



Clinical trial results:

A Phase 2, Open Label, Randomized, Dose Ranging, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study of AG-348 in Adult Patients With Pyruvate Kinase Deficiency

Summary

EudraCT number	2015-000484-13
Trial protocol	GB FR NL IT
Global end of trial date	02 April 2025

Results information

Result version number	v1
This version publication date	08 April 2026
First version publication date	08 April 2026

Trial information

Trial identification

Sponsor protocol code	AG-348-C-003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02476916
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	02 April 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 April 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Study AG348-C-003 is a multicenter study designed to evaluate the safety and efficacy of different dose levels of AG-348 (mitapivat) in subjects with PK deficiency.

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 2015
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: 4
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Canada: 2
Worldwide total number of subjects	52
EEA total number of subjects	21

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)	52

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study across multiple study sites in 6 countries from 26 June 2015 to 02 April 2025.

Pre-assignment

Screening details:

A total of 52 subjects were enrolled in the Core Period of the study. Subjects were randomized 1:1 to receive AG-348 50 mg or AG-348 300 mg. Subjects who completed the 24-week Core Period, had clinical activity, and tolerated the AG-348 dose entered the Extension Period for up to 102 months.

Period 1

Period 1 title	Core Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AG-348 50 mg BID

Arm description:

Subjects with PK deficiency received AG-348, 50 mg, as initial dose, BID for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to treatment emergent AEs and Hb levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were potentially eligible to immediately roll over to the Extension Period for continued treatment. If subjects chose not to enroll, they were followed up to four weeks after the last dose of AG-348.

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 milligrams (mg), twice daily (BID), administered orally for 24 weeks (Core Period).

Arm title	AG-348 300 mg BID
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Arm description:

Subjects with PK deficiency received AG-348, 300 mg, as initial dose, BID for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to treatment emergent AEs and Hb levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were potentially eligible to immediately roll over to the Extension Period for continued treatment. If subjects chose not to enroll, they were followed up to four weeks after the last dose of AG-348.

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, 300 mg, as initial dose, BID, administered orally for 24 weeks (Core Period).

Number of subjects in period 1	AG-348 50 mg BID	AG-348 300 mg BID
Started	27	25
Completed	21	22
Not completed	6	3
Physician decision	1	1
Adverse Event	2	2
Withdrawal by Subject	3	-

Period 2

Period 2 title	Extension Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AG-348 50 mg BID

Arm description:

Subjects with Pyruvate Kinase (PK) deficiency received AG-348, 50 milligrams (mg), as initial dose, twice daily (BID) for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to treatment emergent adverse events (AEs) and hemoglobin (Hb) levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were rolled over to the Extension Period. During the extension period, subjects continued to receive AG-348 300 mg, BID, up to 102 months.

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, BID, administered orally up to 102 months.

Arm title	AG-348 300 mg BID
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Arm description:

Subjects with PK deficiency received AG-348, 300 mg, as initial dose, BID for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to treatment emergent AEs and Hb levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were rolled over to the Extension Period. During the extension period, subjects continued to receive AG-348 300 mg, BID, up to 102 months.

Arm type	Experimental
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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-348 300 mg, BID, administered orally, up to 102 months.

Number of subjects in period 2^[1]	AG-348 50 mg BID	AG-348 300 mg BID
Started	18	18
Completed	1	2
Not completed	17	16
Physician decision	5	5
Adverse Event	1	-
Non-compliance with study drug	1	1
Withdrawal by Subject	1	-
Approved drug available for indication	5	6
Lost to follow-up	1	1
Reason not specified	3	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Out of 43, 36 participants entered Extension Period.

Baseline characteristics

Reporting groups

Reporting group title	AG-348 50 mg BID
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Reporting group description:

Subjects with PK deficiency received AG-348, 50 mg, as initial dose, BID for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to treatment emergent AEs and Hb levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were potentially eligible to immediately roll over to the Extension Period for continued treatment. If subjects chose not to enroll, they were followed up to four weeks after the last dose of AG-348.

Reporting group title	AG-348 300 mg BID
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Reporting group description:

Subjects with PK deficiency received AG-348, 300 mg, as initial dose, BID for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to treatment emergent AEs and Hb levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were potentially eligible to immediately roll over to the Extension Period for continued treatment. If subjects chose not to enroll, they were followed up to four weeks after the last dose of AG-348.

Reporting group values	AG-348 50 mg BID	AG-348 300 mg BID	Total
Number of subjects	27	25	52
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	30.6	37.6	
standard deviation	± 11.20	± 12.02	-
Gender categorical Units: Subjects			
Female	9	11	20
Male	18	14	32
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	24	23	47
Unknown or Not Reported	3	2	5
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	1	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	22	21	43
Other	1	2	3
Unknown or Not Reported	2	1	3

End points

End points reporting groups

Reporting group title	AG-348 50 mg BID
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Reporting group description:

Subjects with PK deficiency received AG-348, 50 mg, as initial dose, BID for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to treatment emergent AEs and Hb levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were potentially eligible to immediately roll over to the Extension Period for continued treatment. If subjects chose not to enroll, they were followed up to four weeks after the last dose of AG-348.

Reporting group title	AG-348 300 mg BID
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Reporting group description:

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Reporting group title	AG-348 50 mg BID
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Reporting group description:

Subjects with Pyruvate Kinase (PK) deficiency received AG-348, 50 milligrams (mg), as initial dose, twice daily (BID) for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to treatment emergent adverse events (AEs) and hemoglobin (Hb) levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were rolled over to the Extension Period. During the extension period, subjects continued to receive AG-348 300 mg, BID, up to 102 months.

Reporting group title	AG-348 300 mg BID
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Reporting group description:

Subjects with PK deficiency received AG-348, 300 mg, as initial dose, BID for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to treatment emergent AEs and Hb levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were rolled over to the Extension Period. During the extension period, subjects continued to receive AG-348 300 mg, BID, up to 102 months.

Subject analysis set title	AG-348 50 mg BID (Core Period+ Extension Period)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects with PK deficiency received AG-348, 50 mg, as initial dose, BID, for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to AEs and Hb levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were rolled over to the Extension Period. During the extension period, subjects continued to receive AG-348 50 mg, BID, up to 102 months.

Subject analysis set title	AG-348 300 mg BID (Core Period + Extension Period)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects with PK deficiency received AG-348, 300 mg, as initial dose, BID, for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to treatment emergent AEs and Hb levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were rolled over to the Extension Period. During the extension period, subjects continued to receive AG-348 300 mg, BID, up to 102 months.

Primary: Percentage of Subjects Experiencing at Least One Adverse Event (AEs) in the Core Period

End point title	Percentage of Subjects Experiencing at Least One Adverse Event (AEs) in the Core Period ^[1]
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End point description:

An AE was defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered study drug-related. The Safety Analysis Set included all subjects who had received at least one dose of study drug.

End point type	Primary
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End point timeframe:

Up to 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: No formal statistical hypotheses were tested for the primary end point.

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	25		
Units: percentage of subjects				
number (not applicable)	96.3	100		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Experiencing at Least One AE up to Month 102

End point title	Percentage of Subjects Experiencing at Least One AE up to Month 102 ^[2]
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End point description:

An AE was defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered study drug-related. Safety data for cumulative period (Core period and Extension period) has been reported in this outcome measure. The Safety Analysis Set included all participants who had received at least one dose of study drug.

End point type	Primary
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End point timeframe:

Up to Month 102

Notes:

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

Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	AG-348 50 mg BID (Core Period+ Extension Period)	AG-348 300 mg BID (Core Period + Extension Period)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	25		
Units: percentage of subjects				
number (not applicable)	100.0	100.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemoglobin (Hb) Value at Week 24

End point title	Change From Baseline in Hemoglobin (Hb) Value at Week 24
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End point description:

Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Increased Hb values indicate improvement. The Full Analysis Set included all randomised subjects. 'n' indicates number of subjects with evaluable data at the given time-point.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	25		
Units: grams per liter (g/L)				
arithmetic mean (standard deviation)				
Baseline (n=27,25)	92.43 (± 14.760)	86.36 (± 11.668)		
Change at Week 24 (n=21, 23)	13.10 (± 13.644)	16.65 (± 16.874)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Hb Value up to Month 102

End point title	Change From Baseline Hb Value up to Month 102
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End point description:

Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Increased Hb values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure. 'n' indicates number of subjects with evaluable data at the given time-point.

End point type	Secondary
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End point timeframe:

Baseline, Months 12, 36, 60, 84, and 102

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	16		
Units: g/L				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 12, 16)	15.25 (± 16.046)	23.93 (± 18.005)		
Change at Month 36 (n= 7, 11)	23.14 (± 8.212)	25.23 (± 13.009)		
Change at Month 60 (n=7, 11)	22.43 (± 7.606)	28.95 (± 12.712)		
Change at Month 84 (n= 7, 10)	20.14 (± 8.037)	26.92 (± 17.440)		
Change at Month 102 (n=2, 3)	20.92 (± 9.075)	25.50 (± 9.918)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hematocrit at Week 24

End point title	Change From Baseline in Hematocrit at Week 24
End point description: Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Increased hematocrit values indicate improvement. The Full Analysis Set included all randomised subjects. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe: Baseline and Week 24	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	25		
Units: fraction of 1				
arithmetic mean (standard deviation)				
Baseline (n=27,25)	0.2881 (± 0.04494)	0.2693 (± 0.03325)		
Change at Week 24 (n=21,23)	0.0360 (± 0.03916)	0.0444 (± 0.04745)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hematocrit up to Month 102

End point title	Change From Baseline in Hematocrit up to Month 102
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End point description:

Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Increased hematocrit values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure. 'n' indicates number of subjects with evaluable data at the given time-point.

End point type	Secondary
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End point timeframe:

Baseline, Months 12, 36, 60, 84, and 102

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	16		
Units: fraction of 1				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 12, 16)	0.0428 (± 0.04823)	0.0673 (± 0.04854)		
Change at Month 36 (n= 7, 11)	0.0550 (± 0.02836)	0.0598 (± 0.04136)		
Change at Month 60 (n= 7, 11)	0.0565 (± 0.02264)	0.0726 (± 0.03137)		
Change at Month 84 (n=7, 10)	0.0475 (± 0.02330)	0.0690 (± 0.04855)		
Change at Month 102 (n= 2, 2)	0.0482 (± 0.01296)	0.0550 (± 0.04525)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Reticulocyte Count at Week 24

End point title	Change From Baseline in Reticulocyte Count at Week 24
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End point description:

Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased reticulocyte count values indicate improvement. The Full Analysis Set included all randomised subjects. 'n' indicates number of subjects with evaluable data at the given time-point.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	25		
Units: cells * 10 ⁹ /liter				
arithmetic mean (standard deviation)				
Baseline (n=27,25)	459.39 (± 230.621)	474.19 (± 233.868)		
Change at Week 24 (n=21,20)	-73.77 (± 300.971)	-3.96 (± 327.426)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Reticulocyte Count up to Month 102

End point title	Change From Baseline in Reticulocyte Count up to Month 102
End point description:	
Change (absolute change) from baseline will be calculated as post-baseline value - baseline value. Decreased reticulocyte count values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure.. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe:	
Baseline, Months 12, 36, 60, 84, and 102	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	15		
Units: cells * 10 ⁹ /liter				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 11, 15)	-272.65 (± 267.001)	-32.51 (± 348.744)		
Change at Month 36 (n= 7, 11)	-225.83 (± 265.429)	-83.61 (± 291.972)		
Change at Month 60 (n= 7, 10)	-188.36 (± 226.949)	-106.67 (± 291.400)		
Change at Month 84 (n= 7, 9)	-157.58 (± 268.248)	-161.47 (± 263.235)		
Change at Month 102 (n= 2, 3)	-64.06 (± 58.277)	-293.01 (± 300.258)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Haptoglobin at Week 24

End point title	Change From Baseline in Haptoglobin at Week 24
End point description: Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Increased haptoglobin values indicate improvement. The Full Analysis Set included all randomised subjects. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe: Baseline and Week 24	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: g/L				
arithmetic mean (standard deviation)				
Baseline (n=7,4)	0.360 (± 0.2568)	0.460 (± 0.5362)		
Change at Week 24 (n=7,3)	0.230 (± 0.2475)	0.260 (± 0.4503)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Haptoglobin up to Month 102

End point title	Change From Baseline in Haptoglobin up to Month 102
End point description: Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Increased haptoglobin values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure. 'n' indicates number of subjects with evaluable data at the given time-point. '9999' signifies that standard deviation was not estimable for a single subject.	
End point type	Secondary
End point timeframe: Baseline, Months 12, 36, 60, 84, and 102	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: g/L				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 4, 4)	0.343 (± 0.3865)	0.523 (± 0.6261)		
Change at Month 36 (n= 2, 1)	0.135 (± 0.2051)	0.940 (± 9999)		

Change at Month 60 (n = 1, 1)	0.110 (± 9999)	0.710 (± 9999)		
Change at Month 84 (n= 1, 1)	0.760 (± 9999)	1.700 (± 9999)		
Change at Month 102 (n= 1, 1)	0.390 (± 9999)	0.610 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Carboxyhemoglobin (COHb) at Week 24

End point title	Change From Baseline in Carboxyhemoglobin (COHb) at Week 24
End point description: Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased COHb values indicate improvement. The Full Analysis Set included all subjects. Number of subjects analysed is the number of subjects with evaluable data. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe: Baseline and Week 24	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: percentage Hb bound to COHb				
arithmetic mean (standard deviation)				
Baseline (n=18,20)	5.5 (± 1.42)	6.2 (± 2.31)		
Change at Week 24 (n=12,13)	-1.3 (± 2.26)	-0.6 (± 1.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in COHb up to Month 30

End point title	Change From Baseline in COHb up to Month 30
End point description: Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased COHb values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe: Baseline, Months 12, 18, 24, and 30	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	10		
Units: percentage Hb bound to CO				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 7, 10)	0.0 (± 1.73)	-0.1 (± 1.79)		
Change at Month 18 (n= 6, 9)	-0.7 (± 1.63)	-1.1 (± 1.54)		
Change at Month 24 (n= 5, 7)	-1.0 (± 2.00)	-0.6 (± 3.26)		
Change at Month 30 (n= 5, 6)	-0.2 (± 0.84)	-1.2 (± 1.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lactate Dehydrogenase (LDH) at Week 24

End point title	Change From Baseline in Lactate Dehydrogenase (LDH) at Week 24
End point description:	
Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased LDH values indicate improvement. The Full Analysis Set included all randomised subjects. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe:	
Baseline and Week 24	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	25		
Units: units per liter (U/L)				
arithmetic mean (standard deviation)				
Baseline (n=27,25)	287.17 (± 172.172)	257.42 (± 129.110)		
Change at Week 24 (n=21,22)	-36.74 (± 140.291)	-4.89 (± 148.024)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in LDH up to Month 30

End point title	Change From Baseline in LDH up to Month 30
End point description: Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased LDH values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe: Baseline, Months 12, 18, 24, and 30	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	17		
Units: U/L				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 12, 17)	-38.13 (± 137.244)	-33.78 (± 155.946)		
Change at Month 18 (n= 11, 15)	-8.50 (± 185.778)	-29.92 (± 166.593)		
Change at Month 24 (n= 9, 11)	-130.28 (± 209.075)	-76.30 (± 169.040)		
Change at Month 30 (n= 6, 11)	-148.25 (± 174.606)	-73.84 (± 169.661)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Bilirubin at Week 24

End point title	Change From Baseline in Total Bilirubin at Week 24
End point description: Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased total bilirubin values indicate improvement. The Full Analysis Set included all randomised subjects. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe: Baseline and Week 24	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	25		
Units: micromole per liter (umol/L)				
arithmetic mean (standard deviation)				

Baseline (n=27,25)	92.91 (± 53.178)	93.44 (± 54.169)		
Change at Week 24 (n=21,23)	-36.05 (± 34.231)	-49.85 (± 40.027)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Bilirubin up to Month 102

End point title	Change From Baseline in Total Bilirubin up to Month 102
End point description: Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased total bilirubin values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe: Baseline, Months 12, 36, 60, 84, and 102	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	17		
Units: umol/L				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 13, 17)	-45.61 (± 34.686)	-55.86 (± 46.161)		
Change at Month 36 (n= 7, 11)	-41.66 (± 41.309)	-42.14 (± 42.841)		
Change at Month 60 (n= 7, 11)	-39.71 (± 37.754)	-41.78 (± 38.803)		
Change at Month 84 (n= 7, 10)	-47.04 (± 38.220)	-46.81 (± 46.865)		
Change at Month 102 (n= 3, 3)	-65.85 (± 57.731)	-96.16 (± 63.521)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Indirect Bilirubin at Week 24

End point title	Change From Baseline in Indirect Bilirubin at Week 24
End point description: Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased indirect bilirubin values indicate improvement. The Full Analysis Set included all randomised subjects. 'n' indicates number of subjects with evaluable data at the given time-point.	

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

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	25		
Units: umol/L				
arithmetic mean (standard deviation)				
Baseline (n=27,25)	85.74 (± 52.881)	86.64 (± 53.717)		
Change at Week 24 (n=21,20)	-36.69 (± 31.979)	-53.99 (± 40.081)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Indirect Bilirubin up to Month 102

End point title	Change From Baseline in Indirect Bilirubin up to Month 102
End point description:	
Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased indirect bilirubin values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe:	
Baseline, Months 12, 36, 60, 84, and 102	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	17		
Units: umol/L				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 12, 17)	-46.32 (± 35.996)	-54.92 (± 45.237)		
Change at Month 36 (n= 7, 10)	-41.17 (± 42.994)	-45.81 (± 42.396)		
Change at Month 60 (n= 7, 10)	-39.46 (± 39.129)	-45.04 (± 39.308)		
Change at Month 84 (n= 7, 9)	-47.52 (± 39.990)	-49.57 (± 46.674)		
Change at Month 102 (n= 3, 3)	-68.42 (± 58.135)	-95.69 (± 60.128)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Erythropoietin (EPO) at Week 24

End point title	Change From Baseline in Erythropoietin (EPO) at Week 24
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End point description:

Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased EPO values indicate improvement. The Full Analysis Set included all randomised subjects. 'n' indicates number of subjects with evaluable data at the given time-point.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	25		
Units: international units per liter (IU/L)				
arithmetic mean (standard deviation)				
Baseline (n=27,25)	85.45 (± 159.409)	60.90 (± 19.519)		
Change at Week 24 (n=21,22)	-7.11 (± 34.754)	-12.61 (± 26.596)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EPO up to Month 30

End point title	Change From Baseline in EPO up to Month 30
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End point description:

Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased EPO values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure. 'n' indicates number of subjects with evaluable data at the given time-point.

End point type	Secondary
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End point timeframe:

Baseline, Months 12, 18, 24, and 30

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	17		
Units: IU/L				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 13, 17)	10.17 (± 38.685)	-11.09 (± 38.484)		
Change at Month 18 (n= 11, 15)	1.17 (± 33.991)	-18.89 (± 24.148)		
Change at Month 24 (n= 9, 11)	-15.50 (± 28.899)	-26.46 (± 20.701)		
Change at Month 30 (n= 8, 10)	-12.01 (± 15.495)	-21.80 (± 24.400)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hepcidin at Week 24

End point title	Change From Baseline in Hepcidin at Week 24
End point description:	
Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased hepcidin values indicate improvement. The Full Analysis Set included all randomised subjects. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe:	
Baseline and Week 24	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: nanograms per liter (ng/L)				
arithmetic mean (standard deviation)				
Baseline (n=6,6)	9471.7 (± 9501.70)	10708.3 (± 10109.53)		
Change at Week 24 (n=6,5)	-1011.7 (± 6156.16)	-4684.0 (± 5631.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hepcidin up to Month 30

End point title	Change From Baseline in Hepcidin up to Month 30
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End point description:

Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased hepcidin values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure. 'n' indicates number of subjects with evaluable data at the given time-point. '9999' signifies that standard deviation was not estimable for a single subject.

End point type	Secondary
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End point timeframe:

Baseline, Months 12, 18, 24, and 30

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: ng/L				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 4, 5)	-2755.0 (± 12485.25)	-6606.0 (± 8980.10)		
Change at Month 18 (n= 3, 3)	3900.0 (± 3334.29)	-1633.3 (± 864.08)		
Change at Month 24 (n= 3, 1)	7076.7 (± 2918.17)	-7930.0 (± 9999)		
Change at Month 30 (n= 3, 1)	4400.0 (± 3450.93)	-3650.0 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Ferritin at Week 24

End point title	Change From Baseline in Ferritin at Week 24
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End point description:

Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased ferritin values indicate improvement. The Full Analysis Set included all randomised subjects. 'n' indicates number of subjects with evaluable data at the given time-point.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	25		
Units: micrograms per liter (ug/L)				
arithmetic mean (standard deviation)				
Baseline (n=27,25)	857.667 (± 681.0690)	868.600 (± 492.1219)		
Change at Week 24 (n=21,21)	60.333 (± 406.5114)	-7.286 (± 232.9322)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Ferritin up to Month 102

End point title	Change From Baseline in Ferritin up to Month 102
End point description:	
Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased ferritin values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe:	
Baseline, Months 12, 36, 60, 84, and 102	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	17		
Units: ug/L				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 13, 17)	-20.692 (± 207.6064)	2.265 (± 196.0776)		
Change at Month 36 (n = 7, 10)	-25.286 (± 396.5967)	-136.150 (± 136.3716)		
Change at Month 60 (n= 6, 9)	-162.667 (± 615.9044)	-279.944 (± 220.8130)		
Change at Month 84 (n= 6, 9)	136.000 (± 163.1086)	-385.722 (± 285.6371)		
Change at Month 102 (n= 3, 3)	193.333 (± 80.7548)	-361.000 (± 163.9909)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Transferrin Saturation at Week 24

End point title	Change From Baseline in Transferrin Saturation at Week 24
End point description:	
Transferrin saturation is the ratio of serum iron to iron-binding capacity. Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased transferrin saturation values indicate improvement. The Full Analysis Set included all randomised subjects. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe:	
Baseline and Week 24	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	24		
Units: fraction of 1				
arithmetic mean (standard deviation)				
Baseline (n=21,24)	0.501 ($\pm$ 0.2374)	0.643 ($\pm$ 0.2188)		
Change at Week 24 (n=13,18)	-0.055 ($\pm$ 0.1490)	-0.036 ($\pm$ 0.1819)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Transferrin Saturation up to Month 102

End point title	Change From Baseline in Transferrin Saturation up to Month 102
End point description:	
Transferrin saturation is the ratio of serum iron to iron-binding capacity. Change (absolute change) from baseline was calculated as post-baseline value - baseline value. Decreased transferrin saturation values indicate improvement. The Full Analysis Set included all randomised subjects. Number of subjects analysed is the number of subjects with evaluable data for this outcome measure. 'n' indicates number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe:	
Baseline, Months 12, 36, 60, 84, and 102	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: fraction of 1				
arithmetic mean (standard deviation)				
Change at Month 12 (n= 10, 15)	-0.039 ($\pm$ 0.1999)	-0.034 ($\pm$ 0.2431)		

Change at Month 36 (n= 5, 9)	-0.074 (± 0.3472)	-0.067 (± 0.2666)		
Change at Month 60 (n= 4, 7)	0.060 (± 0.2128)	-0.031 (± 0.1483)		
Change at Month 84 (n= 5, 6)	-0.190 (± 0.2176)	0.056 (± 0.1319)		
Change at Month 102 (n= 3, 3)	-0.207 (± 0.4200)	0.117 (± 0.3150)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From Time Zero to the Last Non-zero Concentration (AUC0-t) for AG-348 and Its Metabolite AGI-8702

End point title	Area Under the Concentration-time Curve From Time Zero to the Last Non-zero Concentration (AUC0-t) for AG-348 and Its Metabolite AGI-8702
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End point description:

Subjects with pre-dose concentrations on Day 1 were excluded from the pharmacokinetics analysis, if any. The Pharmacokinetic Analysis Set included all subjects from Core Period, without major protocol violation, who were enrolled and received any dose of study treatment, with sufficient plasma sample or whole blood data to assess pharmacokinetic parameters. Number of subjects analysed is the number of subjects with evaluable data. 'n' indicates the number of subjects with evaluable data at the given time-point.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 4, 8, 12 hours post-dose Day 1 and pre-dose, 0.5, 1, 2, 4, 8 hours post-dose Day 15

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: nanograms*hours per milliliter(hr*ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1: AG-348 (n=5,7)	3287 (± 20.9)	27930 (± 38.1)		
Day 15: AG-348 (n=5,5)	3609 (± 38.2)	11610 (± 11.3)		
Day 1: AGI-8702 (n=5,7)	235.6 (± 32.6)	2637 (± 34.9)		
Day 15: AGI-8702 (n=5,5)	425.8 (± 21.8)	2235 (± 19.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) for AG-348 and Its Metabolite AGI-8702

End point title	Maximum Plasma Concentration (Cmax) for AG-348 and Its Metabolite AGI-8702
End point description: Subjects with pre-dose concentrations on Day 1 were excluded from the pharmacokinetics analysis, if any. The Pharmacokinetic Analysis Set included all subjects from Core Period, without major protocol violation, who were enrolled and received any dose of study treatment, with sufficient plasma sample or whole blood data to assess pharmacokinetic parameters. Number of subjects analysed is the number of subjects with evaluable data. 'n' indicates the number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe: pre-dose, 0.5, 1, 2, 4, 8, 12 hours post-dose Day 1 and pre-dose, 0.5, 1, 2, 4, 8 hours post-dose Day 15	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1: AG-348 (n=5,7)	870.0 (± 9.2)	7606 (± 41.8)		
Day 15: AG-348 (n=5,5)	943.4 (± 30.7)	5259 (± 35.6)		
Day 1: AGI-8702 (n=5,7)	41.03 (± 43.6)	414.7 (± 35.6)		
Day 15: AGI-8702 (n=5,5)	71.94 (± 22.0)	533.7 (± 25.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Peak Plasma Concentration (Tmax) for AG-348 and Its Metabolite AGI-8702

End point title	Time to Reach Peak Plasma Concentration (Tmax) for AG-348 and Its Metabolite AGI-8702
End point description: Subjects with pre-dose concentrations on Day 1 were excluded from the pharmacokinetics analysis, if any. The Pharmacokinetic Analysis Set included all subjects from Core Period, without major protocol violation, who were enrolled and received any dose of study treatment, with sufficient plasma sample or whole blood data to assess pharmacokinetic parameters. Number of subjects analysed is the number of subjects with evaluable data. 'n' indicates the number of subjects with evaluable data at the given time-point.	
End point type	Secondary
End point timeframe: pre-dose, 0.5, 1, 2, 4, 8, 12 hours post-dose Day 1 and pre-dose, 0.5, 1, 2, 4, 8 hours post-dose Day 15	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: hour (hr)				
median (full range (min-max))				
Day 1: AG-348 (n=5,7)	1.92 (0.97 to 2.03)	1.97 (1.00 to 2.08)		
Day 15: AG-348 (n=5,5)	1.00 (0.97 to 1.90)	1.00 (0.42 to 2.00)		
Day 1: AGI-8702 (n=5,7)	2.00 (1.92 to 2.03)	1.97 (1.00 to 2.13)		
Day 15: AGI-8702 (n=5,5)	2.00 (1.95 to 4.00)	1.00 (0.93 to 4.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance at Steady-State (Clss/F) for AG-348 and Its Metabolite AGI-8702

End point title	Apparent Clearance at Steady-State (Clss/F) for AG-348 and Its Metabolite AGI-8702
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End point description:

Subjects with pre-dose concentrations on Day 1 were excluded from the pharmacokinetics analysis, if any. The Pharmacokinetic Analysis Set included all subjects from Core Period, without major protocol violation, who were enrolled and received any dose of study treatment, with sufficient plasma sample or whole blood data to assess pharmacokinetic parameters. Number of subjects analysed is the number of subjects with evaluable data. 'n' indicates the number of subjects with evaluable data at the given time-point.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 4, 8 hours post-dose Day 15

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: liter per hour (L/hr)				
geometric mean (geometric coefficient of variation)				
Day 15: AG-348 (n=5,5)	12.27 (± 40.3)	25.31 (± 11.7)		
Day 15: AGI-8702 (n=3,3)	91.50 (± 31.0)	128.2 (± 18.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline Response Value Over 12 Hours Post-dose (BRmax) for Adenosine Triphosphate (ATP)

End point title	Maximum Change From Baseline Response Value Over 12 Hours Post-dose (BRmax) for Adenosine Triphosphate (ATP)
End point description: Pre-dose concentration observed on Day 1 was used as Baseline for calculation of change from baseline. The Pharmacodynamic (PD) Analysis Set included all subjects from Core Period, without major protocol violation, who were enrolled and received any dose of study treatment, with sufficient plasma sample or whole blood data to assess PD parameters. Number of subjects analysed is the number of subjects with evaluable data.	
End point type	Secondary
End point timeframe: pre-dose, 0.5, 1, 2, 4, 8, 12 hours post-dose Day 1	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	6		
Units: µg/mL				
arithmetic mean (standard deviation)	16.50 (± 11.790)	20.67 (± 6.8896)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline Response Value Over 8 Hours Post-dose at Steady State (BRmax ss) for ATP

End point title	Maximum Change From Baseline Response Value Over 8 Hours Post-dose at Steady State (BRmax ss) for ATP
End point description: Pre-dose concentration observed on Day 1 was used as Baseline for calculation of change from baseline. The PD Analysis Set included all subjects from Core Period, without major protocol violation, who were enrolled and received any dose of study treatment, with sufficient plasma sample or whole blood data to assess PD parameters. Number of subjects analysed is the number of subjects with evaluable data.	
End point type	Secondary
End point timeframe: pre-dose, 0.5, 1, 2, 4, 8 hours post-dose Day 15	

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: µg/mL				
arithmetic mean (standard deviation)	1.500 (± 31.032)	45.50 (± 60.995)		

Statistical analyses

No statistical analyses for this end point

Secondary: BRmax for 2,3 - Diphosphoglycerate (2,3-DPG)

End point title	BRmax for 2,3 - Diphosphoglycerate (2,3-DPG)
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End point description:

Pre-dose concentration observed on Day 1 was used as Baseline for calculation of change from baseline. The PD Analysis Set included all participants from Core Period, without major protocol violation, who were enrolled and received any dose of study treatment, with sufficient plasma sample or whole blood data to assess PD parameters. Number of subjects analysed is the number of subjects with evaluable data.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 4, 8, 12 hours post-dose Day 1

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	7		
Units: µg/mL				
arithmetic mean (standard deviation)	42.25 (± 38.836)	59.57 (± 58.569)		

Statistical analyses

No statistical analyses for this end point

Secondary: BRmax ss for 2,3-DPG

End point title	BRmax ss for 2,3-DPG
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End point description:

Pre-dose concentration observed on Day 1 was used as Baseline for calculation of change from baseline. The PD Analysis Set included all participants from Core Period, without major protocol violation, who were enrolled and received any dose of study treatment, with sufficient plasma sample or whole blood data to assess PD parameters. Number of subjects analysed is the number of subjects with evaluable data.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 4, 8 hours post-dose Day 15

End point values	AG-348 50 mg BID	AG-348 300 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: µg/mL				
arithmetic mean (standard deviation)	-65.50 (± 69.745)	8.200 (± 195.13)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Month 102

Adverse event reporting additional description:

The Safety Analysis Set included all subjects who had received at least one dose of study drug. As pre-specified in Protocol, cumulative Safety data for Core period and Extension period was reported.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.1
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Reporting groups

Reporting group title	AG-348 50 mg BID (Core Period+ Extension Period)
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Reporting group description:

Subjects with PK deficiency received AG-348, 50 mg, as initial dose, BID, for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to AEs and Hb levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were rolled over to the Extension Period. During the extension period, subjects continued to receive AG-348 50 mg, BID, up to 102 months.

Reporting group title	AG-348 300 mg BID (Core Period + Extension Period)
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Reporting group description:

Subjects with PK deficiency received AG-348, 300 mg, as initial dose, BID, for 24 weeks (Core Period). Subjects were assigned to initial doses, however, over the course of the Core Period were treated across a range of doses due to treatment emergent AEs and Hb levels exceeding mid-point of sex-adjusted ranges. At the Week 24 visit, Core Period subjects who had safely tolerated AG-348 and demonstrated clinical activity in response to AG-348 were rolled over to the Extension Period. During the extension period, subjects continued to receive AG-348 300 mg, BID, up to 102 months.

Serious adverse events	AG-348 50 mg BID (Core Period+ Extension Period)	AG-348 300 mg BID (Core Period + Extension Period)	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 27 (44.44%)	7 / 25 (28.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fibula fracture			

subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	2 / 27 (7.41%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Inguinal hernia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Initial insomnia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (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			
Fracture delayed union			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infected bite			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected COVID-19			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	AG-348 50 mg BID (Core Period+ Extension Period)	AG-348 300 mg BID (Core Period + Extension Period)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)	25 / 25 (100.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 27 (7.41%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Hot flush			
subjects affected / exposed	2 / 27 (7.41%)	7 / 25 (28.00%)	
occurrences (all)	2	7	

Hypertension subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 7	
Superficial vein thrombosis subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3	0 / 25 (0.00%) 0	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 6	4 / 25 (16.00%) 4	
Chest discomfort subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	6 / 25 (24.00%) 8	
Fatigue subjects affected / exposed occurrences (all)	7 / 27 (25.93%) 11	8 / 25 (32.00%) 39	
Influenza like illness subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	2 / 25 (8.00%) 2	
Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	3 / 25 (12.00%) 5	
Pain subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 4	
Pyrexia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	9 / 25 (36.00%) 15	
Chills subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 25 (4.00%) 1	
Peripheral swelling subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 2	
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 3	
Reproductive system and breast disorders			
Dysmenorrhoea subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	4 / 25 (16.00%) 12	
Breast enlargement subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 7	
Heavy menstrual bleeding subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 18	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 9	7 / 25 (28.00%) 14	
Dyspnoea subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	6 / 25 (24.00%) 9	
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	3 / 25 (12.00%) 4	
Epistaxis subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	3 / 25 (12.00%) 6	
Nasal congestion subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 5	1 / 25 (4.00%) 3	
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 6	5 / 25 (20.00%) 6	
Sneezing subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 25 (0.00%) 0	
Psychiatric disorders			

Initial insomnia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	2 / 25 (8.00%) 3	
Insomnia subjects affected / exposed occurrences (all)	7 / 27 (25.93%) 9	16 / 25 (64.00%) 30	
Middle insomnia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 4	
Anxiety subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 4	2 / 25 (8.00%) 2	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	4 / 25 (16.00%) 6	
Blood bilirubin increased subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 4	1 / 25 (4.00%) 3	
Blood triglycerides increased subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 4	0 / 25 (0.00%) 0	
Haemoglobin decreased subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	2 / 25 (8.00%) 2	
Haemoglobin increased subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 2	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3	2 / 25 (8.00%) 2	
Injury, poisoning and procedural complications Scratch subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 2	
Cardiac disorders			

Palpitations subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	3 / 25 (12.00%) 5	
Nervous system disorders			
Anosmia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 25 (0.00%) 0	
Dizziness subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 7	5 / 25 (20.00%) 18	
Headache subjects affected / exposed occurrences (all)	13 / 27 (48.15%) 34	15 / 25 (60.00%) 54	
Paraesthesia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 4	4 / 25 (16.00%) 5	
Taste Disorder subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 2	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 25 (4.00%) 5	
Lymphadenopathy subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 25 (0.00%) 0	
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 2	
Haemolysis subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 2	
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	2 / 25 (8.00%) 2	
Ear congestion			

subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Ear pain			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 27 (7.41%)	5 / 25 (20.00%)	
occurrences (all)	2	8	
Abdominal pain upper			
subjects affected / exposed	0 / 27 (0.00%)	5 / 25 (20.00%)	
occurrences (all)	0	7	
Diarrhoea			
subjects affected / exposed	6 / 27 (22.22%)	6 / 25 (24.00%)	
occurrences (all)	9	13	
Dyspepsia			
subjects affected / exposed	3 / 27 (11.11%)	4 / 25 (16.00%)	
occurrences (all)	5	7	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	4	
Nausea			
subjects affected / exposed	12 / 27 (44.44%)	12 / 25 (48.00%)	
occurrences (all)	19	20	
Vomiting			
subjects affected / exposed	3 / 27 (11.11%)	8 / 25 (32.00%)	
occurrences (all)	4	8	
Dry Mouth			
subjects affected / exposed	2 / 27 (7.41%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			

Ocular icterus subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 4	1 / 25 (4.00%) 1	
Skin and subcutaneous tissue disorders			
Night sweats subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	4 / 25 (16.00%) 5	
Pruritus subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	4 / 25 (16.00%) 8	
Rash subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2	4 / 25 (16.00%) 7	
Skin ulcer subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	3 / 25 (12.00%) 5	
Rash maculo-papular subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	2 / 25 (8.00%) 4	
Dermatitis contact subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 25 (0.00%) 0	
Dry skin subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 25 (0.00%) 0	
Skin lesion subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 25 (8.00%) 2	
Renal and urinary disorders			
Chromaturia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	3 / 25 (12.00%) 3	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 6	5 / 25 (20.00%) 21	

Back pain			
subjects affected / exposed	6 / 27 (22.22%)	5 / 25 (20.00%)	
occurrences (all)	8	5	
Muscular weakness			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	5	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 27 (3.70%)	5 / 25 (20.00%)	
occurrences (all)	1	5	
Myalgia			
subjects affected / exposed	3 / 27 (11.11%)	2 / 25 (8.00%)	
occurrences (all)	4	3	
Osteopenia			
subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Pain in extremity			
subjects affected / exposed	4 / 27 (14.81%)	2 / 25 (8.00%)	
occurrences (all)	6	17	
Tendonitis			
subjects affected / exposed	0 / 27 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Muscle spasms			
subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Limb discomfort			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Neck pain			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Infections and infestations			
COVID-19			
subjects affected / exposed	3 / 27 (11.11%)	5 / 25 (20.00%)	
occurrences (all)	3	5	
Gastroenteritis			

subjects affected / exposed	3 / 27 (11.11%)	4 / 25 (16.00%)	
occurrences (all)	4	5	
Gastroenteritis viral			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Herpes simplex			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	7 / 27 (25.93%)	2 / 25 (8.00%)	
occurrences (all)	9	2	
Nasopharyngitis			
subjects affected / exposed	11 / 27 (40.74%)	9 / 25 (36.00%)	
occurrences (all)	12	17	
Sinusitis			
subjects affected / exposed	3 / 27 (11.11%)	3 / 25 (12.00%)	
occurrences (all)	3	3	
Upper respiratory tract infection			
subjects affected / exposed	3 / 27 (11.11%)	3 / 25 (12.00%)	
occurrences (all)	9	11	
Urinary tract infection			
subjects affected / exposed	2 / 27 (7.41%)	3 / 25 (12.00%)	
occurrences (all)	2	3	
Rhinitis			
subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Pharyngitis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 27 (3.70%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Hypertriglyceridaemia			
subjects affected / exposed	5 / 27 (18.52%)	4 / 25 (16.00%)	
occurrences (all)	15	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2015	• Corrected errors in the summary of clinical data, safety section. • Added new safety assessment of dual-energy x-ray absorptiometry (DXA) scans (hip and spine) to monitor bone measure density.
05 August 2015	• Added new dosage form of 5 mg capsules. • Updated Inclusion Criteria #13 and #16 to include a revised definition of abstinence. • Updated Exclusion Criterion #11 to clarify rules surrounding glucocorticoids. • Updated clinical data from studies of AG-348 in healthy volunteers. • Added text to explain what Agios will do in case of new, unexpected pre-clinical toxicology findings. • Clarified dose modifications for safety. • Added justification for duration of treatment. • Added clarifications for Day 8 and Day 22 assessments, if being performed by the patient's primary care physician. • Added an additional time point to the complete blood count assessments and removed a PK/PD sampling timepoint. • Updated drug-drug interaction recommendations and prohibited concomitant medications. • Added new safety assessments of 25-hydroxy vitamin D2 and D3 to provide additional context for interpreting any observed changes in DXA scan results and markers of bone turnover, menstrual cycle diary to monitor hormonal changes, and serum osteocalcin-N-mid (removed serum N-terminal telopeptide) because of greater clinical experience with the former than the latter. Added neurological assessment to physical examination.
10 November 2015	• Clearly delineated the first 24 weeks of the study (Core Period) from the safety extension portion of the study (Extension Period). • Added details regarding the Extension Period of the study including objectives, inclusion/exclusion criteria, assessments, duration, and statistical analyses. • Inclusion Criteria #5 and #9 was clarified for the Core Period.
30 March 2016	• Dose modification language was adjusted to account for increases in hemoglobin concentrations. • New assessments of clinical activity of end tidal carbon monoxide (at select sites during the Core Period) and hepcidin were added. • Screening Period was extended to 42 days to better accommodate the turnaround time required for certain specialty laboratory examinations; clarifications were made surrounding recording of concomitant medications during this time period. • Inclusion/exclusion criteria were modified to allow for local laboratory evaluation of pyruvate kinase enzyme activity and G6PD; PKR genotyping from another laboratory will be allowed for enrollment, but genotype must be confirmed by the central laboratory; additional changes were made to other criteria for clarity. • Option for intra-patient dose escalation was added. • Unblinded hormone data from Study AG348-C-002 was added. • Corticosteroids were eliminated from the list of prohibited medications because the likelihood of clinically significant pharmacokinetic interaction between corticosteroids and AG-348 is considered low.

30 June 2017	• Implement within the Extension Period of the study a gradual dose-taper regimen used to identify the optimal maintenance dose for each subject, with corresponding new secondary study objective, rationale, schedule of assessments, and analysis methodology. • Updated information regarding identified and potential risks associated with AG-348, as presented in Version 4.0 of the Investigator's Brochure (22 May 2017). • Incorporated updated toxicology data from nonclinical studies of AG-348 and updated safety and efficacy data from the current study. • Identified a new adverse event of special interest, transaminase increase, and added both a corresponding safety measure/endpoint and corresponding new reporting guidance. • Updated AG-348 dose discontinuation and modification directives. • Added guidance for 2 new concomitant therapy categories: sensitive CYP2B6 substrates and proton-pump inhibitors/H2-receptor antagonists.
14 December 2017	• Added 2 years to the Extension Period (total of up to 4 years). • Introduced a tablet formulation of AG-348. • Removed pharmacokinetic assessments from the Extension Period. • Reduced the number of pharmacodynamic assessments during the Extension Period. • Added a criterion for withdrawal from the Extension Period for subjects who have not had a robust and sustained increase in hemoglobin. • Removed withdrawal criterion for pregnancy to allow pregnant subjects to remain on study, but off treatment. • Added a dose-taper regimen to support discontinuation of AG-348.
04 September 2019	• Simplified the recommended dose taper for discontinuation of study drug. • Extended the duration of the study from 4 years to 8 years following completion of the Core Period. • Removed strict avoidance of concomitant transfusions. • Added further details for assessments following a transaminase increase that meet the criteria for an AESI. • Increased the length of the contraception period for males exposed to study treatment and the pregnancy reporting follow-up in female partners of male subjects. • Reduced the number of DRT reviews during the Extension Period.
27 August 2020	• The Data Review Team (DRT) is no longer required to meet at least annually if there are no subjects still being treated in the Core Period, and the only subjects on treatment are those in the Extension Period. • Telemedicine visits and direct-to-subject shipment of study drug were implemented in the Extension Period (every other visit starting Month 75) to alleviate the burden on subjects associated with on-site study visits. • Photosensitivity was removed from the list of potential risks associated with AG-348 based on the results of a neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts. • Guidance on allowed modifications to study conduct during declared public health emergencies and natural disasters was added for situations during which adherence to protocol-specified procedures is impeded, such as the COVID-19 pandemic. • Management of concomitant therapy was updated per the AG-348 Investigator's Brochure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported