# Clinical trial results:
# Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of two doses (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 24 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis

## Summary

| | |
|---|---|
| EudraCT number | 2021-001285-38 |
| Trial protocol | NL BE IT AT DE FR ES DK PT HR |
| Global end of trial date | 03 May 2024 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 May 2025 |
| First version publication date | 21 May 2025 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 1366-0021 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 018002430127, clintriage.rdg@boehringer-ingelheim.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 August 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 02 May 2024 |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 May 2024 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to estimate the mean difference between treatment groups with placebo in the percentage change in hepatic venous pressure gradient (HVPG) from baseline, measured after 24 weeks. Safety and tolerability were also investigated.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all subjects as required.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 18 May 2022 |
| 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 | Argentina: 8 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | China: 16 |
| Country: Number of subjects enrolled | Croatia: 3 |
| Country: Number of subjects enrolled | Denmark: 2 |
| Country: Number of subjects enrolled | France: 4 |
| Country: Number of subjects enrolled | Germany: 12 |
| Country: Number of subjects enrolled | Israel: 2 |
| Country: Number of subjects enrolled | Italy: 13 |
| Country: Number of subjects enrolled | Japan: 8 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Portugal: 3 |
| Country: Number of subjects enrolled | Romania: 24 |
| Country: Number of subjects enrolled | Singapore: 2 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 5 |
| Country: Number of subjects enrolled | Spain: 5 |
| Country: Number of subjects enrolled | Switzerland: 2 |

| | |
|---|---|
| Country: Number of subjects enrolled | Taiwan: 2 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | United States: 33 |
| Worldwide total number of subjects | 157 |
| EEA total number of subjects | 74 |

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) | 119 |
| From 65 to 84 years | 38 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

In this multicentre trial, patients with compensated alcoholic cirrhosis and significant portal hypertension were randomized to receive one of two avenciguat doses or placebo, all alongside standard care. The primary endpoint was the change in hepatic venous pressure gradient (HVPG) at 24 weeks. Safety and tolerability were also assessed.

### Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

### 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, Monitor, Data analyst, Carer, Assessor |

### Arms

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

Arm description:

Subjects in this dose group received matching placebo twice daily (BID) throughout the study period. At Visit 2 (Week 1), each dose consisted of one 1 mg placebo tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), a pseudo up-titration was implemented, maintaining the same tablets (one 1 mg and one 2 mg placebo per dose) for blinding. From Visit 4 onward (Week 3+), a second pseudo up-titration adjusted the dose to one 2 mg placebo tablet and one 3 mg placebo tablet per dose (four tablets daily). All doses were taken with water, with or without food.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo matching |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects in this dose group received matching placebo twice daily (BID) throughout the study period. At Visit 2 (Week 1), each dose consisted of one 1 mg placebo tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), a pseudo up-titration was implemented, maintaining the same tablets (one 1 mg and one 2 mg placebo per dose) for blinding. From Visit 4 onward (Week 3+), a second pseudo up-titration adjusted the dose to one 2 mg placebo tablet and one 3 mg placebo tablet per dose (four tablets daily). All doses were taken with water, with or without food.

| | |
|---|---|
| **Arm title** | Avenciguat 2 mg BID |

Arm description:

Subjects received Avenciguat combined with matching placebo tablets twice daily (BID). At Visit 2 (Week 1), each dose included one 1 mg Avenciguat tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), the dose was up titrated to 2 mg Avenciguat BID (one 1 mg placebo tablet and one 2 mg Avenciguat tablet (four tablets daily)). From Visit 4 onward (Week 3+), a pseudo up-titration was applied, with participants taking one 2 mg Avenciguat tablet and one 3 mg placebo tablet per dose (four tablets daily) to maintain blinding. This regimen continued for 24 weeks, with doses taken with water, with or without food.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Avenciguat 2 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received Avenciguat twice daily (BID). At Visit 2 (Week 1), each dose included one 1 mg Avenciguat tablet. At Visit 3 (Week 2), the dose was up-titrated to 2 mg Avenciguat BID (one 2 mg active tablet). From Visit 4 onward (Week 3+), participants took one 2 mg Avenciguat tablet per dose. This regimen continued for 24 weeks, with doses taken with water, with or without food.

| | |
|---|---|
| **Arm title** | Avenciguat 3 mg BID |

Arm description:

Subjects received Avenciguat with matching placebo tablets twice daily (BID). At Visit 2 (Week 1), each dose contained one 1 mg Avenciguat tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), the dose was up titrated to 2 mg Avenciguat BID (one 1 mg placebo tablet and one 2 mg active tablet (four tablets daily)). From Visit 4 onward (Week 3+), the dose was further up titrated to 3 mg Avenciguat BID (one 2 mg placebo tablet and one 3 mg active tablet per dose (four tablets daily)). This regimen was maintained for 24 weeks, with doses taken with water, with or without food.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Avenciguat 3 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received Avenciguat twice daily (BID). At Visit 2 (Week 1), each dose contained one 1 mg Avenciguat tablet. At Visit 3 (Week 2), the dose was up-titrated to 2 mg Avenciguat BID (one 2 mg active tablet). From Visit 4 onward (Week 3+), the dose was further up-titrated to 3 mg Avenciguat BID (one 3 mg active tablet per dose). This regimen was maintained for 24 weeks, with doses taken with water, with or without food.

| **Number of subjects in period 1[1]** | Placebo | Avenciguat 2 mg BID | Avenciguat 3 mg BID |
|---|---|---|---|
| Started | 26 | 27 | 27 |
| Treated | 25 | 27 | 27 |
| Completed | 19 | 23 | 17 |
| Not completed | 7 | 4 | 10 |
| Adverse event, non-fatal | 3 | - | 6 |
| Subject decision | - | - | 1 |
| Study terminated by sponsor | 3 | 3 | 2 |
| Withdrawal of consent | - | 1 | 1 |
| Randomised in error and was not treated | 1 | - | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all subjects screened were enrolled and randomized into the trial.

## Baseline characteristics

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

Reporting group description:

Subjects in this dose group received matching placebo twice daily (BID) throughout the study period. At Visit 2 (Week 1), each dose consisted of one 1 mg placebo tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), a pseudo up-titration was implemented, maintaining the same tablets (one 1 mg and one 2 mg placebo per dose) for blinding. From Visit 4 onward (Week 3+), a second pseudo up-titration adjusted the dose to one 2 mg placebo tablet and one 3 mg placebo tablet per dose (four tablets daily). All doses were taken with water, with or without food.

| Reporting group title | Avenciguat 2 mg BID |
|---|---|

Reporting group description:

Subjects received Avenciguat combined with matching placebo tablets twice daily (BID). At Visit 2 (Week 1), each dose included one 1 mg Avenciguat tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), the dose was up titrated to 2 mg Avenciguat BID (one 1 mg placebo tablet and one 2 mg Avenciguat tablet (four tablets daily)). From Visit 4 onward (Week 3+), a pseudo up-titration was applied, with participants taking one 2 mg Avenciguat tablet and one 3 mg placebo tablet per dose (four tablets daily) to maintain blinding. This regimen continued for 24 weeks, with doses taken with water, with or without food.

| Reporting group title | Avenciguat 3 mg BID |
|---|---|

Reporting group description:

Subjects received Avenciguat with matching placebo tablets twice daily (BID). At Visit 2 (Week 1), each dose contained one 1 mg Avenciguat tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), the dose was up titrated to 2 mg Avenciguat BID (one 1 mg placebo tablet and one 2 mg active tablet (four tablets daily)). From Visit 4 onward (Week 3+), the dose was further up titrated to 3 mg Avenciguat BID (one 2 mg placebo tablet and one 3 mg active tablet per dose (four tablets daily)). This regimen was maintained for 24 weeks, with doses taken with water, with or without food.

| Reporting group values | Placebo | Avenciguat 2 mg BID | Avenciguat 3 mg BID |
|---|---|---|---|
| Number of subjects | 26 | 27 | 27 |
| Age categorical | | | |
| Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 21 | 22 | 19 |
| From 65-84 years | 5 | 5 | 8 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |
| Units: years | | | |
| arithmetic mean | 57.8 | 56.6 | 57.1 |
| standard deviation | ± 8.1 | ± 9.2 | ± 10.9 |

| | | | |
|---|---|---|---|
| Sex: Female, Male | | | |
| Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |
| Units: Subjects | | | |
| Female | 9 | 9 | 4 |
| Male | 17 | 18 | 23 |
| Race (NIH/OMB) | | | |
| Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 6 | 6 | 6 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 20 | 21 | 21 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 4 | 9 | 3 |
| Not Hispanic or Latino | 22 | 18 | 24 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Baseline hepatic venous pressure gradient (HVPG) | | | |
| Mean hepatic venous pressure gradient (HVPG) at baseline.<br><br>Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |
| Units: Millimeter mercury (mmHg) | | | |
| arithmetic mean | 15.11 | 14.95 | 14.61 |
| standard deviation | ± 4.10 | ± 4.27 | ± 4.07 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 80 | | |
| Age categorical | | | |
| Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 62 | | |
| From 65-84 years | 18 | | |
| 85 years and over | 0 | | |
| Age Continuous | | | |
| Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |

| | | | |
|---|---|---|---|
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

| | | | |
|---|---|---|---|
| Sex: Female, Male | | | |
| Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |
| Units: Subjects | | | |
| Female | 22 | | |
| Male | 58 | | |
| Race (NIH/OMB) | | | |
| Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 18 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 0 | | |
| White | 62 | | |
| More than one race | 0 | | |
| Unknown or Not Reported | 0 | | |
| Ethnicity (NIH/OMB) | | | |
| Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 16 | | |
| Not Hispanic or Latino | 64 | | |
| Unknown or Not Reported | 0 | | |
| Baseline hepatic venous pressure gradient (HVPG) | | | |
| Mean hepatic venous pressure gradient (HVPG) at baseline.<br><br>Randomised set (RS) – this analysis set includes all enrolled patients that were randomised to the trial medication. One patient in the placebo group was randomised in error and was not treated. | | | |
| Units: Millimeter mercury (mmHg) | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

## End points

### End points reporting groups

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

Reporting group description:

Subjects in this dose group received matching placebo twice daily (BID) throughout the study period. At Visit 2 (Week 1), each dose consisted of one 1 mg placebo tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), a pseudo up-titration was implemented, maintaining the same tablets (one 1 mg and one 2 mg placebo per dose) for blinding. From Visit 4 onward (Week 3+), a second pseudo up-titration adjusted the dose to one 2 mg placebo tablet and one 3 mg placebo tablet per dose (four tablets daily). All doses were taken with water, with or without food.

| Reporting group title | Avenciguat 2 mg BID |
|---|---|

Reporting group description:

Subjects received Avenciguat combined with matching placebo tablets twice daily (BID). At Visit 2 (Week 1), each dose included one 1 mg Avenciguat tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), the dose was up titrated to 2 mg Avenciguat BID (one 1 mg placebo tablet and one 2 mg Avenciguat tablet (four tablets daily)). From Visit 4 onward (Week 3+), a pseudo up-titration was applied, with participants taking one 2 mg Avenciguat tablet and one 3 mg placebo tablet per dose (four tablets daily) to maintain blinding. This regimen continued for 24 weeks, with doses taken with water, with or without food.

| Reporting group title | Avenciguat 3 mg BID |
|---|---|

Reporting group description:

Subjects received Avenciguat with matching placebo tablets twice daily (BID). At Visit 2 (Week 1), each dose contained one 1 mg Avenciguat tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), the dose was up titrated to 2 mg Avenciguat BID (one 1 mg placebo tablet and one 2 mg active tablet (four tablets daily)). From Visit 4 onward (Week 3+), the dose was further up titrated to 3 mg Avenciguat BID (one 2 mg placebo tablet and one 3 mg active tablet per dose (four tablets daily)). This regimen was maintained for 24 weeks, with doses taken with water, with or without food.

### Primary: Percentage change in hepatic venous pressure gradient (HVPG) from baseline after 24 weeks of treatment

| End point title | Percentage change in hepatic venous pressure gradient (HVPG) from baseline after 24 weeks of treatment |
|---|---|

End point description:

HVPG was calculated as the difference between average wedged hepatic venous pressure (WHVP) and either:

Proximal Free Hepatic Venous Pressure (PFHVP), if more reliable, or
Average Free Hepatic Venous Pressure (FHVP), if deemed more reliable.
Based on central reader judgment:

If PFHVP was more reliable: HVPG = WHVP − PFHVP
If FHVP was more reliable: HVPG = WHVP − FHVP
Percentage Change = ((HVPG at 24 weeks − Baseline HVPG) / Baseline HVPG) × 100

A restricted maximum likelihood (REML) approach using a mixed model with repeated measurements (MMRM) estimates adjusted treatment means. The model includes fixed effects for treatment at each visit, NSBB or carvedilol use at baseline (yes/no), and baseline HVPG. An unstructured covariance structure fits the model.

Full Analysis Set (FAS) includes all randomised patients with at least one trial dose and a baseline primary endpoint measurement.

A hypothetical strategy assumes intercurrent events did not occur for the primary analysis.

| End point type | Primary |
|---|---|

End point timeframe:

From first administration of trial medication up to 24 weeks.

| End point values | Placebo | Avenciguat 2 mg BID | Avenciguat 3 mg BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 27 | 27 | |
| Units: Percentage | | | | |
| least squares mean (confidence interval 95%) | 7.07 (-6.07 to 20.21) | -1.33 (-13.41 to 10.75) | -7.11 (-22.02 to 7.80) | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Model includes baseline HVPG as linear covariate and treatment and use of NSBBs or carvedilol as fixed effects, treatment by visit interaction and baseline HVPG by visit interaction. The following covariance structure has been used to fit the mixed model: Unstructured

| | |
|---|---|
| Comparison groups | Placebo v Avenciguat 2 mg BID |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -8.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.25 |
| upper limit | 9.45 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 8.9 |

Notes:

[1] - The adjusted mean values for percentage change at Week 24 are derived for each group using the MMRM. The mean difference for the "Comparison vs Placebo," is the adjusted mean of the treatment group subtracted from the adjusted mean of the placebo group.

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Model includes baseline HVPG as linear covariate and treatment and use of NSBBs or carvedilol as fixed effects, treatment by visit interaction and baseline HVPG by visit interaction. The following covariance structure has been used to fit the mixed model: Unstructured.

| | |
|---|---|
| Comparison groups | Placebo v Avenciguat 3 mg BID |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | other[2] |
| Parameter estimate | Difference of adjusted means |
| Point estimate | -14.18 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -34.09 |
| upper limit | 5.72 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 9.93 |

Notes:

[2] - The adjusted mean values for percentage change at Week 24 are derived for each group using the MMRM. The mean difference for the "Comparison vs Placebo," is the adjusted mean of the treatment group subtracted from the adjusted mean of the placebo group.

## Secondary: Percentage change in hepatic venous pressure gradient (HVPG) from baseline, measured in millimeters of mercury (mmHg), after 8 weeks of treatment

| | |
|---|---|
| End point title | Percentage change in hepatic venous pressure gradient (HVPG) from baseline, measured in millimeters of mercury (mmHg), after 8 weeks of treatment |

End point description:

HVPG was calculated as the difference between the average wedged hepatic venous pressure (WHVP) and either the proximal free hepatic venous pressure (PFHVP) or average free hepatic venous pressure (FHVP), based on the central reader's judgment.

Formula:
If PFHVP was more reliable: HVPG = Average WHVP − PFHVP
If FHVP was more reliable: HVPG = Average WHVP − Average FHVP

Percentage change = (HVPG at 8 weeks − Baseline HVPG) / Baseline HVPG × 100

This endpoint was analysed using the Treatment Policy Estimand and an ANCOVA model, including baseline HVPG as a linear covariate, and treatment and use of NSBBs/carvedilol as fixed effects.

The full analysis set (FAS) included all randomised patients who received at least one dose of trial medication and had a baseline measurement for the primary endpoint. All intercurrent events (ICEs) were handled using the treatment policy, including all post-ICE data.

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

End point timeframe:

From first administration of trial medication up to 8 weeks.

| **End point values** | Placebo | Avenciguat 2 mg BID | Avenciguat 3 mg BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 27 | 27 | |
| Units: Percentage of change | | | | |
| number (confidence interval 95%) | -5.41 (-14.30 to 3.47) | -1.90 (-10.62 to 6.82) | -2.72 (-13.03 to 7.59) | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

ANCOVA model includes baseline hepatic venous pressure gradient (HVPG) as a linear covariate, with treatment and use of non-selective beta-blockers (NSBBs) or carvedilol as fixed effects. All intercurrent events (ICEs) will be handled using the treatment policy for the primary objective as a sensitivity analysis. That is, all data collected after the intercurrent events will be included in the analysis.

| | |
|---|---|
| Comparison groups | Placebo v Avenciguat 3 mg BID |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | other[3] |
| Parameter estimate | Difference of adjusted means |
| Point estimate | 2.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.94 |
| upper limit | 16.33 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.82 |

Notes:

[3] - The adjusted mean values for percentage change at Week 8 are derived for each group using the MMRM. The mean difference for the "Comparison vs Placebo," is the adjusted mean of the treatment group subtracted from the adjusted mean of the placebo group.

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

The analysis of covariance (ANCOVA) model includes baseline hepatic venous pressure gradient (HVPG) as a linear covariate, with treatment and use of non-selective beta-blockers (NSBBs) or carvedilol as fixed effects. All intercurrent events (ICEs) will be handled using the treatment policy for the primary objective as a sensitivity analysis. That is, all data collected after the intercurrent events will be included in the analysis.

| | |
|---|---|
| Comparison groups | Placebo v Avenciguat 2 mg BID |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | other[4] |
| Parameter estimate | Difference of adjusted means |
| Point estimate | 3.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.94 |
| upper limit | 15.96 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.23 |

Notes:

[4] - The adjusted mean values for percentage change at Week 8 are derived for each group using the MMRM. The mean difference for the "Comparison vs Placebo," is the adjusted mean of the treatment group subtracted from the adjusted mean of the placebo group.

## Secondary: Response defined as > 10% reduction from baseline HVPG (measured in mmHg) after 8 weeks of treatment

| End point title | Response defined as > 10% reduction from baseline HVPG (measured in mmHg) after 8 weeks of treatment |
|---|---|

End point description:

Response is defined as greater than 10% reduction from baseline HVPG (measured in mmHg) after 8 weeks of treatment.

Full analysis set (FAS) – this analysis set includes all randomised patients who received at least one dose of trial medication and have a baseline measurement for the primary endpoint recorded. If a patient misses the Week 8 visit, the missing data will not be imputed.

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

End point timeframe:

From first administration of trial medication up to 8 weeks.

| End point values | Placebo | Avenciguat 2 mg BID | Avenciguat 3 mg BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 25 | 18 | |
| Units: Subjects | | | | |
| Yes | 10 | 10 | 7 | |
| No | 14 | 15 | 11 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Response defined as > 10% reduction from baseline HVPG (measured in mmHg) after 24 weeks of treatment

| End point title | Response defined as > 10% reduction from baseline HVPG (measured in mmHg) after 24 weeks of treatment |
|---|---|

End point description:

Response is defined as greater than 10% reduction from baseline HVPG (measured in mmHg) after 24 weeks of treatment.

Full analysis set (FAS) – this analysis set includes all randomised patients who received at least one dose of trial medication and have a baseline measurement for the primary endpoint recorded. If a patient misses the Week 24 visit, the missing data will not be imputed.

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

End point timeframe:

From first administration of trial medication up to 24 weeks.

| End point values | Placebo | Avenciguat 2 mg BID | Avenciguat 3 mg BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 19 | 23 | 17 | |
| Units: Subjects | | | | |
| Yes | 5 | 11 | 4 | |
| No | 14 | 12 | 13 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Occurrence of one or more decompensation events (i.e. ascites, VH, and / or overt HE) during the 24 week treatment period

| End point title | Occurrence of one or more decompensation events (i.e. ascites, VH, and / or overt HE) during the 24 week treatment period |
|---|---|

End point description:

A decompensation event is characterised by the occurrence of any of the following:

-Ascites,
-Variceal hemorrhage,
-Overt hepatic encephalopathy.

Treated set (TS) – the treated set includes all patients who were randomised to the trial medication and were treated with at least one dose.

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

End point timeframe:

From first administration of trial medication up to 24 weeks.

| **End point values** | Placebo | Avenciguat 2 mg BID | Avenciguat 3 mg BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 27 | 27 | |
| Units: Participants | 2 | 0 | 3 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement, during the first 8 weeks of the treatment period

| End point title | Occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement, during the first 8 weeks of the treatment period |
|---|---|

End point description:

The occurrence of CTCAE grade 3 (or higher) hypotension or syncope, based on the investigator's judgment, during the first 8 weeks of the treatment period is reported.

Treated set (TS) – the treated set includes all patients who were randomised to the trial medication and were treated with at least one dose.

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

End point timeframe:

From first administration of trial medication up to 8 weeks.

| **End point values** | Placebo | Avenciguat 2 mg BID | Avenciguat 3 mg BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 27 | 27 | |
| Units: Subjects | 0 | 0 | 1 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement, during the 24 week treatment period

| End point title | Occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement, during the 24 week treatment period |
|---|---|

End point description:

The occurrence of CTCAE grade 3 (or higher) hypotension or syncope, based on the investigator's judgment, during the 24 weeks of the treatment period is reported.

Treated set (TS) – the treated set includes all patients who were randomised to the trial medication and were treated with at least one dose.

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

End point timeframe:

From first administration of trial medication up to 24 weeks.

| End point values | Placebo | Avenciguat 2 mg BID | Avenciguat 3 mg BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 27 | 27 | |
| Units: Subjects | 0 | 0 | 1 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Occurrence of discontinuation due to hypotension or syncope during the first 8 weeks of the treatment period

| End point title | Occurrence of discontinuation due to hypotension or syncope during the first 8 weeks of the treatment period |
|---|---|

End point description:

The occurrence of hypotension or syncope during the first 8 weeks of the treatment period leading to the participant's discontinuation is reported.

Treated set (TS) – the treated set includes all patients who were randomised to the trial medication and were treated with at least one dose.

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

End point timeframe:

From first administration of trial medication up to 8 weeks.

| End point values | Placebo | Avenciguat 2 mg BID | Avenciguat 3 mg BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 27 | 27 | |
| Units: Subjects | 0 | 0 | 1 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Occurrence of discontinuation due to hypotension or syncope during the 24 week treatment period

| End point title | Occurrence of discontinuation due to hypotension or syncope during the 24 week treatment period |
|---|---|

End point description:

The occurrence of hypotension or syncope during the first 24 weeks of the treatment period leading to the participant's discontinuation is reported.

Treated set (TS) – the treated set includes all patients who were randomised to the trial medication and were treated with at least one dose.

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

End point timeframe:

From first administration of trial medication up to 24 weeks.

| End point values | Placebo | Avenciguat 2 mg BID | Avenciguat 3 mg BID | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 25 | 27 | 27 | |
| Units: Subjects | 0 | 0 | 1 | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AE collection: From the first Avenciguat or placebo dose to the last dose, plus a 7-day residual effect period, totaling up to 182 days.

All-cause mortality: From the first Avenciguat or placebo dose to the study's end, totaling up to 196 days.

Adverse event reporting additional description:

Treated set (TS) – the treated set includes all patients who were randomised to the trial medication and were treated with at least one dose.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 27.0 |

### Reporting groups

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

Reporting group description:

Subjects in this dose group received matching placebo twice daily (BID) throughout the study period. At Visit 2 (Week 1), each dose consisted of one 1 mg placebo tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), a pseudo up-titration was implemented, maintaining the same tablets (one 1 mg and one 2 mg placebo per dose) for blinding. From Visit 4 onward (Week 3+), a second pseudo up-titration adjusted the dose to one 2 mg placebo tablet and one 3 mg placebo tablet per dose (four tablets daily). All doses were taken with water, with or without food.

| | |
|---|---|
| Reporting group title | Avenciguat 3mg BID |

Reporting group description:

Subjects received Avenciguat with matching placebo tablets twice daily (BID). At Visit 2 (Week 1), each dose contained one 1 mg Avenciguat tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), the dose was up titrated to 2 mg Avenciguat BID (one 1 mg placebo tablet and one 2 mg active tablet (four tablets daily)). From Visit 4 onward (Week 3+), the dose was further up titrated to 3 mg Avenciguat BID (one 2 mg placebo tablet and one 3 mg active tablet per dose (four tablets daily)). This regimen was maintained for 24 weeks, with doses taken with water, with or without food.

| | |
|---|---|
| Reporting group title | Avenciguat 2mg BID |

Reporting group description:

Subjects received Avenciguat combined with matching placebo tablets twice daily (BID). At Visit 2 (Week 1), each dose included one 1 mg Avenciguat tablet and one 2 mg placebo tablet (four tablets daily). At Visit 3 (Week 2), the dose was up titrated to 2 mg Avenciguat BID (one 1 mg placebo tablet and one 2 mg Avenciguat tablet (four tablets daily)). From Visit 4 onward (Week 3+), a pseudo up-titration was applied, with participants taking one 2 mg Avenciguat tablet and one 3 mg placebo tablet per dose (four tablets daily) to maintain blinding. This regimen continued for 24 weeks, with doses taken with water, with or without food.

| **Serious adverse events** | Placebo | Avenciguat 3mg BID | Avenciguat 2mg BID |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | 3 / 27 (11.11%) | 1 / 27 (3.70%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Hepatic enzyme increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal varices haemorrhage | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 27 (3.70%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bursitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Placebo | Avenciguat 3mg BID | Avenciguat 2mg BID |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 25 (36.00%) | 11 / 27 (40.74%) | 10 / 27 (37.04%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 2 / 27 (7.41%) | 2 / 27 (7.41%) |
| occurrences (all) | 2 | 2 | 2 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 3 / 27 (11.11%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 3 / 27 (11.11%) | 0 / 27 (0.00%) |
| occurrences (all) | 3 | 5 | 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 2 / 27 (7.41%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 1 | 0 | 2 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 1 | 0 | 2 |
| Constipation | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 27 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 0 | 0 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 27 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 2 | 0 | 1 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 2 / 27 (7.41%) | 1 / 27 (3.70%) |
| occurrences (all) | 2 | 2 | 1 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 2 / 27 (7.41%) |
| occurrences (all) | 0 | 1 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 2 / 27 (7.41%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 July 2021 | Global Amendment 1 (15 Jul 2021): Issued before the first patient screening, this amendment added Exclusion Criterion #2 to ensure that trial participants had alcohol-related liver disease by excluding those with other chronic liver diseases (e.g., NASH, HBV, untreated HCV, autoimmune liver disease, Wilson's disease, etc.). It also updated Exclusion Criterion #19 to adjust the contraindication for FibroScan® to apply only in countries where local regulations still restricted its use in patients with active implantable devices. For further details, refer to Section 8.1, CTP Version 7 - Section 11.1. |
| 21 September 2021 | Global Amendment 2 (21 Sep 2021) was issued before screening the first patient and included several changes outlined in Section 8.1, CTP Version 7 - Section 11.2. Version 3 of the CTP, the first version submitted to IECs/IRBs and CAs across all participating countries (previous versions were only submitted in some), incorporated new data from trial 1366-0020 showing Avenciguat's effect on the placebo-corrected change in QTcF (ΔΔQTcF). As a precaution, exclusion and discontinuation criteria were added, along with more frequent ECG monitoring and restricted concomitant therapies, to mitigate potential QT-prolongation risks of Avenciguat.<br><br>A new exclusion criterion (#18) was added: "QTcF-interval > 450 ms in men or > 470 ms in women at screening (Visit 1a), a family history of long QT syndrome, or concomitant use of therapies with a known risk of Torsade de Pointes at screening (Visit 1a) or planned initiation of such therapies during the trial (refer to Section 4.2.2.1)." Additionally, a new discontinuation criterion was added: "patients with a QT or QTcF interval >500 ms, or an increase of QT or QTcF of >60 ms from the value at Visit 2/randomisation (baseline). Such cases must be reported as AEs."<br><br>Also, the wording of exclusion criterion #3 was adjusted to include and remove specific text: "Has received curative anti-viral therapy with direct-acting anti-virals within the last 2 years for HCV, or, if treatment was >2 years ago, and no sustained virological response (SVR) at screening (Visit 1a), or, must take curative anti-viral therapy with direct-acting anti-virals throughout the trial (refer to Section 4.2.2.1). |
| 07 July 2022 | Global Amendment 3 (07 Jul 2022) was issued after the first patient was screened and included important changes outlined in Section 8.1, CTP Version 7 - Section 11.3. This amendment added a description of the potential for drug-drug interaction with CYP2C8 substrates, highlighting related risks and the need for monitoring adverse events (AEs) associated with CYP2C8 substrates when administered as concomitant therapy. |
| 16 August 2022 | Global Amendment 4 (16 Aug 2022) was issued after the first patient was screened and included important changes outlined in Section 8.1, CTP Version 7 - Section 11.4. Due to recruitment difficulties, the requirement for complete abstinence from alcohol prior to the first trial visit was changed to allow screening of patients without significant alcohol misuse/abuse (as judged by the Investigator). The abstinence timeframe was reduced from 6 months to 2 months, though patients were still required to abstain from alcohol during the trial as excessive consumption could cause hypotension when taken with Avenciguat. The wording of inclusion criterion #6 was adjusted as follows: "Abstinence from significant alcohol misuse/abuse for a minimum of 6 months prior to screening (Visit 1a), and the ability, based on Investigator judgement, to abstain from alcohol throughout the trial (both evaluated based on Investigator judgement)."<br><br>In alignment with this change, the wording of exclusion criterion #4 was also adjusted: "ARLD without adequate treatment (e.g., lifestyle modification) or with ongoing pathological drinking behaviour (misuse/abuse based on Investigator judgement). |

| | |
|---|---|
| 14 December 2022 | Global Amendment 5 (14 Dec 2022) was issued after the first patient was screened and included several important changes outlined in Section 8.1, CTP Version 7 - Section 11.5. To assist sites with scheduling difficulties for required screening assessments, the permitted duration of the screening period was extended from 4 to 6 weeks. To increase trial efficiency while preserving the probability of observing a 20% HVPG reduction between at least one dose group of Avenciguat and placebo, the total number of patients randomised was adjusted from 150 to 105, and the number of patients per treatment group was adjusted from 50 to 35. The number of patients expected to be randomised at each site was reduced from 2-3 to 2, with updated probabilities for achieving the assumed treatment effects in the final analysis.<br><br>Additionally, the conditions for using a historical gastroscopy were modified to ease recruitment due to its invasive nature. The admissibility limit for prior gastroscopy was extended from 3 to 6 months before screening, and if therapy with NSBBs/carvedilol had been initiated after a historical gastroscopy, the requirement for a further gastroscopy to confirm the persistence of varices was removed. This change affected the wording of inclusion criterion #3 and other sections. The length of time required for a stable dose of NSBBs or carvedilol prior to screening was reduced from 3 months to 1 month to ease recruitment difficulties, affecting inclusion criterion #9 and other sections. Finally, systemic sclerosis (SSc) was added as a third intended indication for Avenciguat based on an IB update. |
| 02 November 2023 | Global Amendment 6 (02 Nov 2023) was issued after the first patient was screened and included several important changes outlined in Section 8.1, CTP Version 7 - Section 11.6. The total number of patients randomised was reduced from 105 to 78, with the number of patients per treatment group adjusted from 35 to 26. Corresponding probabilities for achieving the assumed treatment effects (a difference of at least 15% HVPG reduction from baseline between at least one dose group of avenciguat and placebo) in the final analysis were updated. These changes were made because a smaller sample size was now required to observe a 15% HVPG reduction, as more recent data indicated that even a 10% reduction in portal pressure positively impacted outcomes. Initially, a 20% reduction was chosen based on academic guidelines for clinical development in pulmonary hypertension (PH) at the start of development in 2018.<br><br>Additionally, a correction/clarification of exclusion criterion #2 was made, now reading: "History of other forms of chronic liver disease (e.g., non-alcoholic steatohepatitis [NASH], Hepatitis B virus [HBV], untreated HCV, autoimmune liver disease, primary biliary cholangitis, primary sclerosing cholangitis, Wilson’s disease, haemochromatosis, alpha-1 antitrypsin [A1At] deficiency). |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported