Clinical trial results:
An Open-Label Study to Evaluate the Efficacy and Safety of AG-348 in Regularly Transfused Adult Subjects With Pyruvate Kinase (PK) Deficiency

Summary

EudraCT number	2017-003803-22
Trial protocol	NL DK GB IE IT ES CZ
Global end of trial date	12 November 2020

Results information

Result version number	v1 (current)
This version publication date	29 November 2021
First version publication date	29 November 2021

Trial information

Trial identification

Sponsor protocol code	AG348-C-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03559699
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	12 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of treatment with AG-348, as assessed by the reduction in transfusion burden.

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	26 June 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Thailand: 2
Worldwide total number of subjects	27
EEA total number of subjects	18

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)	26
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 27 subjects were enrolled and treated in the study which was conducted across multiple sites in 9 countries: United States, Canada, Denmark, France, Ireland, Italy, Netherlands, Thailand, and United Kingdom. The study was conducted from 26 June 2018 to 12 November 2020.

Pre-assignment

Screening details:

Screening was done for a period of 8 weeks 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 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	Not applicable
Blinding used	Not blinded

Arms

Arm title	AG-348

Arm description:

Subjects received 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, for a period of 16 weeks in Part 1. This was followed by optimised dose BID, as determined by the investigator in Part 1, for a period of 24 weeks in Part 2.

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

Dosage and administration details:

AG-348, 5 mg, 20 mg and 50 mg tablets to be administered orally BID in Part 1 and Part 2.

Number of subjects in period 1	AG-348
Started	27
Completed	20
Not completed	7
Lost to follow-up	1
Withdrawal by subject	6

Baseline characteristics

Reporting groups	
Reporting group title	AG-348
Reporting group description:	
Subjects received 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, for a period of 16 weeks in Part 1. This was followed by optimised dose BID, as determined by the investigator in Part 1, for a period of 24 weeks in Part 2.	

Reporting group values	AG-348	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	36.6		
standard deviation	± 13.89	-	
Gender categorical Units: Subjects			
Female	20	20	
Male	7	7	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	20	20	
Unknown or Not Reported	7	7	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	3	3	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	20	20	
More than one race	0	0	
Unknown or Not Reported	4	4	

End points

End points reporting groups

Reporting group title	AG-348

Reporting group description:

Subjects received 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, for a period of 16 weeks in Part 1. This was followed by optimised dose BID, as determined by the investigator in Part 1, for a period of 24 weeks in Part 2.

Primary: Percentage of Subjects Achieving a Reduction in Transfusion Burden in Part 2

End point title	Percentage of Subjects Achieving a Reduction in Transfusion Burden in Part 2[1]

End point description:

Reduction in transfusion burden is defined as a ≥33% reduction in the number of RBC units transfused during the Fixed Dose Period standardised to 24 weeks compared with the historical transfusion burden standardised to 24 weeks (Standardised Control Period). The on-study (Fixed Dose Period) transfusion burden was calculated as the total number of transfused RBC units received in the Fixed Dose Period standardised to 24 weeks. Full analysis set included all subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

From Part 2, Day 1 to Part 2 Week 24

Notes:

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

End point values	AG-348			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage of subjects				
number (confidence interval 95%)	37 (19.4 to 57.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Number of RBC Units Transfused During the Study

End point title	Annualised Number of RBC Units Transfused During the Study

End point description:

The annualised total number of RBC units transfused during the entire study (both Part 1 and Part 2) is reported. It was calculated as the total number of RBC units transfused up to the end of Fixed Dose Period divided by the total number of days from the first dose date until the end date of Fixed Dose Period × 52. Full analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Part 1 Day 1 to Part 2 Week 24

End point values	AG-348			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: RBC units				
arithmetic mean (standard deviation)	11.52 (± 10.543)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Transfusion Episodes in Part 2

End point title	Number of Transfusion Episodes in Part 2

End point description:

This is the number of transfusion episodes in Part 2. The number of transfusion episodes were standardised to 24 weeks. Transfusions received over up to 3 consecutive days were counted as 1 episode. Full analysis set incuded all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From Part 2 Day 1 to Part 2 Week 24

End point values	AG-348			
Subject group type	Reporting group			
Number of subjects analysed	26[2]			
Units: transfusion episodes				
arithmetic mean (standard deviation)	2.88 (± 2.694)			

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Transfusion-Free Participants in Part 2

End point title	Percentage of Transfusion-Free Participants in Part 2

End point description:

Transfusion-free responders are the subjects who were transfusion-free in Part 2. Full analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From Part 2 Day 1 to Part 2 Week 24

End point values	AG-348			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage of subjects				
number (confidence interval 95%)	22.2 (8.6 to 42.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Normal Haemoglobin (Hb) Concentrations in Part 2

End point title	Percentage of Participants Achieving Normal Haemoglobin (Hb) Concentrations in Part 2

End point description:

This is the percentage of subjects who achieved haemoglobin (Hb) concentrations in the normal range at least once, 8 weeks or more after a transfusion in Part 2. Full analysis set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From Part 2 Day 1 to Part 2 Week 24

End point values	AG-348			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage of subjects				
number (confidence interval 95%)	11.1 (2.4 to 29.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs)

End point title	Percentage of Subjects With Adverse Events (AEs)

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 drug. An AE can, therefore, be any unfavourable 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 drug.

End point type	Secondary

End point timeframe:

Through 4 weeks after last dose (approximately Part 2, Week 31)

End point values	AG-348			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: percentage of subjects				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Part 1 Day 1 to end of Part 2, including follow-up (up to Day 197)	
Adverse event reporting additional description:	
Safety analysis set included all subjects who received at least 1 dose of the study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
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, for a period of 16 weeks in Part 1. This was followed by optimised dose BID, as determined by the investigator in Part 1, for a period of 24 weeks in Part 2.	

Serious adverse events	AG-348		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 27 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood Triglyceride Increased			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	AG-348		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 27 (37.04%)		
occurrences (all)	15		
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	6		
Liver iron concentration increased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 27 (37.04%)		
occurrences (all)	14		
Dizziness			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Somnolence			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	10		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	5		

Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3 3 / 27 (11.11%) 5 2 / 27 (7.41%) 2		
Reproductive system and breast disorders Vaginal haemorrhage subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 8 3 / 27 (11.11%) 3		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3		
Psychiatric disorders Initial insomnia subjects affected / exposed occurrences (all) Middle insomnia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3 2 / 27 (7.41%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 6		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Suspected COVID-19 subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4 4 / 27 (14.81%) 5 4 / 27 (14.81%) 7 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2018	• Added markers of iron metabolism to the endpoint of indicators of iron overload • Added an exploratory endpoint for markers of erythropoietic activity • Added an exploratory endpoint for markers of haemolysis • Added an exploratory endpoint for relationship of mitapivat pharmacokinetic and clinical activity • Removed Patient Global Impression of Severity as an exploratory endpoint under health-related quality of life assessments • Revised the dose-escalation restrictions during the Fixed-Dose Period • Revised the instructions for dose optimisation during the Dose Optimisation Period • Revise the language on haemoglobin (Hb) monitoring in relation to the subject's transfusion trigger during the Fixed-Dose Period to make the collection of additional haematology assessments more flexible • Amended the inclusion criterion for renal function • Amended the inclusion criterion for platelet count • Amended the inclusion criterion for contraception requirements and added pregnancy tests every 4-6 weeks • Added an exception for subjects who have genetic findings 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 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 to align with preexisting guidance in the prohibited concomitant medication section of the protocol • Redefined Hb overshoot, and subsequent study treatment dose decrease, to higher than 2 g/dL below the upper limit of normal • Added detailed guidance on re-introducing or escalating study treatment after resolution of a Grade 3 adverse event (AE) that caused study treatment to be stopped or the dose to be reduced
15 October 2018	• 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 language to provide previously ineligible subjects the opportunity to rescreen for enrollment into the study should they become eligible based on an amended protocol • Added new laboratory assessments for iron-related markers and markers of erythropoietic activity • Added collection of historical data for iron chelation therapy, serum iron, serum ferritin, transferrin saturation, and liver iron concentration • Added further details for assessments after a transaminase increase that meets the criteria for an AE of special interest • Removed the use of an Independent Data Monitoring Committee
19 March 2019	• Increased the sample size from "approximately 15-20" to "a minimum of 20, with up to 40 adult subjects". • Revised the central laboratory requirements for additional blood sampling necessary for subjects whose individual transfusion trigger has not been reached. • Increased the length of contraception period for males exposed to mitapivat to cover 1 complete spermatogenesis cycle. • Clarified the central laboratory requirements for urine/serum pregnancy tests.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported