



Clinical trial results:

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

Summary

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

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 24 October 2021 |
| First version publication date | 24 October 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | AG348-C-006 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03548220 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 October 2020 |
| Is this the analysis of the primary completion data? | No |

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

| | |
|----------|---|
| In utero | 0 |
|----------|---|

| | |
|---|----|
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 76 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

Screening was done for a period of 42 days after the subject provided the informed consent. Investigators determined if the subjects met all the inclusion criteria and none of the exclusion criteria to enroll in Part 1: Dose Optimisation Period to receive AG-348 or placebo to determine the optimised dose followed by Part 2: Fixed Dose Period.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|--------|
| Arm title | AG-348 |
|------------------|--------|

Arm description:

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

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

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

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

End points

End points reporting groups

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

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

| | |
|---|---|
| End point title | Percentage of Subjects Achieving a Haemoglobin (Hb) Response (HR) in Part 2 |
| End point description: Haemoglobin response (HR) is defined as a ≥ 1.5 g/dL (0.93 mmol/L) increase in Hb concentration from baseline that is sustained at 2 or more scheduled assessments at Weeks 16, 20, and 24 during the Fixed Dose Period. The baseline Hb concentration is the average of all available Hb concentrations for a subject during the Screening Period up to the first dose of study treatment. Full analysis set included all subjects who were randomised. | |
| End point type | Primary |
| End point timeframe: Baseline, Part 2: Weeks 16, 20, 24 | |

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

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Hemoglobin response Response (HR) in Part 2 |
| Comparison groups | Placebo v AG-348 |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[1] |
| Method | Exact Cochran-Mantel-Haenszel |

Notes:

[1] - 2-sided p-value

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

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

End point description:

This is the change in Hb concentration at Weeks 16, 20 and 24 compared to that of baseline. Data presented represents the average change from baseline at Weeks 16, 20 and 24. Baseline was defined as the average of all screening assessments within 45 (42+3) days before randomisation for subjects randomised and not dosed or before start of study treatment for subjects randomised and dosed. Full analysis set included all subjects who were randomised.

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

End point timeframe:

Baseline, Part 2: Weeks 16, 20, 24

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

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Average Change in Hemoglobin Concentration |
| Comparison groups | AG-348 v Placebo |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed-effect Model Repeated Measure |
| Parameter estimate | LS Mean Difference |
| Point estimate | 18.21 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.41 |
| upper limit | 24.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.913 |

Secondary: Maximum Change From Baseline in Hb Concentration

| | |
|--|--|
| End point title | Maximum Change From Baseline in Hb Concentration |
| End point description: This is the maximum change from baseline in Hb concentration in Part 2. Full analysis set included all subjects who were randomised. | |
| End point type | Secondary |
| End point timeframe: Baseline, Part 2, up to Week 24 | |

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Time to Achieve an Increase in Hb Concentration of 1.5 g/dL or More |
| End point description: This is the time taken to first achieve an increase of haemoglobin concentration of 1.5 g/dL or more from baseline. | |
| End point type | Secondary |
| End point timeframe: Baseline, Part 2, up to Week 24 | |

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The change from baseline in bilirubin levels was summarised. Bilirubin is a marker for haemolysis. Data presented represents the average change from baseline at Week 16, 20 and Week 24. Baseline was defined as the average of all screening assessments within 45 (42+3) days before randomisation for subjects randomised and not dosed or before start of study treatment for subjects randomised and dosed. Full analysis set included all subjects who were randomised.

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

End point timeframe:

Baseline, Part 2: Weeks 16, 20, 24

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

Notes:

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

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

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Average Change From Baseline in Bilirubin |
| Comparison groups | Placebo v AG-348 |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed-effect Model Repeated Measure |
| Parameter estimate | LS Mean Difference |
| Point estimate | -26.26 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -37.82 |
| upper limit | -14.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.788 |

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

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

End point description:

The change from baseline in LDH levels was summarised. LDH is a marker for haemolysis. Data presented represents the average change from baseline at Weeks 16, 20 and Week 24. Baseline was defined as the average of all screening assessments within 45 (42+3) days before randomisation for subjects randomised and not dosed or before start of study treatment for subjects randomised and dosed. Full analysis set included all subjects who were randomised.

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

End point timeframe:

Baseline, Part 2: Weeks 16, 20, 24

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

Notes:

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

Statistical analyses

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

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 22.488 |

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

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

End point description:

The change from baseline in haptoglobin levels were summarised. Haptoglobin levels are markers for haemolysis. Data presented represents the average change from baseline at Weeks 16, 20 and Week 24. Baseline was defined as the average of all screening assessments within 45 (42+3) days before randomisation for subjects randomised and not dosed or before start of study treatment for subjects randomised and dosed. Full analysis set included all subjects who were randomised.

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

End point timeframe:

Baseline, Part 2: Weeks 16, 20, 24

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

Statistical analyses

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

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

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

End point description:

The change from baseline in reticulocyte percentage was summarised. Reticulocyte levels are markers for haematopoietic activity. Baseline was defined as the average of all screening assessments within 45 (42+3) days before randomisation for subjects randomised and not dosed or before start of study treatment for subjects randomised and dosed. Full analysis set included all subjects who were randomised.

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

End point timeframe:

Baseline, Part 2: Weeks 16, 20, 24

| End point values | Placebo | AG-348 | | |
|-------------------------------------|-------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 40 | | |
| Units: fraction of 1 | | | | |
| least squares mean (standard error) | 0.0038 (\pm 0.01390) | -0.0973 (\pm 0.01401) | | |

Statistical analyses

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

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

| | |
|-----------------|--|
| End point title | Change From Baseline in Pyruvate Kinase Deficiency Diary (PKDD) Score at Week 24 |
|-----------------|--|

End point description:

The PKDD is a 7-item patient reported outcome (PRO) measure of the core signs and symptoms

associated with PK deficiency in adults. Subjects rate their experience with symptoms of PK deficiency on the present day. The symptoms include those associated with tiredness, jaundice, bone pain, shortness of breath, and energy level. The score ranges from 25 to 76, with higher scores indicating a higher disease burden. The change from baseline in PKDD weekly scores was evaluated. A negative change from baseline indicates a lower disease burden. Full analysis set included all subjects who were randomised.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, to Week 24 | |

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

Notes:

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

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

Statistical analyses

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

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

| | |
|-----------------|---|
| End point title | Change From Baseline in Pyruvate Kinase Deficiency Impact Assessment (PKDIA) Score at Week 24 |
|-----------------|---|

End point description:

The PKDIA is a 12-item patient reported outcome (PRO) measure of the common impacts of PK deficiency on activities of daily living. Subjects rate how PK deficiency has impacted aspects of daily living in the past 7 days, including impacts on relationships; perceived appearance; work performance; and leisure, social, mental, and physical activities. The score range is 30 to 76, with higher scores indicating a higher disease burden. The change from baseline in PKDIA scores was evaluated. A negative change from baseline indicates a lower disease burden. Full analysis set included all subjects who were

randomised.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, to Week 24 | |

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

Notes:

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

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

Statistical analyses

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

Secondary: Percentage of Subjects With Adverse Events

| | |
|---|--|
| End point title | Percentage of Subjects With Adverse Events |
| End point description: | |
| An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the study treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Safety analysis set included all subjects who received at least 1 dose of study treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| From Part 1 Day 1 to end of Part 2, including follow-up (up to Day 197) | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|------------------------|---|
| End point title | Area Under the Curve From Time 0 to the Last Quantifiable Concentration [AUC(0-last)] for AG-348 at Week 12 |
| End point description: | Pharmacokinetic analysis population consisted of all subjects who were enrolled and received a dose of study medication (mitapivat) with at least 1 non-zero pharmacokinetic plasma concentration of mitapivat at the Week 12 visit. 99999 indicates the standard deviation for AG-348 arm due to low number of subjects evaluated. |
| End point type | Secondary |
| End point timeframe: | Pre-dose, 30 minutes and 1, 2, 4 and 8 hours post-dose Day 85 (Week 12) |

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|------------------------|---|
| End point title | Maximum Plasma Concentration (Cmax) for AG-348 |
| End point description: | Pharmacokinetic analysis population consisted of all subjects who were enrolled and received a dose of study medication (mitapivat) with at least 1 non-zero pharmacokinetic plasma concentration of mitapivat at the Week 12 visit. 99999 indicates the standard deviation for AG-348 arm due to low number of subjects evaluated. |
| End point type | Secondary |

End point timeframe:

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|--------------------------------|
| End point title | Time to Cmax (Tmax) for AG-348 |
| End point description: Pharmacokinetic analysis population consisted of all subjects who were enrolled and received a dose of study medication (mitapivat) with at least 1 non-zero pharmacokinetic plasma concentration of mitapivat at the Week 12 visit. 99999 indicates the standard deviation for AG-348 arm due to low number of subject evaluated. | |
| End point type | Secondary |
| End point timeframe: Pre-dose, 30 minutes and 1, 2, 4 and 8 hours post-dose Day 85 (Week 12) | |

| End point values | AG-348 5mg | AG-348 20mg | AG-348 50mg | |
|-------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 2 | 3 | 26 ^[15] | |
| Units: hours (h) | | | | |
| median (full range (min-max)) | 0.75 (0.50 to 1.00) | 1.02 (0.92 to 2.17) | 0.50 (0.42 to 1.92) | |

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|--|
| End point title | Time to Last Measurable Concentration (Tlast) for AG-348 |
| End point description: Pharmacokinetic analysis population consisted of all subjects who were enrolled and received a dose of study medication (mitapivat) with at least 1 non-zero pharmacokinetic plasma concentration of mitapivat at the Week 12 visit. 99999 indicates the standard deviation for AG-348 arm due to low number of subjects evaluated. | |

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Pre-dose, 30 minutes and 1, 2, 4 and 8 hours post-dose Day 85 (Week 12) | |

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

| | |
|-----------------------|--------|
| Reporting group title | AG-348 |
|-----------------------|--------|

Reporting group description:

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 26 February 2018 | <p>Removed dose escalation restrictions after the Week 8 Visit.</p> <ul style="list-style-type: none">• Added detailed guidance on re-introducing or escalating study treatment after resolution of a Grade 3 AE that caused study treatment to be stopped or reduced.• Removed the requirement that subjects must be receiving study treatment at Week 24 to be potentially eligible for an extension study.• Added an exclusion criterion to exclude subjects who have not stopped using haematopoietic stimulating agents at least 28 days before the first dose of study treatment.• Added clarity to the dose modification guidance for Grade 3 and Grade 4 AEs that are deemed by the Investigator to be related to study treatment.• Added new laboratory assessments for biomarkers (iron-related markers, known markers of erythropoietic activity, circulating haeme, and to be identified markers of iron metabolism or erythropoiesis). |
| 15 August 2018 | <p>Consolidated iron-related secondary and exploratory endpoints into 1 exploratory endpoint for markers of iron metabolism.</p> <ul style="list-style-type: none">• Revised the instructions for dose optimisation.• Clarified that unblinding before database lock will occur only in the subjects who enter the planned mitapivat extension study and that subjects undergoing a dose taper should remain blinded through the taper.• Amended the inclusion criterion for renal function.• Amended the absolute neutrophil count (ANC) and platelet count inclusion criteria to be assessed via 2 measurements.• Amended the inclusion criterion for contraception requirements and added monthly pregnancy tests for applicable subjects.• Added an exception for subjects who have concurrent disorders that in isolation are predicted to be insufficient to explain the observed clinical phenotype to the exclusion criterion for congenital or genetic disorders.• Corrected the exclusion criterion for splenectomy to require subjects to wait at least 12 months after splenectomy before starting screening.• Added a subsection under Section 9.3, Blinding, to provide details on handling of restricted data and to add the role of an Independent Medical Monitor to handle restricted data.• Amended the unblinding language such that the unblinding of a subject for a medical emergency or pregnancy does not require confirmation by the Sponsor's Medical Monitor.• Redefined the definition of Hb overshoot, and subsequent study treatment dose decrease, to higher than 20 g/L (2 g/dL) below the upper limit of normal (ULN).• Added historical data for iron chelation therapy, iron serum, transferrin saturation, and liver iron concentration (LIC) and removed some iron-related laboratory assessments.• Added further details for assessments after a transaminase increase |

| | |
|----------------|---|
| 14 August 2019 | <p>Revised the dose optimisation language to allow dosing decisions to be based on results from local laboratories at the Week 4 and Week 8 Visit</p> <ul style="list-style-type: none"> • Revised the inclusion criterion for platelet count • Increased the length of the contraception period for males exposed to study treatment to cover 1 complete spermatogenesis cycle • Revised the handling of restricted data such that the subject's dose levels were no longer maintained as part of the restricted data and hormone data were considered restricted data for Investigators • Removed the option for a rapid dose taper and simplified the recommended gradual dose taper • Added language to provide previously ineligible subjects the opportunity to rescreen for enrollment into the study should they become eligible based on an amended protocol • Revised the requirements for clinical laboratory results, allowing Investigators the flexibility to use local laboratory results when results from central laboratories are not available • Added further details for assessments after a transaminase increase that meet the criteria for an AESI • Added ability to extend the Screening Period duration beyond 42 days |
|----------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported