



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
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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, clintrriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 018002430127, clintrriage.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
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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
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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
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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.			
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.			
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 = $((HVPg \text{ at 24 weeks} - \text{Baseline HVPg}) / \text{Baseline HVPg}) \times 100$ 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
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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: $HVPG = \text{Average WHVP} - \text{PFHVP}$

If FHVP was more reliable: $HVPG = \text{Average WHVP} - \text{Average FHVP}$

Percentage change = $(HVPG \text{ at 8 weeks} - \text{Baseline HVPG}) / \text{Baseline HVPG} \times 100$

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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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Reporting groups

Reporting group title	Placebo
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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
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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
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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 occurrences (all)	0 / 25 (0.00%) 0	0 / 27 (0.00%) 0	2 / 27 (7.41%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 27 (0.00%) 0	1 / 27 (3.70%) 1
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	2 / 27 (7.41%) 2	1 / 27 (3.70%) 1
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 27 (3.70%) 1	2 / 27 (7.41%) 2
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2	2 / 27 (7.41%) 2	0 / 27 (0.00%) 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	<p>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 ($\Delta\Delta\text{QTcF}$). 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.</p> <p>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."</p> <p>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).</p>
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	<p>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)."</p> <p>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).</p>

14 December 2022	<p>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.</p> <p>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.</p>
02 November 2023	<p>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.</p> <p>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).</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported