	17	
Units: count of subjects	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: All Cohorts: Number of Subjects With Clinically Significant Abnormalities in Bone Mineral Density (BMD)

End point title	All Cohorts: Number of Subjects With Clinically Significant Abnormalities in Bone Mineral Density (BMD) ^[6]
-----------------	--

End point description:

BMD was measured by DXA scans during the study. Number of subjects with clinically significant bone abnormalities ((i.e., grade 2 bone density decreased) were reported. Clinical significance was determined based on the judgment of the Investigator. The safety analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Primary
End point timeframe:	
Up to 197 weeks	

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this end point.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	35	17	
Units: count of subjects	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: All Cohorts: Change From Baseline in Adjusted Spine T-score

End point title	All Cohorts: Change From Baseline in Adjusted Spine T-score ^[7]
-----------------	--

End point description:

T-score of adjusted spine were assessed by DXA scans. The T-score is the number of standard deviations that bone density is above or below the average. A score of ≥ -1 indicates normal bone density; score between < -1 and > -2.5 indicates a sign of osteopenia (bone density below normal), and score of ≤ -2.5 indicates a sign of osteoporosis. The baseline was the last assessment before start of study treatment (mitapivat). The safety analysis set included all subjects who received at least 1 dose of study treatment. Here, number of subjects analysed indicates the number of subjects who were evaluable for this end point, and "n" indicates number of subjects who were evaluable for this end point at the specified time points.

End point type	Primary
----------------	---------

End point timeframe:

Baseline, Week 192

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis has been reported for this end point.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	34	17	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 38, 34, 17)	-1.143 (\pm 1.0926)	-1.808 (\pm 1.1589)	-1.161 (\pm 1.0469)	
Week 192 (n = 24, 20, 8)	0.046 (\pm 0.4874)	0.234 (\pm 0.4383)	0.416 (\pm 1.1090)	

Statistical analyses

No statistical analyses for this end point

Primary: All Cohorts: Change From Baseline in Adjusted Spine Z-score

End point title	All Cohorts: Change From Baseline in Adjusted Spine Z-score ^[8]
-----------------	--

End point description:

The Z-score of adjusted spine was assessed by DXA scans. The Z-score is a statistical measure to describe whether a value was above or below the standard. A Z-score of 0 is equal to the standard. Lower numbers indicate values lower than the standard and higher numbers indicate values higher than the standard. The baseline was the last assessment before start of study treatment (mitapivat). The safety analysis set included all subjects who received at least 1 dose of study treatment. Here, number of subjects analysed indicates the number of subjects who were evaluable for this end point, and "n" indicates number of subjects who were evaluable for this end point at the specified time points.

End point type	Primary
----------------	---------

End point timeframe:

Baseline, Week 192

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis has been reported for this end point.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	34	17	
Units: Z-score				
arithmetic mean (standard deviation)				
Baseline (n = 38, 34, 17)	-0.804 (± 1.2529)	-1.536 (± 1.2469)	-0.848 (± 1.0420)	
Week 192 (n = 24, 20, 8)	0.152 (± 0.4585)	0.332 (± 0.4002)	0.530 (± 1.2409)	

Statistical analyses

No statistical analyses for this end point

Primary: All Cohorts: Change From Baseline in Femoral Total T-score

End point title	All Cohorts: Change From Baseline in Femoral Total T-score ^[9]
-----------------	---

End point description:

T-score of femoral total were assessed by DXA scans. The T-score is the number of standard deviations that bone density is above or below the average. A score of ≥ -1 indicates normal bone density; score between < -1 and > -2.5 indicates a sign of osteopenia (bone density below normal), and score of ≤ -2.5 indicates a sign of osteoporosis. The baseline was the last assessment before start of study treatment (mitapivat). The safety analysis set included all subjects who received at least 1 dose of study treatment. Here, number of subjects analysed indicates the number of subjects who were evaluable for this end point, and "n" indicates number of subjects who were evaluable for this end point at the specified time points.

End point type	Primary
----------------	---------

End point timeframe:

Baseline, Week 192

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis has been reported for this end point.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	34	17	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 38, 34, 17)	-0.834 (± 1.1182)	-1.139 (± 1.0995)	-0.813 (± 0.6748)	
Week 192 (n = 24, 20, 8)	-0.020 (± 0.2612)	0.047 (± 0.3893)	0.114 (± 0.5050)	

Statistical analyses

No statistical analyses for this end point

Primary: All Cohorts: Change From Baseline in Femoral Total Z-score

End point title	All Cohorts: Change From Baseline in Femoral Total Z-score ^[10]
-----------------	--

End point description:

The Z-score of femoral total was assessed by DXA scans. The Z-score is a statistical measure to describe whether a value was above or below the standard. A Z-score of 0 is equal to the standard. Lower numbers indicate values lower than the standard and higher numbers indicate values higher than the standard. The baseline was the last assessment before start of study treatment (mitapivat). The safety analysis set included all subjects who received at least 1 dose of study treatment. Here, number of subjects analysed indicates the number of subjects who were evaluable for this end point, and "n" indicates number of subjects who were evaluable for this end point at the specified time points.

End point type	Primary
----------------	---------

End point timeframe:

Baseline, Week 192

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis has been reported for this end point.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	34	17	
Units: Z-score				
arithmetic mean (standard deviation)				
Baseline (n = 38, 34, 17)	-0.548 (± 1.1574)	-0.916 (± 1.0657)	-0.529 (± 0.7137)	
Week 192 (n = 24, 20, 8)	0.054 (± 0.2468)	0.126 (± 0.3631)	0.214 (± 0.5099)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: Percentage of Subjects Who Achieved a Hemoglobin (Hb) Response

End point title	Cohort 1: Percentage of Subjects Who Achieved a Hemoglobin (Hb) Response ^[11]
-----------------	--

End point description:

The Hb response was defined as a ≥ 1.5 grams per deciliter (g/dL) (0.93 millimoles per liter [mmol/L]) increase in Hb concentration from baseline that is sustained at 2 or more scheduled assessments, excluding those within 2 months (61 days) of transfusion. The baseline value for cohort 1 subjects was the average of all available measurements from the central laboratory within 45 (42+3) days before start of study treatment in study AG348-C-011, excluding values within 61 days after a transfusion, or the baseline value from study AG348-C-006 if no assessment is available. Full analysis set (FAS) included all subjects who received at least 1 dose of study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to Week 24

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the protocol, data for this end point was planned to be reported for Cohort 1 only based on FAS.

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: percentage of subjects				
number (not applicable)	39.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: Average Change From Baseline in Hb Concentration at Weeks 16, 20, and 24

End point title	Cohort 1: Average Change From Baseline in Hb Concentration at Weeks 16, 20, and 24 ^[12]
-----------------	--

End point description:

The baseline value for subjects was the average of all available measurements from the central laboratory within 45 (42+3) days before start of study treatment in study AG348-C-011, excluding values within 61 days after a transfusion, or the baseline value from study AG348-C-006 if no assessment is available. The mean of average change from baseline in Hb concentration across Weeks 16, 20 and 24 is reported. FAS included all subjects who received at least 1 dose of study treatment. Here, number of subjects analysed indicates the number of subjects who were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Weeks 16, 20, and 24

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the protocol, data for this endpoint was planned to be reported for Cohort 1 only based on FAS.

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: grams per litre				
arithmetic mean (standard deviation)	16.45 (± 15.634)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: Area Under the Plasma Concentration-Time Curve From Time Zero to 8-hours Post-dose (AUC0-8) of Mitapivat

End point title	Cohort 1: Area Under the Plasma Concentration-Time Curve From Time Zero to 8-hours Post-dose (AUC0-8) of Mitapivat ^[13]
-----------------	--

End point description:

Pharmacokinetics (PK) analysis population included all subjects who were enrolled and received at least 1 dose of study treatment (mitapivat) with at least 1 non-zero plasma concentration of mitapivat at the Week 12 visit. Here, number of subjects analyzed indicates the number of subjects who received 50 mg

BID mitapivat in Cohort 1 and were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose at Week 12

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the protocol, data for this endpoint was planned to be reported for Cohort 1 only.

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: hour*nanograms/millilitre (hr*ng/mL)				
geometric mean (geometric coefficient of variation)	3016 (\pm 27.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: Area Under the Plasma Concentration-Time Curve From Time Zero to Last Quantifiable Concentration (AUC0-last) of Mitapivat

End point title	Cohort 1: Area Under the Plasma Concentration-Time Curve From Time Zero to Last Quantifiable Concentration (AUC0-last) of Mitapivat ^[14]
-----------------	---

End point description:

PK analysis population included all subjects who were enrolled and received at least 1 dose of study treatment (mitapivat) with at least 1 non-zero plasma concentration of mitapivat at the Week 12 visit. Here, number of subjects analyzed indicates the number of subjects who received 50 mg BID mitapivat in Cohort 1 and were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose at Week 12

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the protocol, data for this endpoint was planned to be reported for Cohort 1 only.

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	2990 (\pm 26.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: Maximum Observed Plasma Concentration (C_{max}) of Mitapivat

End point title	Cohort 1: Maximum Observed Plasma Concentration (C _{max}) of Mitapivat ^[15]
-----------------	--

End point description:

PK analysis population included all subjects who were enrolled and received at least 1 dose of study treatment (mitapivat) with at least 1 non-zero plasma concentration of mitapivat at the Week 12 visit. Here, number of subjects analysed indicates the number of subjects who received 50 mg BID mitapivat in Cohort 1 and were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose at Week 12

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the protocol, data for this endpoint was planned to be reported for Cohort 1 only.

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: nanograms/millilitre (ng/mL)				
geometric mean (geometric coefficient of variation)	1018 (± 22.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: Time to Reach Maximum Observed Plasma Concentration (T_{max}) of Mitapivat

End point title	Cohort 1: Time to Reach Maximum Observed Plasma Concentration (T _{max}) of Mitapivat ^[16]
-----------------	--

End point description:

PK analysis population included all subjects who were enrolled and received at least 1 dose of study treatment (mitapivat) with at least 1 non-zero plasma concentration of mitapivat at the Week 12 visit. Here, number of subjects analysed indicates the number of subjects who received 50 mg BID mitapivat in Cohort 1 and were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose at Week 12

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the protocol, data for this endpoint was planned to be reported for Cohort 1 only.

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: hours				
median (full range (min-max))	1.00 (0.45 to 4.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: Plasma Concentration (Ctrough) at the End of a Dosing Interval of Mitapivat

End point title	Cohort 1: Plasma Concentration (Ctrough) at the End of a Dosing Interval of Mitapivat ^[17]
-----------------	---

End point description:

PK analysis population included all subjects who were enrolled and received at least 1 dose of study treatment (mitapivat) with at least 1 non-zero plasma concentration of mitapivat at the Week 12 visit. Here, number of subjects analyzed indicates the number of subjects who received 50 mg BID mitapivat in Cohort 1 and were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose at Week 12

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the protocol, data for this endpoint was planned to be reported for Cohort 1 only.

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	62.8 (± 72.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: Exposure-response (E-R) Relationship Between Safety Parameters and Mitapivat Concentration and Relevant Mitapivat Pharmacokinetic Parameters

End point title	Cohort 1: Exposure-response (E-R) Relationship Between Safety Parameters and Mitapivat Concentration and Relevant Mitapivat Pharmacokinetic Parameters
-----------------	--

End point description:

Statistically significant E-R relationships were identified for safety parameters including all grade insomnia and all grade hot flush and were reported in terms of percent probability based on E-R model. The safety E-R analysis was based on pooled data, consisting of all 155 subjects from Study AG348-C-

003 (SAS-003, only core part): 52 subjects , Study AG348-C-006 (SAS-006): 40 subjects , Study AG348 C-007 (SAS-007): 27 subjects , and Study AG348-C-011 (SAS-011, Cohort 1): 36 subjects , as well as the placebo-treated subjects from Study AG348-C-006. As pre-specified in the protocol, data for this end point was planned to be reported for Cohort 1 only. Subjects analysed is the number of subjects who were evaluable for this end point.

End point type	Secondary
End point timeframe:	
First dose to up to 24 weeks	

End point values	MItapivat: 5 mg	MItapivat: 20 mg	MItapivat: 50 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	155	155	155	
Units: percent probability				
arithmetic mean (confidence interval 95%)				
Hot Flush	3.37 (1.22 to 7.35)	4.03 (1.61 to 8.36)	5.5 (2.48 to 10.5)	
Insomnia	19.9 (13.3 to 28.0)	22.1 (15.5 to 29.9)	26.0 (19.3 to 33.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Change From Baseline in Hb Concentration

End point title	Cohorts 1 and 2: Change From Baseline in Hb Concentration ^[18]
-----------------	---

End point description:

The baseline value for cohort 1 subjects was the average of all available measurements from the central laboratory within 45 (42+3) days before start of study treatment in study AG348-C-011, excluding values within 61 days after a transfusion, or the baseline value from study AG348-C-006 if no assessment was available. The baseline value for cohort 2 was from Study AG348-C-006. FAS included all subjects who received at least 1 dose of study treatment. Here, number of subjects analysed indicates the number of subjects who were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 192

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the statistical analysis plan (SAP), data for this endpoint was planned to be reported for Cohort 1 and 2 only based on FAS.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	23		
Units: grams per litre				
arithmetic mean (standard deviation)	22.39 (± 21.211)	21.32 (± 20.721)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Change From Baseline in Indirect Bilirubin

End point title	Cohorts 1 and 2: Change From Baseline in Indirect Bilirubin ^[19]
-----------------	---

End point description:

The baseline value for cohort 1 subjects was the average of all available measurements from the central laboratory within 45 (42+3) days before start of study treatment in study AG348-C-011, excluding values within 61 days after a transfusion, or the baseline value from study AG348-C-006 if no assessment is available. The baseline value for cohort 2 was from Study AG348-C-006. FAS included all subjects who received at least 1 dose of study treatment. Here, number of subjects analysed indicates the number of subjects who were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 192

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the SAP, data for this endpoint was planned to be reported for Cohort 1 and 2 only based on FAS.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: micromoles per litre (µmol/L)				
arithmetic mean (standard deviation)	-57.50 (± 54.542)	-36.73 (± 35.511)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Change From Baseline in Lactate Dehydrogenase (LDH)

End point title	Cohorts 1 and 2: Change From Baseline in Lactate Dehydrogenase (LDH) ^[20]
-----------------	--

End point description:

The baseline value for cohort 1 subjects was the average of all available measurements from the central laboratory within 45 (42+3) days before start of study treatment in study AG348-C-011, excluding values within 61 days after a transfusion, or the baseline value from study AG348-C-006 if no assessment was available. The baseline value for cohort 2 was from Study AG348-C-006. FAS included all subjects who received at least 1 dose of study treatment. Here, number of subjects analysed indicates the number of subjects who were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 192

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the SAP, data for this endpoint was planned to be reported for Cohort 1 and 2 only based on FAS.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	22		
Units: Units per Litre (U/L)				
arithmetic mean (standard deviation)	-46.10 (\pm 75.310)	-130.80 (\pm 275.424)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Change From Baseline in Haptoglobin Levels

End point title	Cohorts 1 and 2: Change From Baseline in Haptoglobin
-----------------	--

End point description:

The baseline value for cohort 1 subjects was the average of all available measurements from the central laboratory within 45 (42+3) days before start of study treatment in study AG348-C-011, excluding values within 61 days after a transfusion, or the baseline value from study AG348-C-006 if no assessment is available. The baseline value for cohort 2 was from Study AG348-C-006. FAS included all subjects who received at least 1 dose of study treatment. Here, number of subjects analysed indicates the number of subjects who were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 192

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the SAP, data for this endpoint was planned to be reported for Cohort 1 and 2 only based on FAS.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: grams per litre				
arithmetic mean (standard deviation)	0.254 (\pm 0.4340)	0.250 (\pm 0.4689)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Change From Baseline in Reticulocytes/Erythrocytes

Ratio

End point title	Cohorts 1 and 2: Change From Baseline in Reticulocytes/Erythrocytes Ratio ^[22]
-----------------	---

End point description:

The baseline value for cohort 1 subjects was the average of all available measurements from the central laboratory within 45 (42+3) days before start of study treatment in study AG348-C-011, excluding values within 61 days after a transfusion, or the baseline value from study AG348-C-006 if no assessment is available. The baseline value for cohort 2 was from Study AG348-C-006. FAS included all subjects who received at least 1 dose of study treatment. Here, number of subjects analysed indicates the number of subjects who were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 192

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the SAP, data for this endpoint was planned to be reported for Cohort 1 and 2 only based on FAS.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: Reticulocytes/Erythrocytes Ratio				
arithmetic mean (standard deviation)	-0.1696 (± 0.16243)	-0.1565 (± 0.14631)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 3: Change From Baseline in Number of Transfusion Episodes

End point title	Cohort 3: Change From Baseline in Number of Transfusion Episodes ^[23]
-----------------	--

End point description:

Number of transfusions at baseline was determined based on the transfusion data during the 52 weeks before informed consent for Cohort 3. Number of on-study transfusions was based on transfusions collected up to the end of the fixed dose period and standardized to 52 weeks. The change from baseline in number of transfusions was summarized for Cohort 3. FAS included all subjects who received at least 1 dose of study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 192

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As per planned analysis, data for this end point was reported for Cohort 3 only based on FAS.

End point values	Cohort 3			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: number of transfusion episodes				
arithmetic mean (standard deviation)	4.14 (\pm 5.487)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 3: Change from Baseline in Number of Red Blood Cell (RBC) Units Transfused

End point title	Cohort 3: Change from Baseline in Number of Red Blood Cell (RBC) Units Transfused ^[24]
-----------------	---

End point description:

Annualized total number of RBC units transfused (units/52-week) during the study, including data up to end of study (EOS), was the total number of RBC units transfused during the entire study*52 / [(date of EOS – date of start of study treatment + 1)/7]. Number of RBC units were determined based on the transfusion data during the 52 weeks before informed consent of the antecedent study for Cohort 3. Number of on-study RBC units was based on transfusion data collected up to the end of the fixed dose period and standardized to 52 weeks. FAS included all subjects who received at least 1 dose of study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Week 192

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the SAP, analysis of number of RBC units transfused at baseline was planned for Cohort 3 only.

End point values	Cohort 3			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: number of RBC units transfused				
arithmetic mean (standard deviation)	7.25 (\pm 7.915)			

Statistical analyses

No statistical analyses for this end point

Secondary: All Cohorts: Change From Baseline in Health-Related Quality of Life (HRQoL) Patient-Reported Outcome (PRO) Scores: Pyruvate Kinase Deficiency Diary (PKDD)

End point title	All Cohorts: Change From Baseline in Health-Related Quality of Life (HRQoL) Patient-Reported Outcome (PRO) Scores: Pyruvate Kinase Deficiency Diary (PKDD)
-----------------	--

End point description:

PKDD is a 7-item PRO measure of core signs & symptoms associated with PK deficiency in adults.

Subjects rate their experience with symptoms of PK deficiency on present day. Symptoms include tiredness, jaundice, bone pain, shortness of breath, & energy level. Score ranges from 25 to 76, with higher scores indicating more severe symptoms & higher disease burden. Change from baseline in weekly mean scores was summarized. Negative change from baseline indicates lower disease burden. Baseline of weekly mean score was defined as average of daily scores collected within 7 days before start of study treatment (mitapivat). For Cohort 1, last measurement before start of study treatment in AG348-C-011 was used as baseline; if baseline was missing, baseline value from AG348-c-006 was used. For Cohorts 2 & 3, baseline values from 006 & 007, respectively, were used. FAS included all subjects who received at least 1 dose of study treatment. Subjects analysed: number of subjects evaluable for endpoint

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	24	10	
Units: score on a scale				
arithmetic mean (standard deviation)	-3.75 (± 5.805)	-6.09 (± 7.617)	-5.04 (± 12.273)	

Statistical analyses

No statistical analyses for this end point

Secondary: All Cohorts: Change From Baseline in HRQoL PRO Scores: Pyruvate Kinase Deficiency Impact Assessment (PKDIA)

End point title	All Cohorts: Change From Baseline in HRQoL PRO Scores: Pyruvate Kinase Deficiency Impact Assessment (PKDIA)
-----------------	---

End point description:

PKDIA is a 12-item PRO measure of common impacts of PK deficiency on activities of daily living. Subjects rated how PK deficiency has impacted aspects of daily living in past 7 days, including impacts on relationships & leisure and social, mental, and physical activities. Score ranges from 30 to 76, with higher scores indicating higher disease burden. Negative change from baseline indicates lower disease burden. Baseline was defined as the last complete assessment (with no missing item in response) before start of study treatment. For Cohort 1, the last measurement before the start of study treatment in AG348-C-011 was used as the baseline; if baseline was missing, the baseline value from AG348-C-006 was used. For Cohort 2 and Cohort 3, the baseline values from 006 and 007, respectively, were used. FAS included all subjects who received at least 1 dose of study treatment. Subjects analysed indicates the number of subjects evaluable for this end point.

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	28	14	
Units: score on a scale				
arithmetic mean (standard deviation)	-3.9 (± 7.38)	-6.6 (± 8.75)	-5.4 (± 12.83)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: Time of Last Quantifiable Concentration (Tlast) of Mitapivat

End point title	Cohort 1: Time of Last Quantifiable Concentration (Tlast) of Mitapivat ^[25]
-----------------	--

End point description:

PK analysis population included all subjects who were enrolled and received at least 1 dose of study treatment (mitapivat) with at least 1 non-zero plasma concentration of mitapivat at the Week 12 visit. Here, number of subjects analyzed indicates the number of subjects who received 50 mg BID mitapivat in Cohort 1 and were evaluable for this end point.

End point type	Secondary
----------------	-----------

End point timeframe:

Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose at Week 12

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the protocol, data for this endpoint was planned to be reported for Cohort 1 only.

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: hours				
median (full range (min-max))	7.61 (3.57 to 8.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1: E-R Relationship Between Safety Parameters and Mitapivat Concentration and Relevant Mitapivat Pharmacokinetic Parameters

End point title	Cohort 1: E-R Relationship Between Safety Parameters and Mitapivat Concentration and Relevant Mitapivat Pharmacokinetic Parameters
-----------------	--

End point description:

Statistically significant E-R relationships were identified for safety parameters including all grade male sex hormones including estrone, total testosterone and free testosterone and were reported in terms of percent change based on E-R model. Safety analysis set was used. The safety E-R analysis was based on pooled data, consisting of 68 subjects from Study AG348-C-003 (only core part): 32 subjects, Study AG348-C-006: 15 subjects, Study AG348 C-007: 7subjects and Study AG348-C-011 (Cohort 1): 14 subjects, as well as the placebo-treated subjects from Study AG348-C-006. As pre-specified in the

protocol, data for this end point was planned to be reported for Cohort 1 only. Subjects analysed is the number of subjects who were evaluable for this end point. Here, "n" is number of subjects with data available for analysis for the specified category.

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	MItapivat: 5 mg	MItapivat: 20 mg	MItapivat: 50 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	68	68	68	
Units: percent change				
arithmetic mean (confidence interval 95%)				
Total Testosterone	0.877 (0.41 to 1.43)	3.18 (1.49 to 5.4)	7.59 (3.29 to 13.7)	
Free Testosterone	6.01 (1.66 to 13.2)	14.1 (4 to 27.5)	26.0 (7.14 to 55.1)	
Estrone (n=67)	-31.5 (-51 to -21.1)	-56.5 (-67.3 to -48.4)	-68.2 (-74.5 to -62.6)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 197 weeks

Adverse event reporting additional description:

The safety analysis set included all subjects who received at least 1 dose of study treatment.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	27.0
--------------------	------

Reporting groups

Reporting group title	Cohort 1
-----------------------	----------

Reporting group description:

Subjects who received placebo in Study AG348-C-006 and met the eligibility criteria of this extension study were enrolled to receive mitapivat tablets, 5 mg, BID, administered orally, for 4 weeks as a starting dose, followed by two potential sequential dose level increases to 20 mg and 50 mg BID at Weeks 4 and 8 respectively as determined by the investigator based on safety and efficacy. The optimized dose for each subject was determined at Week 12, and subjects then received that optimized dose for a period of 12 weeks (Weeks 13-24) as a fixed dose and from Week 25 to Week 193, until study withdrawal, or the study was closed.

Reporting group title	Cohort 2
-----------------------	----------

Reporting group description:

Subjects who received mitapivat at a dose of 5 mg, 20 mg, or 50 mg, BID, in the fixed dose period of Study AG348-C-006 and met the eligibility criteria of this extension study continued to receive the same mitapivat dose up to Week 193 or until study withdrawal, or the study was closed.

Reporting group title	Cohort 3
-----------------------	----------

Reporting group description:

Subjects who received mitapivat at a dose of 5 mg, 20 mg, or 50 mg, BID, in the fixed dose period of Study AG348-C-007 and met the eligibility criteria of this extension study continued to receive the same mitapivat dose up to Week 193 or until study withdrawal, or the study was closed.

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 38 (28.95%)	8 / 35 (22.86%)	4 / 17 (23.53%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hodgkin's disease			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			

subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Tibia fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accident			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Femur fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Vascular stenosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 38 (2.63%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery aneurysm			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	3 / 38 (7.89%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			

subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 38 (94.74%)	31 / 35 (88.57%)	15 / 17 (88.24%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Back pain			
subjects affected / exposed	5 / 38 (13.16%)	3 / 35 (8.57%)	2 / 17 (11.76%)
occurrences (all)	6	4	3
Meningioma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	2 / 17 (11.76%)
occurrences (all)	3	0	2
Hypertension			
subjects affected / exposed	1 / 38 (2.63%)	2 / 35 (5.71%)	0 / 17 (0.00%)
occurrences (all)	2	2	0
Arteriosclerosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Haematoma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Vertigo positional			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 38 (28.95%)	8 / 35 (22.86%)	4 / 17 (23.53%)
occurrences (all)	16	10	6
Pyrexia			
subjects affected / exposed	10 / 38 (26.32%)	9 / 35 (25.71%)	3 / 17 (17.65%)
occurrences (all)	16	15	4
Influenza like illness			
subjects affected / exposed	4 / 38 (10.53%)	2 / 35 (5.71%)	2 / 17 (11.76%)
occurrences (all)	4	2	4
Oedema peripheral			
subjects affected / exposed	3 / 38 (7.89%)	1 / 35 (2.86%)	2 / 17 (11.76%)
occurrences (all)	3	1	2
Asthenia			
subjects affected / exposed	2 / 38 (5.26%)	3 / 35 (8.57%)	0 / 17 (0.00%)
occurrences (all)	2	5	0
Injection site pain			
subjects affected / exposed	2 / 38 (5.26%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences (all)	3	1	0
Chest pain			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Face oedema			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Inflammation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	2 / 38 (5.26%)	2 / 35 (5.71%)	0 / 17 (0.00%)
occurrences (all)	2	2	0
Menstruation irregular			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	2 / 17 (11.76%)
occurrences (all)	0	2	2
Intermenstrual bleeding			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Bartholin's cyst			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Breast cyst			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Perineal cyst			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Uterine polyp			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 38 (10.53%)	5 / 35 (14.29%)	4 / 17 (23.53%)
occurrences (all)	4	5	5
Oropharyngeal pain			
subjects affected / exposed	5 / 38 (13.16%)	2 / 35 (5.71%)	2 / 17 (11.76%)
occurrences (all)	12	2	2
Dyspnoea			
subjects affected / exposed	5 / 38 (13.16%)	3 / 35 (8.57%)	0 / 17 (0.00%)
occurrences (all)	5	3	0
Asthma			
subjects affected / exposed	1 / 38 (2.63%)	1 / 35 (2.86%)	2 / 17 (11.76%)
occurrences (all)	1	1	2
Rhinitis allergic			

subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 9	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0
Pulmonary mass subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Psychiatric disorders			
Middle insomnia subjects affected / exposed occurrences (all)	8 / 38 (21.05%) 19	2 / 35 (5.71%) 2	1 / 17 (5.88%) 1
Initial insomnia subjects affected / exposed occurrences (all)	10 / 38 (26.32%) 12	0 / 35 (0.00%) 0	0 / 17 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 35 (2.86%) 1	1 / 17 (5.88%) 1
Anxiety subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0
Panic attack subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 35 (0.00%) 0	0 / 17 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Stress subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	8 / 38 (21.05%) 8	5 / 35 (14.29%) 5	3 / 17 (17.65%) 5
Aspartate aminotransferase increased			

subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 6	3 / 35 (8.57%) 4	4 / 17 (23.53%) 6
Vitamin D decreased subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 35 (2.86%) 1	1 / 17 (5.88%) 1
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 35 (2.86%) 1	1 / 17 (5.88%) 1
High density lipoprotein increased subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 35 (2.86%) 1	1 / 17 (5.88%) 1
Weight decreased subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 35 (2.86%) 1	1 / 17 (5.88%) 3
Haemoglobin increased subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Liver iron concentration increased subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	3 / 35 (8.57%) 4	1 / 17 (5.88%) 1
Immunisation reaction subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 6	3 / 35 (8.57%) 3	0 / 17 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 4	1 / 35 (2.86%) 1	0 / 17 (0.00%) 0
Bone contusion subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 35 (5.71%) 2	0 / 17 (0.00%) 0
Foot fracture			

subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Ankle fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Fibula fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Lip injury			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Lipohaemarthrosis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Tibia fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 38 (2.63%)	2 / 35 (5.71%)	0 / 17 (0.00%)
occurrences (all)	1	2	0
Sinus bradycardia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Hypertensive heart disease			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 38 (55.26%)	8 / 35 (22.86%)	4 / 17 (23.53%)
occurrences (all)	50	11	4
Dizziness			
subjects affected / exposed	3 / 38 (7.89%)	2 / 35 (5.71%)	1 / 17 (5.88%)
occurrences (all)	3	6	1
Anosmia			

subjects affected / exposed	1 / 38 (2.63%)	2 / 35 (5.71%)	2 / 17 (11.76%)
occurrences (all)	1	2	2
Migraine			
subjects affected / exposed	3 / 38 (7.89%)	1 / 35 (2.86%)	1 / 17 (5.88%)
occurrences (all)	3	1	1
Ageusia			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	2 / 17 (11.76%)
occurrences (all)	0	2	2
Neuropathy peripheral			
subjects affected / exposed	2 / 38 (5.26%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences (all)	2	2	0
Paraesthesia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Carotid artery aneurysm			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Cerebrovascular accident			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Intracranial aneurysm			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 38 (13.16%)	2 / 35 (5.71%)	1 / 17 (5.88%)
occurrences (all)	8	3	1
Haemolysis			
subjects affected / exposed	2 / 38 (5.26%)	1 / 35 (2.86%)	1 / 17 (5.88%)
occurrences (all)	2	1	1
Lymphadenopathy			
subjects affected / exposed	3 / 38 (7.89%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	5	0	0
Blood loss anaemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1

Thrombocytosis subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	0 / 35 (0.00%) 0	0 / 17 (0.00%) 0
Tinnitus subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 10	0 / 35 (0.00%) 0	0 / 17 (0.00%) 0
Deafness unilateral subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Eye disorders			
Cataract subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	1 / 35 (2.86%) 1	1 / 17 (5.88%) 2
Vision blurred subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 35 (0.00%) 0	0 / 17 (0.00%) 0
Lacrimation increased subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Meibomian gland dysfunction subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Gastrointestinal disorders			
Diarrhea subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 7	5 / 35 (14.29%) 5	2 / 17 (11.76%) 3
Nausea subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 6	3 / 35 (8.57%) 4	3 / 17 (17.65%) 3
Vomiting subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 35 (2.86%) 1	4 / 17 (23.53%) 8
Abdominal pain			

subjects affected / exposed	1 / 38 (2.63%)	3 / 35 (8.57%)	2 / 17 (11.76%)
occurrences (all)	1	4	2
Dyspepsia			
subjects affected / exposed	0 / 38 (0.00%)	5 / 35 (14.29%)	1 / 17 (5.88%)
occurrences (all)	0	6	1
Constipation			
subjects affected / exposed	2 / 38 (5.26%)	2 / 35 (5.71%)	0 / 17 (0.00%)
occurrences (all)	2	2	0
Abdominal pain upper			
subjects affected / exposed	3 / 38 (7.89%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	3	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	2	0	2
Toothache			
subjects affected / exposed	2 / 38 (5.26%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences (all)	2	1	0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 38 (2.63%)	2 / 35 (5.71%)	0 / 17 (0.00%)
occurrences (all)	1	4	0
Hepatic steatosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Biliary colic			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2
Hepatic pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	2	0	1
Alopecia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Erythema			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Hair growth abnormal			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Skin hypertrophy			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 38 (5.26%)	3 / 35 (8.57%)	0 / 17 (0.00%)
occurrences (all)	2	3	0
Nephrolithiasis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 35 (5.71%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Polyuria			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Proteinuria			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Renal cyst			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 38 (23.68%)	7 / 35 (20.00%)	3 / 17 (17.65%)
occurrences (all)	9	12	5
Pain in extremity			

subjects affected / exposed	5 / 38 (13.16%)	3 / 35 (8.57%)	1 / 17 (5.88%)
occurrences (all)	7	4	1
Osteoporosis			
subjects affected / exposed	4 / 38 (10.53%)	4 / 35 (11.43%)	0 / 17 (0.00%)
occurrences (all)	4	4	0
Myalgia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 35 (2.86%)	3 / 17 (17.65%)
occurrences (all)	2	1	3
Muscle spasms			
subjects affected / exposed	3 / 38 (7.89%)	1 / 35 (2.86%)	1 / 17 (5.88%)
occurrences (all)	3	2	1
Osteopenia			
subjects affected / exposed	0 / 38 (0.00%)	5 / 35 (14.29%)	0 / 17 (0.00%)
occurrences (all)	0	6	0
Joint effusion			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	2 / 17 (11.76%)
occurrences (all)	2	0	2
Bone pain			
subjects affected / exposed	1 / 38 (2.63%)	1 / 35 (2.86%)	1 / 17 (5.88%)
occurrences (all)	1	1	1
Joint swelling			
subjects affected / exposed	1 / 38 (2.63%)	1 / 35 (2.86%)	1 / 17 (5.88%)
occurrences (all)	1	1	1
Arthritis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	1 / 17 (5.88%)
occurrences (all)	0	5	1
Neck pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Osteoarthritis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Synovial cyst			

subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	2
Gouty arthritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Infections and infestations			
COVID-19			
subjects affected / exposed	12 / 38 (31.58%)	16 / 35 (45.71%)	6 / 17 (35.29%)
occurrences (all)	15	20	8
Nasopharyngitis			
subjects affected / exposed	6 / 38 (15.79%)	6 / 35 (17.14%)	3 / 17 (17.65%)
occurrences (all)	8	8	3
Upper respiratory tract infection			
subjects affected / exposed	9 / 38 (23.68%)	4 / 35 (11.43%)	1 / 17 (5.88%)
occurrences (all)	20	4	2
Sinusitis			
subjects affected / exposed	5 / 38 (13.16%)	1 / 35 (2.86%)	4 / 17 (23.53%)
occurrences (all)	14	3	4
Influenza			
subjects affected / exposed	2 / 38 (5.26%)	4 / 35 (11.43%)	2 / 17 (11.76%)
occurrences (all)	2	4	2
Urinary tract infection			
subjects affected / exposed	2 / 38 (5.26%)	3 / 35 (8.57%)	3 / 17 (17.65%)
occurrences (all)	2	4	3
Gastroenteritis			
subjects affected / exposed	2 / 38 (5.26%)	4 / 35 (11.43%)	0 / 17 (0.00%)
occurrences (all)	2	5	0
Suspected COVID-19			
subjects affected / exposed	4 / 38 (10.53%)	0 / 35 (0.00%)	2 / 17 (11.76%)
occurrences (all)	13	0	2
Respiratory tract infection			
subjects affected / exposed	4 / 38 (10.53%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	10	0	0

Hordeolum			
subjects affected / exposed	3 / 38 (7.89%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	3	0	0
Oral herpes			
subjects affected / exposed	1 / 38 (2.63%)	2 / 35 (5.71%)	0 / 17 (0.00%)
occurrences (all)	1	2	0
Pharyngitis			
subjects affected / exposed	3 / 38 (7.89%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	3	0	0
Respiratory tract infection viral			
subjects affected / exposed	2 / 38 (5.26%)	1 / 35 (2.86%)	0 / 17 (0.00%)
occurrences (all)	2	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 35 (0.00%)	2 / 17 (11.76%)
occurrences (all)	2	0	3
Acarodermatitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Bronchitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	8	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Conjunctivitis viral			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Ear lobe infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Enterovirus infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 35 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1

Escherichia urinary tract infection subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Eye infection subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Helminthic infection subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Implant site infection subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Infective tenosynovitis subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Pharyngitis streptococcal subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Viral infection subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Viral sinusitis subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	0 / 35 (0.00%) 0	1 / 17 (5.88%) 1
Metabolism and nutrition disorders			
Vitamin D deficiency subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	4 / 35 (11.43%) 4	4 / 17 (23.53%) 4
Iron overload subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	2 / 35 (5.71%) 2	0 / 17 (0.00%) 0
Decreased appetite subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	1 / 35 (2.86%) 1	1 / 17 (5.88%) 1
Type 2 diabetes mellitus			

subjects affected / exposed	2 / 38 (5.26%)	0 / 35 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2019	The following changes were made as per Amendment 2: Revised the text explaining an allowance for a lapse between signing the ICF/screening and the start of study treatment to specify that this was allowed only for subjects in Cohort 1 (i.e., subjects who were previously receiving placebo). Additionally, the text was revised to clarify that it is anticipated that no lapse will occur between the last visit of the antecedent study and signing the ICF/screening of this extension study for all cohorts. For subjects in Cohort 1, text was added to ensure that investigators assess subjects for clinical benefit after the fixed-dose period before proceeding into the continued treatment period. Revised text to include additional reasons a subject may not continue the mitapivat dose regimen they were receiving at the end of their fixed-dose period (either on the antecedent study [Cohorts 2 and 3] or in this extension study [Cohort 1]). Revised the dose titration language for subjects in Cohort 1 to allow dosing decisions to be based on results from local laboratories at the Week 4 and Week 8 Visits. Increased the sample size based on the increase in Study 007. Increased the length of contraception period for males exposed to study treatment to cover 1 complete spermatogenesis cycle. Removed the option for a rapid dose taper and simplified the recommended gradual dose taper. Revised the requirements for clinical laboratory results. Added text to specify that the requirements for pregnancy reporting are for female subjects and consented female partners of male subjects.
26 August 2020	The following changes were made as per Amendment 3: Management of concomitant therapy was updated per the mitapivat Investigator's Brochure: a. Digoxin and strong inhibitors of P-gp were removed from the list of therapies that are prohibited. Accordingly, receipt of digoxin or strong inhibitors of P-gp was removed from the exclusion criteria. b. Moderate inducers of CYP3A4 were added to the list of therapies that require careful monitoring. c. Deferoxamine, deferasirox, and deferiprone, which are iron chelators, were added to the list of therapies that require careful monitoring. d. Sensitive substrates of CYP2B6 were removed from the list of therapies requiring careful monitoring. Guidance on allowed modifications to study conduct during declared public health emergencies and natural disasters was added for situations during which adherence to protocol-specified procedures is impeded, such as the COVID-19 pandemic. Modified Exclusion Criterion #5 to exclude subjects who were currently receiving medications that are strong inducers of CYP3A4 that had not been stopped for a duration of at least 28 days or a time frame equivalent to 5 half-lives (whichever was longer) before start of study drug. Previously, the duration to stop receiving medications that are strong inducers of CYP3A4 was at least 5 days or a time frame equivalent to 5 half-lives (whichever was longer) before start of study drug. Telemedicine visits and direct-to-subject shipment of study drug were implemented (every other visit starting at Week 109).

19 July 2022	<p>The following changes were made as per Amendment 4: Transaminase increase was removed as an AESI per updated mitapivat Investigator's Brochure, in which transaminase increase is no longer classified as a risk or ADR of treatment with mitapivat. Added guidance for managing subjects who transition to receiving treatment with mitapivat outside of Study AG348-C-011, as subjects may choose to obtain mitapivat from other available sources (eg, commercial). Removed or reduced frequency of following assessments to reduce subject burden and/or because more frequent monitoring of these assessments is no longer warranted based on established safety profile of mitapivat. Schedule of assessments was modified on or after Week 37 and was not modified through Week 24 (last scheduled visit before Week 37) because all subjects enrolled in study have discontinued before or completed Week 24 visit. a. Removed electrocardiogram assessments from Week 37 through End of Study, which are no longer warranted based on established safety profile of mitapivat. b. Removed PE assessments from Week 37 through Week 145 because frequent PE assessments are no longer warranted based on established safety profile of mitapivat. c. Removed menstrual cycle eDiary assessments from Week 37 through End of Study to reduce subject burden. Identified risk, changes in sex hormones, can be monitored adequately with laboratory assessments. Assessments of reproductive potential from Week 37 through End of Study have been added to support analyses of changes in sex hormones. d. Reduced frequency of lipid assessments from Week 37 through End of Study to be performed annually and removed requirement for lipid tests to be performed after a fast because hypertriglyceridemia is no longer considered an important potential risk (now considered a nonimportant potential risk) or ADR of treatment with mitapivat and can be monitored adequately with annual assessments.</p>
--------------	---

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported