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	v1
This version publication date	24 October 2021
First version publication date	24 October 2021

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 enroll in Part 1: Dose Optimisation Period to receive AG-348 or placebo to determine the optimised dose followed by Part 2: Fixed Dose Period.

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	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received matching placebo to AG-348 tablets, administered orally, at a starting dose of 5 milligrams (mg) twice daily (BID) followed by two sequential dose level increases to 20 mg and 50 mg BID at Weeks 4 and 8 respectively, for a period of 12 weeks in Part 1. This was followed by the optimised dose BID, as determined by the investigator in Part 1, for a period of 12 weeks in Part 2.

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:

AG-348 matching-placebo tablets BID administered orally in Part 1 and Part 2.

Arm title	AG-348

Arm description:

Subjects received AG-348 tablets, administered orally, at a starting dose of 5 mg BID followed by two sequential dose level increases to 20 mg and 50 mg BID at Weeks 4 and 8 respectively, for a period of 12 weeks in Part 1. This was followed by the optimised dose BID, as determined by investigator in Part 1, for a period of 12 weeks in Part 2.

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 5mg, 20mg. and 50mg tablets BID administered orally in Part 1 and Part 2.

Number of subjects in period 1	Placebo	AG-348
Started	40	40
Completed	39	40
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo to AG-348 tablets, administered orally, at a starting dose of 5 milligrams (mg) twice daily (BID) followed by two sequential dose level increases to 20 mg and 50 mg BID at Weeks 4 and 8 respectively, for a period of 12 weeks in Part 1. This was followed by the optimised dose BID, as determined by the investigator in Part 1, for a period of 12 weeks in Part 2.	
Reporting group title	AG-348
Reporting group description:	
Subjects received AG-348 tablets, administered orally, at a starting dose of 5 mg BID followed by two sequential dose level increases to 20 mg and 50 mg BID at Weeks 4 and 8 respectively, for a period of 12 weeks in Part 1. This was followed by the optimised dose BID, as determined by investigator in Part 1, for a period of 12 weeks in Part 2.	

Reporting group values	Placebo	AG-348	Total
Number of subjects	40	40	80
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	37.2	36.0	
standard deviation	± 15.92	± 15.18	-
Gender categorical Units: Subjects			
Female	24	24	48
Male	16	16	32
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	5	8
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	0	0	0
White	32	28	60
More than one race	1	0	1
Unknown or Not Reported	4	6	10
Ethinicity Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	34	28	62
Unknown or Not Reported	5	10	15

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo to AG-348 tablets, administered orally, at a starting dose of 5 milligrams (mg) twice daily (BID) followed by two sequential dose level increases to 20 mg and 50 mg BID at Weeks 4 and 8 respectively, for a period of 12 weeks in Part 1. This was followed by the optimised dose BID, as determined by the investigator in Part 1, for a period of 12 weeks in Part 2.	
Reporting group title	AG-348
Reporting group description:	
Subjects received AG-348 tablets, administered orally, at a starting dose of 5 mg BID followed by two sequential dose level increases to 20 mg and 50 mg BID at Weeks 4 and 8 respectively, for a period of 12 weeks in Part 1. This was followed by the optimised dose BID, as determined by investigator in Part 1, for a period of 12 weeks in Part 2.	
Subject analysis set title	AG-348 5mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received 5mg AG-348 tablets BID at Week 12.	
Subject analysis set title	AG-348 20mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received 20mg AG-348 tablets BID at Week 12.	
Subject analysis set title	AG-348 50mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received 50mg AG-348 tablets BID at Week 12.	

Primary: Percentage of Subjects Achieving a Haemoglobin (Hb) Response (HR) in Part 2

End point title	Percentage of Subjects Achieving a Haemoglobin (Hb) Response (HR) in Part 2
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 during the Fixed Dose Period. 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. Full analysis set included all subjects who were randomised.	
End point type	Primary
End point timeframe:	
Baseline, Part 2: Weeks 16, 20, 24	

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
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) in Part 2
Comparison groups	Placebo v AG-348
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Exact Cochran-Mantel-Haenszel

Notes:

[1] - 2-sided p-value

Secondary: Average Change From Baseline in Hb Concentration at Weeks 16, 20 and 24 in Part 2

End point title	Average Change From Baseline in Hb Concentration at Weeks 16, 20 and 24 in Part 2

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 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. Full analysis set included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Baseline, Part 2: Weeks 16, 20, 24

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: 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	AG-348 v Placebo
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

End point description:

This is the maximum change from baseline in Hb concentration in Part 2. Full analysis set included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Baseline, Part 2, up to Week 24

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[2]	39[3]		
Units: g/L				
arithmetic mean (standard deviation)	4.76 (± 4.217)	23.94 (± 21.367)		

Notes:

[2] - Number analysed is the number of subjects evaluated for the endpoint.

[3] - Number analysed is the number of subjects evaluated for the endpoint.

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.

End point type	Secondary

End point timeframe:

Baseline, Part 2, up to Week 24

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	17[5]		
Units: weeks				
arithmetic mean (standard deviation)	()	7.66 (± 4.050)		

Notes:

[4] - No subjects were analysed for this endpoint in this arm.

[5] - Number analysed is the number of subjects evaluated for the endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Average Change From Baseline in Bilirubin at Weeks 16, 20 and 24 in Part 2

End point title	Average Change From Baseline in Bilirubin at Weeks 16, 20 and 24 in Part 2

End point description:

The change from baseline in bilirubin levels was summarised. Bilirubin is a marker for haemolysis. Data presented represents the average change from baseline at Week 16, 20 and Week 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. Full analysis set included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Baseline, Part 2: Weeks 16, 20, 24

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[6]	37[7]		
Units: micromoles per litre (µmol/L)				
least squares mean (standard error)	5.10 (± 4.061)	-21.16 (± 4.228)		

Notes:

[6] - Number analysed is the number of subjects evaluated for the endpoint.

[7] - Number analysed is the number of subjects evaluated for the endpoint.

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 in Part 2

End point title	Average Change From Baseline in Lactic Acid Dehydrogenase (LDH) at Weeks 16, 20 and 24 in Part 2

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 Week 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. Full analysis set included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Baseline, Part 2: Weeks 16, 20, 24

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	39[8]		
Units: units per litre (U/L)				
least squares mean (standard error)	-21.18 (± 16.040)	-91.99 (± 16.222)		

Notes:

[8] - Number analysed is the number of subjects evaluated for the endpoint.

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 in Part 2

End point title	Average Change From Baseline in Haptoglobin at Weeks 16, 20 and 24 in Part 2

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 Week 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. Full analysis set included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Baseline, Part 2: Weeks 16, 20, 24

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
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 in Part 2

End point title	Average Change From Baseline in Reticulocyte Percentages at Weeks 16, 20 and 24 in Part 2

End point description:

The change from baseline in reticulocyte percentage was summarised. Reticulocyte levels are markers for haematopoietic activity. 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. Full analysis set included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Baseline, Part 2: Weeks 16, 20, 24

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: fraction of 1				
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

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. Full analysis set included all subjects who were randomised.

End point type	Secondary

End point timeframe:

Baseline, to Week 24

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[9]	37[10]		
Units: score on a scale				
least squares mean (standard error)	-2.05 (± 0.976)	-5.16 (± 0.955)		

Notes:

[9] - Number analysed is the number of subjects evaluated for the endpoint.

[10] - Number analysed is the number of subjects evaluated for the endpoint.

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

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. Full analysis set included all subjects who were

randomised.

End point type	Secondary

End point timeframe:

Baseline, to Week 24

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[11]	39[12]		
Units: score on a scale				
least squares mean (standard error)	-1.39 (± 1.157)	-4.65 (± 1.123)		

Notes:

[11] - Number analysed is the number of subjects evaluated for the endpoint.

[12] - Number analysed is the number of subjects evaluated for the endpoint.

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 Part 1 Day 1 to end of Part 2, including follow-up (up to Day 197)

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: percentage of subjects				
number (not applicable)	89.7	87.5		

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

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. 99999 indicates the standard deviation for AG-348 arm 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 Day 85 (Week 12)

End point values	AG-348 5mg	AG-348 20mg	AG-348 50mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	3	24[13]	
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	565.9 (± 99999)	1481.2 (± 26.9)	2973.3 (± 35.6)	

Notes:

[13] - Number analysed is the number of subjects evaluated for the endpoint.

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

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. 99999 indicates the standard deviation for AG-348 arm 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 Day 85 (Week 12)

End point values	AG-348 5mg	AG-348 20mg	AG-348 50mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	3	26[14]	
Units: nanogram/millilitre (ng/mL)				
geometric mean (geometric coefficient of variation)	156.9 (± 99999)	373.1 (± 13.6)	1033 (± 31.2)	

Notes:

[14] - Number analysed is the number of subjects evaluated for the endpoint.

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

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. 99999 indicates the standard deviation for AG-348 arm due to low number of subject evaluated.

End point type	Secondary

End point timeframe:

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

End point values	AG-348 5mg	AG-348 20mg	AG-348 50mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	3	26[15]	
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)	

Notes:

[15] - Number analysed is the number of subjects evaluated for the endpoint.

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

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. 99999 indicates the standard deviation for AG-348 arm 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 Day 85 (Week 12)

End point values	AG-348 5mg	AG-348 20mg	AG-348 50mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2	3	24[16]	
Units: hours (h)				
geometric mean (geometric coefficient of variation)	7.787 (± 99999)	7.809 (± 4.2)	7.162 (± 28.0)	

Notes:

[16] - Number analysed is the number of subjects evaluated for the endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs) Based on Exposure -Safety Response Relationship

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs) Based on Exposure -Safety Response Relationship

End point description:

This is the relationship between the TEAEs and study drug exposure. Safety analysis set included all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

From Part 1 Day 1 to end of Part 2, including follow-up (up to Day 197)

End point values	Placebo	AG-348		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: subjects				
Insomnia	7	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

F rom signing of informed consent form to end of Part 2, including follow-up (up to Day 197)

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	23.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo to AG-348 tablets, administered orally, at a starting dose of 5 milligrams (mg) twice daily (BID) followed by two sequential dose level increases to 20mg and 50mg BID at Weeks 4 and 8 respectively, for a period of 12 weeks in Part 1. This was followed by the optimised dose BID, as determined by the investigator in Part 1, for a period of 12 weeks in Part 2.

Reporting group title	AG-348

Reporting group description:

Participants received AG-348 tablets, administered orally, at a starting dose of 5 mg BID followed by two sequential dose level increases to 20 mg and 50 mg BID at Weeks 4 and 8 respectively, for a period of 12 weeks in Part 1. This was followed by the optimized dose BID, as determined by investigator in Part 1, for a period of 12 weeks in Part 2.

Serious adverse events	Placebo	AG-348	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 39 (5.13%)	4 / 40 (10.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Obstructive pancreatitis			

subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	AG-348	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 39 (89.74%)	35 / 40 (87.50%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 39 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Hypertension			
subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 39 (10.26%)	5 / 40 (12.50%)	
occurrences (all)	6	5	
Influenza like illness			

subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Breast discomfort			
subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	4	
Dysmenorrhoea			
subjects affected / exposed	3 / 39 (7.69%)	1 / 40 (2.50%)	
occurrences (all)	6	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 39 (10.26%)	3 / 40 (7.50%)	
occurrences (all)	4	3	
Cough			
subjects affected / exposed	2 / 39 (5.13%)	3 / 40 (7.50%)	
occurrences (all)	2	3	
Oropharyngeal pain			
subjects affected / exposed	2 / 39 (5.13%)	3 / 40 (7.50%)	
occurrences (all)	3	4	
Nasal congestion			
subjects affected / exposed	3 / 39 (7.69%)	2 / 40 (5.00%)	
occurrences (all)	5	3	
Rhinitis allergic			
subjects affected / exposed	3 / 39 (7.69%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Epistaxis			
subjects affected / exposed	2 / 39 (5.13%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Psychiatric disorders			
Middle insomnia			
subjects affected / exposed	3 / 39 (7.69%)	3 / 40 (7.50%)	
occurrences (all)	18	3	
Insomnia			

subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Initial insomnia			
subjects affected / exposed	4 / 39 (10.26%)	1 / 40 (2.50%)	
occurrences (all)	4	1	
Stress			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 39 (15.38%)	1 / 40 (2.50%)	
occurrences (all)	7	1	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 39 (7.69%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 39 (2.56%)	2 / 40 (5.00%)	
occurrences (all)	1	3	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 39 (33.33%)	6 / 40 (15.00%)	
occurrences (all)	19	12	
Dizziness			
subjects affected / exposed	3 / 39 (7.69%)	4 / 40 (10.00%)	
occurrences (all)	4	5	
Presyncope			
subjects affected / exposed	1 / 39 (2.56%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Paraesthesia			
subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 39 (23.08%)	7 / 40 (17.50%)	
occurrences (all)	9	11	
Diarrhoea			
subjects affected / exposed	7 / 39 (17.95%)	4 / 40 (10.00%)	
occurrences (all)	8	4	
Abdominal pain			
subjects affected / exposed	2 / 39 (5.13%)	4 / 40 (10.00%)	
occurrences (all)	3	4	
Abdominal distension			
subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Abdominal pain upper			
subjects affected / exposed	3 / 39 (7.69%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 39 (7.69%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Dermatitis acneiform			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Dry skin			
subjects affected / exposed	1 / 39 (2.56%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 39 (7.69%)	5 / 40 (12.50%)	
occurrences (all)	5	5	

Arthralgia			
subjects affected / exposed	2 / 39 (5.13%)	4 / 40 (10.00%)	
occurrences (all)	5	5	
Pain in extremity			
subjects affected / exposed	3 / 39 (7.69%)	2 / 40 (5.00%)	
occurrences (all)	4	2	
Neck pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 39 (15.38%)	5 / 40 (12.50%)	
occurrences (all)	9	6	
Gastroenteritis			
subjects affected / exposed	0 / 39 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Urinary tract infection			
subjects affected / exposed	3 / 39 (7.69%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Upper respiratory tract infection			
subjects affected / exposed	4 / 39 (10.26%)	0 / 40 (0.00%)	
occurrences (all)	4	0	
Oral herpes			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 39 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	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