Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AG-348 in Not Regularly Transfused Adult Subjects With Pyruvate Kinase Deficiency

Summary

EudraCT number	2017-003823-31
Trial protocol	DE GB FR PT ES DK NL CZ IT
Global end of trial date	09 October 2020

Results information

Result version number	v2 (current)
This version publication date	14 October 2022
First version publication date	24 October 2021
Version creation reason	• Correction of full data set The study record is being modified to align with the ClinicalTials.gov record of the same study.

Trial information

Trial identification

Sponsor protocol code	AG348-C-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03548220
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	09 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of treatment with AG-348 compared with placebo in increasing haemoglobin (Hb) concentrations.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Turkey: 1
Worldwide total number of subjects	80
EEA total number of subjects	34

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)	76
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 80 subjects were randomised in the study which was conducted across multiple sites in 14 countries: Brazil, Canada, Denmark, France, Germany, Italy, Japan, Republic of Korea, Netherlands, Spain, Switzerland, Turkey, United Kingdom and United States. The study was conducted from 9 August 2018 to 9 October 2020.

Pre-assignment

Screening details:

Screening was done for a period of 42 days after the subject provided the informed consent. Investigators determined if the subjects met all the inclusion criteria and none of the exclusion criteria to receive AG-348 or placebo to determine the optimised dose to be received for 12 weeks as fixed-dose.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received a matching placebo to AG-348 tablets, for a period of 12 weeks as an optimised dose. This was followed by matching placebo further, for a period of 12 weeks as a fixed-dose.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching AG-348 tablets, administered to maintain the blind.

Arm title	AG-348, 5 mg

Arm description:

Subjects received AG-348 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 optimised dose for each subject was determined as 5 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.

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

Dosage and administration details:

AG-348 5 mg tablets BID administered orally.

Arm title	AG-348, 20 mg

Arm description:

Subjects received AG-348 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 optimised dose for each subject was determined as 20 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.

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

Dosage and administration details:

AG-348 20 mg tablets BID administered orally.

Arm title	AG-348, 50 mg

Arm description:

Subjects received AG-348 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 optimised dose for each subject was determined as 50 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.

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

Dosage and administration details:

AG-348 50 mg tablets BID administered orally.

Number of subjects in period 1	Placebo	AG-348, 5 mg	AG-348, 20 mg
Started	40	2	3
Completed	39	2	3
Not completed	1	0	0
Lost to follow-up	1	-	-

Number of subjects in period 1	AG-348, 50 mg
Started	35
Completed	35
Not completed	0
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received a matching placebo to AG-348 tablets, for a period of 12 weeks as an optimised dose. This was followed by matching placebo further, for a period of 12 weeks as a fixed-dose.	
Reporting group title	AG-348, 5 mg
Reporting group description:	
Subjects received AG-348 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 optimised dose for each subject was determined as 5 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.	
Reporting group title	AG-348, 20 mg
Reporting group description:	
Subjects received AG-348 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 optimised dose for each subject was determined as 20 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.	
Reporting group title	AG-348, 50 mg
Reporting group description:	
Subjects received AG-348 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 optimised dose for each subject was determined as 50 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.	

Reporting group values	Placebo	AG-348, 5 mg	AG-348, 20 mg
Number of subjects	40	2	3
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	37.2	21.5	48.0
standard deviation	± 15.92	± 4.95	± 26.21
Gender categorical Units: Subjects			
Female	24	0	2
Male	16	2	1
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	32	2	3
More than one race	1	0	0
Unknown or Not Reported	4	0	0
Ethinicity			

Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	34	1	2
Unknown or Not Reported	5	1	1

Reporting group values	AG-348, 50 mg	Total	
Number of subjects	35	80	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	35.8		
standard deviation	± 14.07	-	
Gender categorical Units: Subjects			
Female	22	48	
Male	13	32	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	5	8	
Native Hawaiian or Other Pacific Islander	1	1	
Black or African American	0	0	
White	23	60	
More than one race	0	1	
Unknown or Not Reported	6	10	
Ethinicity Units: Subjects			
Hispanic or Latino	2	3	
Not Hispanic or Latino	25	62	
Unknown or Not Reported	8	15	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received a matching placebo to AG-348 tablets, for a period of 12 weeks as an optimised dose. This was followed by matching placebo further, for a period of 12 weeks as a fixed-dose.

Reporting group title	AG-348, 5 mg

Reporting group description:

Subjects received AG-348 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 optimised dose for each subject was determined as 5 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.

Reporting group title	AG-348, 20 mg

Reporting group description:

Subjects received AG-348 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 optimised dose for each subject was determined as 20 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.

Reporting group title	AG-348, 50 mg

Reporting group description:

Subjects received AG-348 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 optimised dose for each subject was determined as 50 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.

Subject analysis set title	AG-348
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received AG-348 tablets, 5 mg for 4 weeks followed by the respective optimised dose of 5 mg or 20 mg or 50 mg BID as determined by the investigator, administered orally, up to Weeks 8 and 12 respectively, as an optimised dose and continued to receive the same dose for a period of 12 weeks as a fixed-dose.

Subject analysis set title	AG-348 50 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received AG-348 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 optimised dose for each subject was determined as 50 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.

Primary: Percentage of Subjects Achieving a Haemoglobin (Hb) Response (HR)

End point title	Percentage of Subjects Achieving a Haemoglobin (Hb) Response (HR)[1]

End point description:

Haemoglobin response (HR) is defined as a ≥1.5 g/dL (0.93 mmol/L) increase in Hb concentration from baseline that is sustained at 2 or more scheduled assessments at Weeks 16, 20, and 24. The baseline Hb concentration is the average of all available Hb concentrations for a subject during the Screening Period up to the first dose of study treatment. As pre-specified in the protocol, the data for this end point is summarised between the active arm vs the placebo arm (AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo). Full analysis set included all subjects who were randomised.

End point type	Primary

End point timeframe:

Baseline, Weeks 16, 20, 24

Notes:

[1] - 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, AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo for this end point. Hence, only data for AG 348 and Placebo arms have been reported.

End point values	Placebo	AG-348		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40	40		
Units: percentage of subjects				
number (not applicable)	0	40.0		

Statistical analyses

Statistical analysis title	Hemoglobin response Response (HR)
Comparison groups	Placebo v AG-348
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Exact Cochran-Mantel-Haenszel

Notes:

[2] - 2-sided p-value

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

End point title	Average Change From Baseline in Hb Concentration at Weeks 16, 20 and 24[3]

End point description:

This is the change in Hb concentration at Weeks 16, 20 and 24 compared to that of baseline. Data presented represents the value of change from baseline at Weeks 16, 20 and 24. Baseline was defined as the average of all screening assessments within 45 (42+3) days before randomisation for subjects randomised and not dosed or before start of study treatment for subjects randomised and dosed. As pre-specified in the protocol, the data for this end point is summarised between the active arm vs the placebo arm (AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo). Full analysis set included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Baseline, Weeks 16, 20, 24

Notes:

[3] - 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, AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo for this end point. Hence, only data for AG 348 and Placebo arms have been reported.

End point values	Placebo	AG-348		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40	40		
Units: grams per litre (g/L)				
least squares mean (standard error)	-1.48 (± 2.082)	16.73 (± 2.075)		

Statistical analyses

Statistical analysis title	Average Change in Hemoglobin Concentration
Comparison groups	Placebo v AG-348
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effect Model Repeated Measure
Parameter estimate	LS Mean Difference
Point estimate	18.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.41
upper limit	24.01
Variability estimate	Standard error of the mean
Dispersion value	2.913

Secondary: Maximum Change From Baseline in Hb Concentration

End point title	Maximum Change From Baseline in Hb Concentration[4]

End point description:

This is the maximum change from baseline in Hb concentration up to Week 24. As pre-specified in the protocol, the data for this end point is summarised between the active arm vs the placebo arm (AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo). Full analysis set included all subjects who were randomised. Overall number of subjects analysed is the number of subjects evaluated for the endpoint.

End point type	Secondary

End point timeframe:

Baseline, up to Week 24

Notes:

[4] - 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, AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo for this end point. Hence, only data for AG 348 and Placebo arms have been reported.

End point values	Placebo	AG-348		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	39	39		
Units: g/L				
arithmetic mean (standard deviation)	4.76 (± 4.217)	23.94 (± 21.367)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Achieve an Increase in Hb Concentration of 1.5 g/dL or More

End point title	Time to Achieve an Increase in Hb Concentration of 1.5 g/dL or More

End point description:

This is the time taken to first achieve an increase of haemoglobin concentration of 1.5 g/dL or more from baseline. As pre-specified in the protocol, the data for this end point is summarised between the active arm vs the placebo arm (AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo). Full analysis set included all subjects who were randomised. Overall number of subjects analysed is the number of subjects evaluated for the end point.

End point type	Secondary

End point timeframe:

Baseline, up to Week 24

End point values	AG-348			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: weeks				
arithmetic mean (standard deviation)	7.66 (± 4.050)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Change From Baseline in Indirect Bilirubin at Weeks 16, 20 and 24

End point title	Average Change From Baseline in Indirect Bilirubin at Weeks 16, 20 and 24[5]

End point description:

The change from baseline in indirect bilirubin levels was summarised. Indirect bilirubin is a marker for haemolysis. Data presented represents the average change from baseline at Week 16, 20 and 24. Baseline was defined as the average of all screening assessments within 45 (42+3) days before randomisation for subjects randomised and not dosed or before start of study treatment for subjects randomised and dosed. As pre-specified in the protocol, the data for this outcome measure is summarised between the active arm vs the placebo arm (AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo). Full analysis set included all subjects who were randomised. Overall number of subjects analysed is the number of subjects evaluated for the end point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 16, 20, 24

Notes:

[5] - 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, AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo for this end point. Hence, only data for AG 348 and Placebo arms have been reported.

End point values	Placebo	AG-348		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	39	37		
Units: micromoles per litre (µmol/L)				
least squares mean (standard error)	5.10 (± 4.061)	-21.16 (± 4.228)		

Statistical analyses

Statistical analysis title	Average Change From Baseline in Bilirubin
Comparison groups	Placebo v AG-348
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effect Model Repeated Measure
Parameter estimate	LS Mean Difference
Point estimate	-26.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.82
upper limit	-14.7
Variability estimate	Standard error of the mean
Dispersion value	5.788

Secondary: Average Change From Baseline in Lactic Acid Dehydrogenase (LDH) at Weeks 16, 20 and 24

End point title	Average Change From Baseline in Lactic Acid Dehydrogenase (LDH) at Weeks 16, 20 and 24[6]

End point description:

The change from baseline in LDH levels was summarised. LDH is a marker for haemolysis. Data presented represents the average change from baseline at Weeks 16, 20 and 24. Baseline was defined as the average of all screening assessments within 45 (42+3) days before randomisation for subjects randomised and not dosed or before start of study treatment for subjects randomised and dosed. As pre-specified in the protocol, the data for this end point is summarised between the active arm vs the placebo arm (AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo). Full analysis set included all subjects who were randomised. Overall number of subjects analysed is the number of subjects evaluated for the end point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 16, 20, 24

Notes:

[6] - 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, AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo for this end point. Hence, only data for AG 348 and Placebo arms have been reported.

End point values	Placebo	AG-348		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40	39		
Units: units per litre (U/L)				
least squares mean (standard error)	-21.18 (± 16.040)	-91.99 (± 16.222)		

Statistical analyses

Statistical analysis title	Average Change From Baseline in Lactic Acid Dehydr
Comparison groups	Placebo v AG-348
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0027
Method	Mixed-effect Model Repeated Measure
Parameter estimate	LS Mean Difference
Point estimate	-70.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-115.88
upper limit	-25.74
Variability estimate	Standard error of the mean
Dispersion value	22.488

Secondary: Average Change From Baseline in Haptoglobin at Weeks 16, 20 and 24

End point title	Average Change From Baseline in Haptoglobin at Weeks 16, 20 and 24[7]

End point description:

The change from baseline in haptoglobin levels were summarised. Haptoglobin levels are markers for haemolysis. Data presented represents the average change from baseline at Weeks 16, 20 and 24. Baseline was defined as the average of all screening assessments within 45 (42+3) days before randomisation for subjects randomised and not dosed or before start of study treatment for subjects randomised and dosed. As pre-specified in the protocol, the data for this end point is summarised between the active arm vs the placebo arm (AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo). Full analysis set included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Baseline, Weeks 16, 20, 24

Notes:

[7] - 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, AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo for this end point. Hence, only data for AG 348 and Placebo arms have been reported.

End point values	Placebo	AG-348		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40	40		
Units: g/L				
least squares mean (standard error)	0.012 (± 0.0412)	0.169 (± 0.0408)		

Statistical analyses

Statistical analysis title	Average Change From Baseline in Haptoglobin
Comparison groups	Placebo v AG-348
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0079
Method	Mixed-effect Model Repeated Measure
Parameter estimate	LS Mean Difference
Point estimate	0.158
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.043
upper limit	0.273
Variability estimate	Standard error of the mean
Dispersion value	0.0578

Secondary: Average Change From Baseline in Reticulocyte Percentages at Weeks 16, 20 and 24

End point title	Average Change From Baseline in Reticulocyte Percentages at Weeks 16, 20 and 24[8]

End point description:

The change from baseline in reticulocyte percentage was summarised. Reticulocyte levels are markers for hematopoietic activity. Data presented represents the value of the change from baseline averaged over Weeks 16, 20 and 24. Baseline was defined as the average of all screening assessments within 45 (42+3) days before randomisation for subjects randomised and not dosed or before the start of study treatment for subjects randomised and dosed. As pre-specified in the protocol, the data for this end point is summarised between the active arm vs the placebo arm (AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo). Full analysis set included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Baseline, Weeks 16, 20, 24

Notes:

[8] - 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, AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo for this end point. Hence, only data for AG 348 and Placebo arms have been reported.

End point values	Placebo	AG-348		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40	40		
Units: Reticulocyte percentages				
least squares mean (standard error)	0.0038 (± 0.01390)	-0.0973 (± 0.01401)		

Statistical analyses

Statistical analysis title	Change From Baseline in Reticulocyte Percentage
Comparison groups	Placebo v AG-348
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effect Model Repeated Measure
Parameter estimate	LS Mean Difference
Point estimate	-0.1011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1391
upper limit	-0.0632
Variability estimate	Standard error of the mean
Dispersion value	0.01904

Secondary: Change From Baseline in Pyruvate Kinase Deficiency Diary (PKDD) Score at Week 24

End point title	Change From Baseline in Pyruvate Kinase Deficiency Diary (PKDD) Score at Week 24[9]

End point description:

The PKDD is a 7-item patient reported outcome (PRO) measure of the core signs and symptoms associated with PK deficiency in adults. Subjects rate their experience with symptoms of PK deficiency on the present day. The symptoms include those associated with tiredness, jaundice, bone pain, shortness of breath, and energy level. The score ranges from 25 to 76, with higher scores indicating a higher disease burden. The change from baseline in PKDD weekly scores was evaluated. A negative change from baseline indicates a lower disease burden. As pre-specified in the protocol, the data for this end point is summarised between the active arm vs the placebo arm (AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo). Full analysis set included all subjects who were randomised. Overall number of subjects analysed is the number of subjects evaluated for the end point.

End point type	Secondary

End point timeframe:

Baseline, to Week 24

Notes:

[9] - 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, AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo for this end point. Hence, only data for AG 348 and Placebo arms have been reported.

End point values	Placebo	AG-348		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	36	37		
Units: score on a scale				
least squares mean (standard error)	-2.05 (± 0.976)	-5.16 (± 0.955)		

Statistical analyses

Statistical analysis title	Change From Baseline in PKDD Score
Comparison groups	Placebo v AG-348
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0247
Method	Mixed-effect Model Repeated Measure
Parameter estimate	LS Mean Difference
Point estimate	-3.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	-0.41
Variability estimate	Standard error of the mean
Dispersion value	1.352

Secondary: Change From Baseline in Pyruvate Kinase Deficiency Impact Assessment (PKDIA) Score at Week 24

End point title	Change From Baseline in Pyruvate Kinase Deficiency Impact Assessment (PKDIA) Score at Week 24[10]

End point description:

The PKDIA is a 12-item patient reported outcome (PRO) measure of the common impacts of PK deficiency on activities of daily living. Subjects rate how PK deficiency has impacted aspects of daily living in the past 7 days, including impacts on relationships; perceived appearance; work performance; and leisure, social, mental, and physical activities. The score range is 30 to 76, with higher scores indicating a higher disease burden. The change from baseline in PKDIA scores was evaluated. A negative change from baseline indicates a lower disease burden. As pre-specified in the protocol, the data for this end point is summarised between the active arm vs the placebo arm (AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo). Full analysis set included all subjects who were randomised. Overall number of subjects analysed is the number of subjects evaluated for the end point.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[10] - 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, AG-348 5 mg, 20 mg and 50 mg arms are analysed and reported together in comparison to Placebo for this end point. Hence, only data for AG 348 and Placebo arms have been reported.

End point values	Placebo	AG-348		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	39	39		
Units: score on a scale				
least squares mean (standard error)	-1.39 (± 1.157)	-4.65 (± 1.123)		

Statistical analyses

Statistical analysis title	Change From Baseline in PKDIA Score
Comparison groups	Placebo v AG-348
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0421
Method	Mixed-effect Model Repeated Measure
Parameter estimate	LS Mean Difference
Point estimate	-3.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.39
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	1.574

Secondary: Percentage of Subjects With Adverse Events

End point title	Percentage of Subjects With Adverse Events

End point description:

An 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 treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Safety analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

From signing of informed consent form to the end of study, including follow-up (up to Day 197)

End point values	Placebo	AG-348, 5 mg	AG-348, 20 mg	AG-348, 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	2	3	35
Units: percentage of subjects				
number (not applicable)	89.7	50.0	100	88.6

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time 0 to the Last Quantifiable Concentration [AUC(0-last)] for AG-348 at Week 12

End point title	Area Under the Curve From Time 0 to the Last Quantifiable Concentration [AUC(0-last)] for AG-348 at Week 12[11]

End point description:

Pharmacokinetic analysis population consisted of all subjects who were enrolled and received a dose of study medication (mitapivat) with at least 1 non-zero pharmacokinetic plasma concentration of mitapivat at the Week 12 visit. Overall number of subjects analysed is the number of subjects evaluated for the end point. 9999 indicates the standard deviation for AG-348 arm was not reported due to low number of subjects evaluated.

End point type	Secondary

End point timeframe:

Pre-dose, 30 minutes and 1, 2, 4 and 8 hours post-dose on Day 85 (Week 12)

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: The endpoint is for AG-348 only. Hence, only data for AG-348 5mg, AG-348 20mg, and AG-348 50mg arms have been reported.

End point values	AG-348, 5 mg	AG-348, 20 mg	AG-348, 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	3	24	
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	565.9 (± 9999)	1481.2 (± 26.9)	2973.3 (± 35.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) for AG-348

End point title	Maximum Plasma Concentration (Cmax) for AG-348[12]

End point description:

Pharmacokinetic analysis population consisted of all subjects who were enrolled and received a dose of study medication (mitapivat) with at least 1 non-zero pharmacokinetic plasma concentration of mitapivat at the Week 12 visit. Overall number of subjects analysed is the number of subjects evaluated for the end point. 9999 indicates the standard deviation for AG-348 arm was not reported due to low number of subjects evaluated.

End point type	Secondary

End point timeframe:

Pre-dose, 30 minutes and 1, 2, 4 and 8 hours post-dose on Day 85 (Week 12)

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: The endpoint is for AG-348 only. Hence, only data for AG-348 5mg, AG 348 20mg and AG-348 50mg arms have been reported.

End point values	AG-348, 5 mg	AG-348, 20 mg	AG-348, 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	3	26	
Units: nanogram/millilitre (ng/mL)				
geometric mean (geometric coefficient of variation)	156.9 (± 9999)	373.1 (± 13.6)	1033 (± 31.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cmax (Tmax) for AG-348

End point title	Time to Cmax (Tmax) for AG-348[13]

End point description:

Pharmacokinetic analysis population consisted of all subjects who were enrolled and received a dose of study medication (mitapivat) with at least 1 non-zero pharmacokinetic plasma concentration of mitapivat at the Week 12 visit. Overall number of subjects analysed is the number of subjects evaluated for the end point.

End point type	Secondary

End point timeframe:

Pre-dose, 30 minutes and 1, 2, 4 and 8 hours post-dose on Day 85 (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: The endpoint is for AG-348 only. Hence, only data for AG-348 5mg, AG-348 20mg, and AG-348 50mg arms have been reported.

End point values	AG-348, 5 mg	AG-348, 20 mg	AG-348, 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	3	26	
Units: hours (h)				
median (full range (min-max))	0.75 (0.50 to 1.00)	1.02 (0.92 to 2.17)	0.50 (0.42 to 1.92)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Last Measurable Concentration (Tlast) for AG-348

End point title	Time to Last Measurable Concentration (Tlast) for AG-348[14]

End point description:

Pharmacokinetic analysis population consisted of all subjects who were enrolled and received a dose of study medication (mitapivat) with at least 1 non-zero pharmacokinetic plasma concentration of mitapivat at the Week 12 visit. Overall number of subjects analysed is the number of subjects evaluated for the end point. 9999 indicates the standard deviation for AG-348 arm was not reported due to low number of subjects evaluated.

End point type	Secondary

End point timeframe:

Pre-dose, 30 minutes and 1, 2, 4 and 8 hours post-dose on Day 85 (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: The endpoint is for AG-348 only. Hence, only data for AG-348 5mg, AG-348 20mg, and AG-348 50mg arms have been reported.

End point values	AG-348, 5 mg	AG-348, 20 mg	AG-348, 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	3	24	
Units: hours (h)				
geometric mean (geometric coefficient of variation)	7.787 (± 9999)	7.809 (± 4.2)	7.162 (± 28.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure-Response Relationship of Adverse Event (Hot Flush) and AG-348 Concentration and Relevant AG-348 Pharmacokinetic Parameters

End point title	Exposure-Response Relationship of Adverse Event (Hot Flush) and AG-348 Concentration and Relevant AG-348 Pharmacokinetic Parameters[15]

End point description:

Predicted probability of experiencing all grade hot flush at the doses of 5, 20, and 50 mg mitapivat BID based on exposure-response model. Safety set included subjects who were administered the study drug. Subjects who received mitapivat in studies: study AG348-C-003 (NCT02476916): 52 subjects; study AG348-C-006 (NCT03548220): 40 subjectts; study AG348-C-007 (NCT03559699): 27 subjects; and study AG348-C-011 (NCT03853798): 36 subjects, were pooled for the analysis of this end point.

End point type	Secondary

End point timeframe:

From first dose of mitapivat to the end of study, including follow-up (up to Day 197)

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: The endpoint is for AG-348 only. Hence, only data for AG-348 5mg, AG-348 20mg, and AG-348 50mg arms have been reported.

End point values	AG-348, 5 mg	AG-348, 20 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	3		
Units: percent probability				
arithmetic mean (confidence interval 95%)	3.37 (1.22 to 7.35)	4.03 (1.61 to 8.36)		

Attachments (see zip file)	AG348-C-006_ Subject Analysis Set/AG348-C-006_Subject

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure-Response Relationship Between Safety Parameters (Sex Hormone in Male Subjects) and AG-348 Concentration and Relevant AG-348 Pharmacokinetic Parameters

End point title	Exposure-Response Relationship Between Safety Parameters (Sex Hormone in Male Subjects) and AG-348 Concentration and Relevant AG-348 Pharmacokinetic Parameters[16]

End point description:

Predicted percent change from baseline at Week 24 in the sex hormone measures (total testosterone, free testosterone, and estrone) at the doses of 5, 20, and 50 mg mitapivat BID in male subjects. Safety set included subjects who were administered the study drug. Male subjects who received mitapivat in studies: study AG348-C-003 (NCT02476916): 32 subjects; study AG348-C-006 (NCT03548220):15 subjects; study AG348-C-007 (NCT03559699): 7 subjects; and study AG348-C-011 (NCT03853798): 14 subjects were pooled for analysis of this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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: The endpoint is for AG-348 only. Hence, only data for AG-348 5mg, AG-348 20mg, and AG-348 50mg arms have been reported.

End point values	AG-348, 5 mg	AG-348, 20 mg	AG-348 50 mg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2	3	63	
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 (4.0 to 27.5)	26.0 (7.14 to 55.1)	
Estrone	-31.5 (-51.0 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:

From time of signing of informed consent form to end of study, including follow-up (up to Day 197)

Adverse event reporting additional description:

The placebo arm includes AEs that occurred in subjects who received at least 1 dose of AG-348 matching placebo during the study. As pre-specified in SAP, AEs that occurred in AG-348 arms for subjects who received AG-348 treatment during the study are reported based on the fixed dose treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received a matching placebo to AG-348 tablets, for a period of 12 weeks as an optimised dose. This was followed by matching placebo further, for a period of 12 weeks as a fixed-dose.

Reporting group title	AG-348, 5 mg

Reporting group description:

Subjects received AG-348 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 optimised dose for each subject was determined as 5 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.

Reporting group title	AG-348, 20 mg

Reporting group description:

Subjects received AG-348 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 optimised dose for each subject was determined as 20 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.

Reporting group title	AG-348, 50 mg

Reporting group description:

Subjects received AG-348 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 optimised dose for each subject was determined as 50 mg BID at Week 12, and subjects then received that optimised dose for a period of 12 weeks as a fixed dose.

Serious adverse events	Placebo	AG-348, 5 mg	AG-348, 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	1 / 3 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Rib fracture			

subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Obstructive pancreatitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 2 (0.00%)	0 / 3 (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
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metapneumovirus infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 2 (0.00%)	0 / 3 (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

Serious adverse events	AG-348, 50 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 35 (8.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Rib fracture			

subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Obstructive pancreatitis			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metapneumovirus infection			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	AG-348, 5 mg	AG-348, 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 39 (89.74%)	1 / 2 (50.00%)	3 / 3 (100.00%)
Vascular disorders			

Hot flush			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 39 (10.26%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	6	0	1
Influenza like illness			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			
Breast discomfort			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	3 / 39 (7.69%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	2	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 39 (10.26%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	4	0	1
Cough			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Nasal congestion			

subjects affected / exposed	3 / 39 (7.69%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Rhinitis allergic			
subjects affected / exposed	3 / 39 (7.69%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Epistaxis			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Middle insomnia			
subjects affected / exposed	3 / 39 (7.69%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	18	0	0
Insomnia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Initial insomnia			
subjects affected / exposed	4 / 39 (10.26%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Stress			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 39 (15.38%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	7	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 39 (7.69%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 39 (2.56%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 39 (33.33%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	19	0	1

Dizziness			
subjects affected / exposed	3 / 39 (7.69%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Presyncope			
subjects affected / exposed	1 / 39 (2.56%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 39 (23.08%)	0 / 2 (0.00%)	2 / 3 (66.67%)
occurrences (all)	9	0	3
Diarrhoea			
subjects affected / exposed	7 / 39 (17.95%)	0 / 2 (0.00%)	2 / 3 (66.67%)
occurrences (all)	8	0	2
Abdominal pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Abdominal distension			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	3	0	1
Abdominal pain upper			
subjects affected / exposed	3 / 39 (7.69%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	3 / 39 (7.69%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Dermatitis acneiform			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Dry skin			
subjects affected / exposed	1 / 39 (2.56%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 39 (7.69%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Arthralgia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Pain in extremity			
subjects affected / exposed	3 / 39 (7.69%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Neck pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 39 (15.38%)	0 / 2 (0.00%)	2 / 3 (66.67%)
occurrences (all)	9	0	3
Gastroenteritis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	3 / 39 (7.69%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 39 (10.26%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Oral herpes			

subjects affected / exposed	2 / 39 (5.13%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	AG-348, 50 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 35 (88.57%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Influenza like illness			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Breast discomfort			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	4		
Dysmenorrhoea			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	4		
Nasal congestion			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	3		
Rhinitis allergic			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Psychiatric disorders			
Middle insomnia			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Initial insomnia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Stress			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Aspartate aminotransferase increased			

subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	 2 / 35 (5.71%) 3		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Presyncope subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	 5 / 35 (14.29%) 11 4 / 35 (11.43%) 5 2 / 35 (5.71%) 2 2 / 35 (5.71%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 0 / 35 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all)	 5 / 35 (14.29%) 8 2 / 35 (5.71%) 2 4 / 35 (11.43%) 4 2 / 35 (5.71%) 3		

Constipation subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Dyspepsia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Dermatitis acneiform subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Dry skin subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5		
Arthralgia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3		
Pain in extremity subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Neck pain subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3		

Gastroenteritis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2 1 / 35 (2.86%) 1 0 / 35 (0.00%) 0 0 / 35 (0.00%) 0		
Metabolism and nutrition disorders Hypertriglyceridaemia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2018	Removed dose escalation restrictions after the Week 8 Visit. • Added detailed guidance on re-introducing or escalating study treatment after resolution of a Grade 3 AE that caused study treatment to be stopped or reduced. • Removed the requirement that subjects must be receiving study treatment at Week 24 to be potentially eligible for an extension study. • Added an exclusion criterion to exclude subjects who have not stopped using haematopoietic stimulating agents at least 28 days before the first dose of study treatment. • Added clarity to the dose modification guidance for Grade 3 and Grade 4 AEs that are deemed by the Investigator to be related to study treatment. • Added new laboratory assessments for biomarkers (iron-related markers, known markers of erythropoietic activity, circulating haeme, and to be identified markers of iron metabolism or erythropoiesis).
15 August 2018	Consolidated iron-related secondary and exploratory endpoints into 1 exploratory endpoint for markers of iron metabolism. • Revised the instructions for dose optimisation. • Clarified that unblinding before database lock will occur only in the subjects who enter the planned mitapivat extension study and that subjects undergoing a dose taper should remain blinded through the taper. • Amended the inclusion criterion for renal function. • Amended the absolute neutrophil count (ANC) and platelet count inclusion criteria to be assessed via 2 measurements. • Amended the inclusion criterion for contraception requirements and added monthly pregnancy tests for applicable subjects. • Added an exception for subjects who have concurrent disorders that in isolation are predicted to be insufficient to explain the observed clinical phenotype to the exclusion criterion for congenital or genetic disorders. • Corrected the exclusion criterion for splenectomy to require subjects to wait at least 12 months after splenectomy before starting screening. • Added a subsection under Section 9.3, Blinding, to provide details on handling of restricted data and to add the role of an Independent Medical Monitor to handle restricted data. • Amended the unblinding language such that the unblinding of a subject for a medical emergency or pregnancy does not require confirmation by the Sponsor’s Medical Monitor. • Redefined the definition of Hb overshoot, and subsequent study treatment dose decrease, to higher than 20 g/L (2 g/dL) below the upper limit of normal (ULN). • Added historical data for iron chelation therapy, iron serum, transferrin saturation, and liver iron concentration (LIC) and removed some iron-related laboratory assessments. • Added further details for assessments after a transaminase increase

14 August 2019	Revised the dose optimisation language to allow dosing decisions to be based on results from local laboratories at the Week 4 and Week 8 Visit • Revised the inclusion criterion for platelet count • Increased the length of the contraception period for males exposed to study treatment to cover 1 complete spermatogenesis cycle • Revised the handling of restricted data such that the subject's dose levels were no longer maintained as part of the restricted data and hormone data were considered restricted data for Investigators • Removed the option for a rapid dose taper and simplified the recommended gradual dose taper • Added language to provide previously ineligible subjects the opportunity to rescreen for enrollment into the study should they become eligible based on an amended protocol • Revised the requirements for clinical laboratory results, allowing Investigators the flexibility to use local laboratory results when results from central laboratories are not available • Added further details for assessments after a transaminase increase that meet the criteria for an AESI • Added ability to extend the Screening Period duration beyond 42 days

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported