Clinical trial results:
A Phase 2, Dose-Ranging, Randomized, Double-Blind, Placebo-Controlled Study of GS-4997 in Subjects with Pulmonary Arterial Hypertension

Summary

EudraCT number	2014-002131-34
Trial protocol	DE NL ES GB IT
Global end of trial date	13 December 2016

Results information

Result version number	v1 (current)
This version publication date	05 November 2017
First version publication date	05 November 2017

Trial information

Trial identification

Sponsor protocol code	GS-US-357-1394

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02234141
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Clinical Trials Mailbox, Gilead Sciences International Ltd , ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trials Mailbox, Gilead Sciences International Ltd , ClinicalTrialDisclosures@gilead.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	13 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of selonsertib (GS-4997) on pulmonary vascular resistance (PVR), as measured by right heart catheterization (RHC) in participants with pulmonary arterial hypertension (PAH).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	United States: 83
Country: Number of subjects enrolled	Canada: 18
Worldwide total number of subjects	151
EEA total number of subjects	50

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)	122
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America and Europe. The first participant was screened on 12 November 2014. The last study visit occurred on 13 December 2016.

Pre-assignment

Screening details:

185 participants were screened.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Selonsertib 2 mg

Arm description:

Selonsertib 2 mg for 24 weeks during the treatment phase (Period 1)

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg administered once daily

Arm title	Selonsertib 6 mg

Arm description:

Selonsertib 6 mg for 24 weeks during the treatment phase (Period 1)

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

6 mg administered once daily

Arm title	Selonsertib 18 mg

Arm description:

Selonsertib 18 mg for 24 weeks during the treatment phase (Period 1)

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

18 mg administered once daily

Arm title	Placebo

Arm description:

Placebo for 24 weeks (Period 1) and may have been rerandomized 1:1:1 to selonsertib 2, 6, or 18 mg during the long-term treatment phase (Period 2)

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

Dosage and administration details:

Administered once daily

Number of subjects in period 1[1]	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg
Started	39	37	37
Completed	33	31	33
Not completed	6	6	4
Adverse event, serious fatal	1	3	-
Subject Withdrew Consent	-	-	1
Adverse event, non-fatal	5	1	3
Protocol Deviation	-	-	-
Investigator's discretion	-	2	-

Number of subjects in period 1[1]	Placebo
Started	37
Completed	32
Not completed	5
Adverse event, serious fatal	2
Subject Withdrew Consent	-
Adverse event, non-fatal	2
Protocol Deviation	1
Investigator's discretion	-

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: 1 participant who was randomized but not treated is not included in the subject disposition table.

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Selonsertib 2 mg

Arm description:

Participants continued treatment with selonsertib 2 mg during the long-term treatment phase (Period 2)

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg administered once daily

Arm title	Selonsertib 6 mg

Arm description:

Participants continued treatment with selonsertib 6 mg during the long-term treatment phase (Period 2)

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

6 mg administered once daily

Arm title	Selonsertib 18 mg

Arm description:

Participants continued treatment with selonsertib 18 mg during the long-term treatment phase (Period 2)

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

18 mg administered once daily

Arm title	Placebo to Selonsertib 2 mg

Arm description:

Participants were on placebo in Period 1 and were rerandomized to receive selonsertib 2 mg during the long-term treatment phase (Period 2)

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg administered once daily

Arm title	Placebo to Selonsertib 6 mg

Arm description:

Participants were on placebo in Period 1 and were rerandomized to receive selonsertib 6 mg during the long-term treatment phase (Period 2)

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

6 mg administered once daily

Arm title	Placebo to Selonsertib 18 mg

Arm description:

Participants were on placebo in Period 1 and were rerandomized to receive selonsertib 18 mg during the long-term treatment phase (Period 2)

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

18 mg administered once daily

Number of subjects in period 2	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg
Started	33	31	33
Completed	0	0	0
Not completed	33	31	33
Adverse event, serious fatal	-	-	1
Subject Withdrew Consent	-	1	1
Adverse event, non-fatal	3	-	4
Death	-	-	-
Study Discontinued by Sponsor	29	27	25
Investigator's discretion	1	3	2

Number of subjects in period 2	Placebo to Selonsertib 2 mg	Placebo to Selonsertib 6 mg	Placebo to Selonsertib 18 mg

Started	10	12	10
Completed	0	0	0
Not completed	10	12	10
Adverse event, serious fatal	-	-	-
Subject Withdrew Consent	-	-	-
Adverse event, non-fatal	-	1	1
Death	-	1	-
Study Discontinued by Sponsor	9	10	8
Investigator's discretion	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Selonsertib 2 mg
Reporting group description:	
Selonsertib 2 mg for 24 weeks during the treatment phase (Period 1)	
Reporting group title	Selonsertib 6 mg
Reporting group description:	
Selonsertib 6 mg for 24 weeks during the treatment phase (Period 1)	
Reporting group title	Selonsertib 18 mg
Reporting group description:	
Selonsertib 18 mg for 24 weeks during the treatment phase (Period 1)	
Reporting group title	Placebo
Reporting group description:	
Placebo for 24 weeks (Period 1) and may have been rerandomized 1:1:1 to selonsertib 2, 6, or 18 mg during the long-term treatment phase (Period 2)	

Reporting group values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg
Number of subjects	39	37	37
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	50	49	48
standard deviation	± 13.9	± 13.7	± 14.1
Gender categorical Units: Subjects			
Female	30	27	32
Male	9	10	5
Race Units: Subjects			
American Indian or Alaska Native	2	1	0
Asian	0	3	0
Black	1	0	0
White	35	33	36
Not Permitted	1	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	6	5	3
Not Hispanic or Latino	31	31	32
Not Permitted	2	1	2
WHO Functional Class Units: Subjects			
Class II	24	23	19
Class III	15	14	18

6 Minute Walk Distance			
Units: meter			
arithmetic mean	452	449	437
standard deviation	± 111.9	± 85.3	± 102.7
NT-proBNP			
Units: pg/mL			
geometric mean	385	431	352
inter-quartile range (Q1-Q3)	86 to 1177	174 to 1134	135 to 822
Borg Dyspnea Index			
Units: units on a scale			
arithmetic mean	3.5	3.7	3.5
standard deviation	± 2.13	± 2.41	± 1.53
RVFAC			
Units: percentage			
arithmetic mean	34.7	33.6	37.3
standard deviation	± 8.00	± 9.68	± 8.47
TAPSE			
Units: centimeter			
arithmetic mean	1.5	1.5	1.5
standard deviation	± 0.31	± 0.37	± 0.29
mRAP			
Units: mm Hg			
arithmetic mean	8	9	9
standard deviation	± 4.3	± 4.4	± 4.3
mPAP			
Units: mm Hg			
arithmetic mean	53.4	56.7	55.0
standard deviation	± 15.28	± 10.79	± 12.51
PVR			
Units: dyn*sec/cm^5			
arithmetic mean	734	806	809
standard deviation	± 313.4	± 381.2	± 366.1
Cardiac Index			
Units: L/min/m^2			
arithmetic mean	2.87	2.86	2.69
standard deviation	± 0.818	± 0.679	± 0.649

Reporting group values	Placebo	Total	
Number of subjects	37	150	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	55		
standard deviation	± 15.5	-	
Gender categorical			
Units: Subjects			
Female	30	119	
Male	7	31	

Race Units: Subjects			
American Indian or Alaska Native	0	3	
Asian	2	5	
Black	0	1	
White	35	139	
Not Permitted	0	2	
Ethnicity Units: Subjects			
Hispanic or Latino	2	16	
Not Hispanic or Latino	35	129	
Not Permitted	0	5	
WHO Functional Class Units: Subjects			
Class II	24	90	
Class III	13	60	
6 Minute Walk Distance Units: meter			
arithmetic mean	412		
standard deviation	± 109.3	-	
NT-proBNP Units: pg/mL			
geometric mean	492		
inter-quartile range (Q1-Q3)	158 to 1424	-	
Borg Dyspnea Index Units: units on a scale			
arithmetic mean	3.6		
standard deviation	± 1.94	-	
RVFAC Units: percentage			
arithmetic mean	32.3		
standard deviation	± 9.59	-	
TAPSE Units: centimeter			
arithmetic mean	1.5		
standard deviation	± 0.31	-	
mRAP Units: mm Hg			
arithmetic mean	8		
standard deviation	± 3.5	-	
mPAP Units: mm Hg			
arithmetic mean	51.3		
standard deviation	± 9.94	-	
PVR Units: dyn*sec/cm^5			
arithmetic mean	743		
standard deviation	± 268.2	-	
Cardiac Index Units: L/min/m^2			
arithmetic mean	2.64		

standard deviation	± 0.501	-	

End points

End points reporting groups

Reporting group title	Selonsertib 2 mg
Reporting group description:	
Selonsertib 2 mg for 24 weeks during the treatment phase (Period 1)	
Reporting group title	Selonsertib 6 mg
Reporting group description:	
Selonsertib 6 mg for 24 weeks during the treatment phase (Period 1)	
Reporting group title	Selonsertib 18 mg
Reporting group description:	
Selonsertib 18 mg for 24 weeks during the treatment phase (Period 1)	
Reporting group title	Placebo
Reporting group description:	
Placebo for 24 weeks (Period 1) and may have been rerandomized 1:1:1 to selonsertib 2, 6, or 18 mg during the long-term treatment phase (Period 2)	

Reporting group title	Selonsertib 2 mg
Reporting group description:	
Participants continued treatment with selonsertib 2 mg during the long-term treatment phase (Period 2)	
Reporting group title	Selonsertib 6 mg
Reporting group description:	
Participants continued treatment with selonsertib 6 mg during the long-term treatment phase (Period 2)	
Reporting group title	Selonsertib 18 mg
Reporting group description:	
Participants continued treatment with selonsertib 18 mg during the long-term treatment phase (Period 2)	
Reporting group title	Placebo to Selonsertib 2 mg
Reporting group description:	
Participants were on placebo in Period 1 and were rerandomized to receive selonsertib 2 mg during the long-term treatment phase (Period 2)	

Reporting group title	Placebo to Selonsertib 6 mg
Reporting group description:	
Participants were on placebo in Period 1 and were rerandomized to receive selonsertib 6 mg during the long-term treatment phase (Period 2)	
Reporting group title	Placebo to Selonsertib 18 mg
Reporting group description:	
Participants were on placebo in Period 1 and were rerandomized to receive selonsertib 18 mg during the long-term treatment phase (Period 2)	

Primary: Change from Baseline in Pulmonary Vascular Resistance (PVR) at Week 24, as Measured by Right Heart Catheterization

End point title	Change from Baseline in Pulmonary Vascular Resistance (PVR) at Week 24, as Measured by Right Heart Catheterization
End point description:	
Full Analysis Set: all randomized participants who received ≥ 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Baseline; Week 24	

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	36	31
Units: dyne.sec/cm^5				
arithmetic mean (standard error)	35 (± 35.4)	-28 (± 30.2)	-21 (± 37.9)	6 (± 28.0)

Statistical analyses

Statistical analysis title	Change in PVR - Selonsertib 2 mg vs Placebo
Comparison groups	Selonsertib 2 mg v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.214 [2]
Method	gvE/vE

Notes:

[1] - Statistical comparison

[2] - P-value was calculated using the generalized van Elteren test/van Elteren test (gvE/vE; stratified Wilcoxon rank sum test).

Statistical analysis title	Change in PVR - Selonsertib 6 mg vs Placebo
Comparison groups	Selonsertib 6 mg v Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.27 [4]
Method	gvE/vE

Notes:

[3] - Statistical comparison

[4] - P-value was calculated using the generalized van Elteren test/van Elteren test (gvE/vE; stratified Wilcoxon rank sum test).

Statistical analysis title	Change in PVR - Selonsertib 18 mg vs Placebo
Comparison groups	Selonsertib 18 mg v Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.604 [6]
Method	gvE/vE

Notes:

[5] - Statistical comparison

[6] - P-value was calculated using the generalized van Elteren test/van Elteren test (gvE/vE; stratified Wilcoxon rank sum test).

Secondary: Change from Baseline at Week 24 in Other Cardiopulmonary Hemodynamic Measures: Cardiac Index (CI)

End point title	Change from Baseline at Week 24 in Other Cardiopulmonary

	Hemodynamic Measures: Cardiac Index (CI)

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	36	31
Units: L/min/m^2				
arithmetic mean (standard error)	-0.1 (± 0.10)	0.1 (± 0.09)	0.0 (± 0.09)	0.0 (± 0.09)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in Other Cardiopulmonary Hemodynamic Measures: Mean Pulmonary Artery Pressure (mPAP)

End point title	Change from Baseline at Week 24 in Other Cardiopulmonary Hemodynamic Measures: Mean Pulmonary Artery Pressure (mPAP)

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	34	36	31
Units: mm Hg				
arithmetic mean (standard error)	1 (± 1.3)	-1 (± 1.1)	-3 (± 1.4)	0 (± 1.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in Other Cardiopulmonary Hemodynamic Measures: Mean Right Atrial Pressure (mRAP)

End point title	Change from Baseline at Week 24 in Other Cardiopulmonary Hemodynamic Measures: Mean Right Atrial Pressure (mRAP)

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	34	36	31
Units: mm Hg				
arithmetic mean (standard error)	1 (± 0.5)	0 (± 0.7)	-1 (± 0.5)	1 (± 0.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in Other Cardiopulmonary Hemodynamic Measures: Mixed Venous Oxygen Saturation (SVO2)

End point title	Change from Baseline at Week 24 in Other Cardiopulmonary Hemodynamic Measures: Mixed Venous Oxygen Saturation (SVO2)

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	34	35	31
Units: percentage				
arithmetic mean (standard error)	0.0 (± 0.85)	0.1 (± 2.13)	1.1 (± 2.07)	-2.0 (± 1.00)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in Other Cardiopulmonary Hemodynamic Measures: Right Ventricular Cardiac Power (RVCP)

End point title	Change from Baseline at Week 24 in Other Cardiopulmonary Hemodynamic Measures: Right Ventricular Cardiac Power (RVCP)

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	34	36	31
Units: watts				
arithmetic mean (standard error)	-0.01 (± 0.026)	0.00 (± 0.024)	-0.03 (± 0.028)	-0.01 (± 0.027)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in 6-minute Walk Distance (6MWD)

End point title	Change from Baseline at Week 24 in 6-minute Walk Distance (6MWD)

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	37	37	37
Units: meter				
arithmetic mean (standard error)	4.7 (± 6.63)	3.5 (± 8.27)	-15.9 (± 8.01)	-15.0 (± 8.60)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in Borg Dyspnea index (BDI) after the 6MWT

End point title	Change from Baseline at Week 24 in Borg Dyspnea index (BDI) after the 6MWT

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	37	37	37
Units: units on a scale				
arithmetic mean (standard error)	-0.1 (± 0.24)	0.1 (± 0.26)	0.1 (± 0.23)	0.3 (± 0.27)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in World Health Organization (WHO) Functional Class

End point title	Change from Baseline at Week 24 in World Health Organization (WHO) Functional Class

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	37	37	37
Units: participants				
number (not applicable)				
Improved	7	6	5	1
Unchanged	27	24	28	29
Worsened	2	3	4	2

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in N-terminal Pro-brain Natriuretic Peptide (NT-proBNP)

End point title	Change from Baseline at Week 24 in N-terminal Pro-brain Natriuretic Peptide (NT-proBNP)

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	37	37	37
Units: pg/mL				
geometric mean (standard error)	1.17 (± 0.093)	1.01 (± 0.093)	1.01 (± 0.082)	1.25 (± 0.103)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in SF-36 Physical Functioning Scale

End point title	Change from Baseline at Week 24 in SF-36 Physical Functioning Scale

End point description:

Quality of life was assessed using the SF-36 questionnaire. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	35	36	36
Units: units on a scale				
arithmetic mean (standard error)	0 (± 0.8)	2 (± 0.9)	0 (± 0.8)	0 (± 0.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in emPHasis-10 Questionnaire Score

End point title	Change from Baseline at Week 24 in emPHasis-10 Questionnaire Score

End point description:

Quality of life was assessed using the emPHasis-10 questionnaire. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	35	37	36
Units: units on a scale				
arithmetic mean (standard error)	0 (± 1.1)	-1 (± 1.2)	1 (± 1.1)	-1 (± 1)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 24 in Heart Rate Recovery After the 6MWT

End point title	Change from Baseline at Week 24 in Heart Rate Recovery After the 6MWT

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	37	37	37
Units: bpm				
arithmetic mean (standard error)	4.0 (± 2.42)	0.1 (± 2.52)	-3.0 (± 3.07)	2.4 (± 2.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Clinical Worsening (TTCW) Evaluated in Period 1

End point title	Time to Clinical Worsening (TTCW) Evaluated in Period 1

End point description:

TTCW was defined as time to the first occurrence of: death (all-cause), hospitalization for worsening PAH (any hospitalization for worsening PAH, lung or heart/lung transplant, atrial septostomy, or initiation of continuously infused prostanoid therapy), or disease progression (defined as both > 15% decrease from baseline in 6MWD and WHO class III or IV symptoms at two consecutive postbaseline clinic visits separated by ≥ 14 days). Participants in the Full Analysis Set with available data were analyzed.

9999 = Not applicable; not reached due to insufficient number of events

End point type	Secondary

End point timeframe:

Up to 24 weeks

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	37	37	37
Units: day				
median (inter-quartile range (Q1-Q3))	9999 (9999 to 9999)	9999 (9999 to 9999)	225.0 (225.0 to 225.0)	178.0 (178.0 to 9999)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Echocardiographic Measures of Right Ventricular Function at Week 24: Tricuspid Annular Plane Systolic Excursion (TAPSE)

End point title	Change from Baseline in Echocardiographic Measures of Right Ventricular Function at Week 24: Tricuspid Annular Plane Systolic Excursion (TAPSE)

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	35	35	32
Units: centimeter				
arithmetic mean (standard error)	0.0 (± 0.04)	-0.1 (± 0.06)	0.0 (± 0.04)	0.0 (± 0.04)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Echocardiographic Measures of Right Ventricular Function at Week 24: Right Ventricular Myocardial Strain

End point title	Change from Baseline in Echocardiographic Measures of Right Ventricular Function at Week 24: Right Ventricular Myocardial Strain

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	26	24
Units: percentage				
arithmetic mean (standard error)	1 (± 0.7)	2 (± 0.6)	-1 (± 0.7)	1 (± 0.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Echocardiographic Measures of Right Ventricular Function at Week 24: Tricuspid Annular Peak Sys Myocard Velocity (TAS)

End point title	Change from Baseline in Echocardiographic Measures of Right Ventricular Function at Week 24: Tricuspid Annular Peak Sys Myocard Velocity (TAS)

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	37	35	32
Units: cm/sec				
arithmetic mean (standard error)	1 (± 0.4)	0 (± 0.3)	0 (± 0.2)	0 (± 0.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Echocardiographic Measures of Right Ventricular Function at Week 24: Right Ventricular Tei Index (RVTI)

End point title	Change from Baseline in Echocardiographic Measures of Right Ventricular Function at Week 24: Right Ventricular Tei Index (RVTI)

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	34	32	29
Units: units on a scale				
arithmetic mean (standard error)	0.08 (± 0.037)	0.05 (± 0.052)	0.01 (± 0.021)	-0.02 (± 0.038)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Echocardiographic Measures of Right Ventricular Function at Week 24: Right Ventricular Fractional Area Change (RVFAC)

End point title	Change from Baseline in Echocardiographic Measures of Right Ventricular Function at Week 24: Right Ventricular Fractional Area Change (RVFAC)

End point description:

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	36	33	33
Units: percentage				
arithmetic mean (standard error)	-0.3 (± 1.16)	0.0 (± 1.23)	-1.1 (± 1.25)	-0.6 (± 1.12)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 97 weeks plus 30 days

Adverse event reporting additional description:

Safety Analysis Set: all randomized participants who received ≥ 1 dose of study drug. For Period 2 crossover participants and the Active Period, the Safety Analysis Set comprised participants who received ≥ 1 dose of selonsertib.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Selonsertib 2 mg

Reporting group description:

Selonsertib 2 mg for 24 weeks during the treatment phase (Period 1) and during the long-term treatment phase (Period 2). Adverse events (AEs) in this reporting group include AEs that occurred in 10 participants who were rerandomized from the Placebo Period 1 group to receive selonsertib 2 mg during the long-term treatment phase.

Reporting group title	Selonsertib 6 mg

Reporting group description:

Selonsertib 6 mg for 24 weeks during the treatment phase (Period 1) and during the long-term treatment phase (Period 2). Adverse events (AEs) in this reporting group include AEs that occurred in 12 participants who were rerandomized from the Placebo Period 1 group to receive selonsertib 6 mg during the long-term treatment phase.

Reporting group title	Selonsertib 18 mg

Reporting group description:

Selonsertib 18 mg for 24 weeks during the treatment phase (Period 1) and during the long-term treatment phase (Period 2). Adverse events (AEs) in this reporting group include AEs that occurred in 10 participants who were rerandomized from the Placebo Period 1 group to receive selonsertib 18 mg during the long-term treatment phase.

Reporting group title	Placebo

Reporting group description:

Adverse events reported in this group only include AEs that occurred during Period 1.

Serious adverse events	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 49 (28.57%)	17 / 49 (34.69%)	16 / 47 (34.04%)
number of deaths (all causes)	3	5	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			

subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Vascular disorders			
Aortic arteriosclerosis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Shock haemorrhagic			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (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
General disorders and administration site conditions			
Catheter site extravasation			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (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
Chest pain			
subjects affected / exposed	1 / 49 (2.04%)	2 / 49 (4.08%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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

Infusion site inflammation			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (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
Pyrexia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 49 (0.00%)	2 / 49 (4.08%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Haemoptysis			
subjects affected / exposed	1 / 49 (2.04%)	1 / 49 (2.04%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	3 / 47 (6.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

Respiratory failure			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device breakage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (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
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Injury, poisoning and procedural complications			
Transplant dysfunction			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Upper limb fracture			

subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (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			
Angina unstable			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (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 failure acute			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	2 / 49 (4.08%)	4 / 49 (8.16%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 2	2 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 3	0 / 0
Tachycardia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Ventricular extrasystoles			

subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dysarthria			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Presyncope			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	3 / 49 (6.12%)	0 / 49 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Haemorrhagic anaemia			

subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 49 (2.04%)	1 / 49 (2.04%)	0 / 47 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (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
Oesophageal achalasia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Oesophagitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Cholelithiasis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Hepatomegaly			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (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
Cellulitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	2 / 49 (4.08%)	0 / 49 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diverticulitis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (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
Gastroenteritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (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
Pneumonia			
subjects affected / exposed	1 / 49 (2.04%)	3 / 49 (6.12%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hypokalaemia			

subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (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
Malnutrition			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 37 (18.92%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic arteriosclerosis			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			

subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Catheter site extravasation			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Generalised oedema			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infusion site inflammation			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Dyspnoea exertional				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary arterial hypertension				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Psychiatric disorders				
Mental status changes				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device breakage				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device dislocation				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Transplant dysfunction			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			

subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Tachycardia				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular extrasystoles				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dysarthria				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolic encephalopathy				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				

subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 37 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic anaemia				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain lower				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				

subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal achalasia				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatomegaly				
subjects affected / exposed	0 / 37 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				

Acute kidney injury			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			

subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicella			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Selonsertib 2 mg	Selonsertib 6 mg	Selonsertib 18 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 49 (87.76%)	44 / 49 (89.80%)	44 / 47 (93.62%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 49 (2.04%)	4 / 49 (8.16%)	4 / 47 (8.51%)
occurrences (all)	1	6	4
Hypotension			

subjects affected / exposed	2 / 49 (4.08%)	0 / 49 (0.00%)	3 / 47 (6.38%)
occurrences (all)	2	0	4
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 49 (4.08%)	3 / 49 (6.12%)	3 / 47 (6.38%)
occurrences (all)	2	5	4
Fatigue			
subjects affected / exposed	6 / 49 (12.24%)	7 / 49 (14.29%)	11 / 47 (23.40%)
occurrences (all)	6	9	13
Oedema peripheral			
subjects affected / exposed	1 / 49 (2.04%)	8 / 49 (16.33%)	5 / 47 (10.64%)
occurrences (all)	1	9	5
Pyrexia			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	0 / 47 (0.00%)
occurrences (all)	3	3	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 49 (6.12%)	14 / 49 (28.57%)	8 / 47 (17.02%)
occurrences (all)	3	18	11
Dyspnoea			
subjects affected / exposed	7 / 49 (14.29%)	12 / 49 (24.49%)	7 / 47 (14.89%)
occurrences (all)	8	15	8
Epistaxis			
subjects affected / exposed	0 / 49 (0.00%)	5 / 49 (10.20%)	3 / 47 (6.38%)
occurrences (all)	0	6	3
Nasal congestion			
subjects affected / exposed	5 / 49 (10.20%)	3 / 49 (6.12%)	4 / 47 (8.51%)
occurrences (all)	5	3	4
Oropharyngeal pain			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	3 / 47 (6.38%)
occurrences (all)	3	2	3
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	2 / 49 (4.08%)	2 / 49 (4.08%)	5 / 47 (10.64%)
occurrences (all)	2	2	5
Anxiety			

subjects affected / exposed	0 / 49 (0.00%)	3 / 49 (6.12%)	1 / 47 (2.13%)
occurrences (all)	0	3	1
Insomnia			
subjects affected / exposed	3 / 49 (6.12%)	3 / 49 (6.12%)	3 / 47 (6.38%)
occurrences (all)	3	3	4
Investigations			
International normalised ratio increased			
subjects affected / exposed	5 / 49 (10.20%)	2 / 49 (4.08%)	1 / 47 (2.13%)
occurrences (all)	5	2	1
Weight decreased			
subjects affected / exposed	3 / 49 (6.12%)	1 / 49 (2.04%)	3 / 47 (6.38%)
occurrences (all)	3	1	3
Weight increased			
subjects affected / exposed	1 / 49 (2.04%)	3 / 49 (6.12%)	3 / 47 (6.38%)
occurrences (all)	1	4	3
White blood cell count decreased			
subjects affected / exposed	3 / 49 (6.12%)	1 / 49 (2.04%)	0 / 47 (0.00%)
occurrences (all)	3	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	3 / 49 (6.12%)	0 / 49 (0.00%)	0 / 47 (0.00%)
occurrences (all)	3	0	0
Palpitations			
subjects affected / exposed	3 / 49 (6.12%)	7 / 49 (14.29%)	4 / 47 (8.51%)
occurrences (all)	4	10	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 49 (16.33%)	7 / 49 (14.29%)	13 / 47 (27.66%)
occurrences (all)	8	9	15
Headache			
subjects affected / exposed	8 / 49 (16.33%)	15 / 49 (30.61%)	20 / 47 (42.55%)
occurrences (all)	8	19	27
Presyncope			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	8 / 47 (17.02%)
occurrences (all)	0	1	8
Syncope			

subjects affected / exposed	1 / 49 (2.04%)	2 / 49 (4.08%)	2 / 47 (4.26%)
occurrences (all)	1	2	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 49 (2.04%)	3 / 49 (6.12%)	4 / 47 (8.51%)
occurrences (all)	1	3	4
Iron deficiency anaemia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 49 (2.04%)	4 / 47 (8.51%)
occurrences (all)	1	1	5
Leukocytosis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	1 / 47 (2.13%)
occurrences (all)	0	2	1
Thrombocytopenia			
subjects affected / exposed	4 / 49 (8.16%)	1 / 49 (2.04%)	0 / 47 (0.00%)
occurrences (all)	4	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 49 (6.12%)	1 / 49 (2.04%)	2 / 47 (4.26%)
occurrences (all)	3	1	2
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	4 / 47 (8.51%)
occurrences (all)	0	0	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 49 (2.04%)	5 / 49 (10.20%)	1 / 47 (2.13%)
occurrences (all)	2	5	1
Abdominal pain upper			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	3 / 47 (6.38%)
occurrences (all)	5	3	3
Constipation			
subjects affected / exposed	2 / 49 (4.08%)	1 / 49 (2.04%)	9 / 47 (19.15%)
occurrences (all)	2	1	11
Diarrhoea			
subjects affected / exposed	9 / 49 (18.37%)	15 / 49 (30.61%)	14 / 47 (29.79%)
occurrences (all)	11	17	18
Vomiting			

subjects affected / exposed	3 / 49 (6.12%)	6 / 49 (12.24%)	4 / 47 (8.51%)
occurrences (all)	3	8	10
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 49 (6.12%)	5 / 49 (10.20%)	6 / 47 (12.77%)
occurrences (all)	3	6	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 49 (8.16%)	3 / 49 (6.12%)	3 / 47 (6.38%)
occurrences (all)	4	3	3
Back pain			
subjects affected / exposed	3 / 49 (6.12%)	1 / 49 (2.04%)	4 / 47 (8.51%)
occurrences (all)	3	1	5
Muscle spasms			
subjects affected / exposed	6 / 49 (12.24%)	1 / 49 (2.04%)	3 / 47 (6.38%)
occurrences (all)	6	1	3
Musculoskeletal chest pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	2 / 49 (4.08%)	1 / 49 (2.04%)	4 / 47 (8.51%)
occurrences (all)	2	1	4
Pain in extremity			
subjects affected / exposed	4 / 49 (8.16%)	1 / 49 (2.04%)	8 / 47 (17.02%)
occurrences (all)	4	2	9
Pain in jaw			
subjects affected / exposed	4 / 49 (8.16%)	3 / 49 (6.12%)	5 / 47 (10.64%)
occurrences (all)	4	3	6
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 49 (4.08%)	1 / 49 (2.04%)	4 / 47 (8.51%)
occurrences (all)	3	1	5
Cellulitis			
subjects affected / exposed	1 / 49 (2.04%)	4 / 49 (8.16%)	0 / 47 (0.00%)
occurrences (all)	1	4	0
Gastroenteritis			

subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	0 / 47 (0.00%)
occurrences (all)	3	3	0
Gastrointestinal viral infection			
subjects affected / exposed	4 / 49 (8.16%)	0 / 49 (0.00%)	3 / 47 (6.38%)
occurrences (all)	4	0	4
Influenza			
subjects affected / exposed	4 / 49 (8.16%)	1 / 49 (2.04%)	0 / 47 (0.00%)
occurrences (all)	4	1	0
Nasopharyngitis			
subjects affected / exposed	9 / 49 (18.37%)	6 / 49 (12.24%)	7 / 47 (14.89%)
occurrences (all)	10	12	10
Pneumonia			
subjects affected / exposed	2 / 49 (4.08%)	4 / 49 (8.16%)	1 / 47 (2.13%)
occurrences (all)	2	4	1
Respiratory tract infection			
subjects affected / exposed	2 / 49 (4.08%)	2 / 49 (4.08%)	0 / 47 (0.00%)
occurrences (all)	3	2	0
Sepsis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	2 / 47 (4.26%)
occurrences (all)	3	3	2
Upper respiratory tract infection			
subjects affected / exposed	7 / 49 (14.29%)	13 / 49 (26.53%)	7 / 47 (14.89%)
occurrences (all)	8	17	7
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 49 (6.12%)	4 / 49 (8.16%)	0 / 47 (0.00%)
occurrences (all)	4	4	0
Hypokalaemia			
subjects affected / exposed	2 / 49 (4.08%)	6 / 49 (12.24%)	4 / 47 (8.51%)
occurrences (all)	2	7	6

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	34 / 37 (91.89%)		
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 37 (16.22%)		
occurrences (all)	6		
Dyspnoea			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			

subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		

Headache			
subjects affected / exposed	8 / 37 (21.62%)		
occurrences (all)	8		
Presyncope			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Iron deficiency anaemia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Leukocytosis			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		

Constipation			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	5 / 37 (13.51%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	5 / 37 (13.51%)		
occurrences (all)	5		
Pain in jaw			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
Infections and infestations			

Bronchitis subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Cellulitis subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3		
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0		
Gastrointestinal viral infection subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Influenza subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 3		
Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 37 (24.32%) 12		
Pneumonia subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Respiratory tract infection subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3		
Sepsis subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Sinusitis subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 4		
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2014	• The ClinicalTrials.gov Identifier was provided. • Data from two Phase 1 drug-drug interaction studies (GS-US-223-1432 and GS-US-223-1434) were included. Accordingly, updates were made to the guidance on concomitant medication use. • Inclusion Criteria 7 was clarified to state that pulmonary function tests may be performed with or without bronchodilation. • Exclusion Criteria 22 and 23, which prohibited the concomitant use of P-gp substrates and organic anion transporting polypeptide 1 inhibitors, were removed. • The percentage of subjects to be randomized who were receiving stable treatment with bosentan was limited to 25%. • The duration of treatment for Canadian subjects in the long-term treatment period was reduced from a maximum of 7 years to 2.5 years. • The maximum limit on the number of subjects enrolled per site was added. • The duration of time that certain PAH medications (eg, oral and inhaled prostanoids) must be held prior to efficacy assessments was reduced. • The recommended sequence of study assessments was revised so that blood collection was performed prior to exercise (the 6-minute walk test [6MWT]). • A list of recommended assessments to perform at unscheduled visits was added. • Instructions for conducting the 6MWT and Borg category-ratio (CR) 10 scale were added. • Instructions for retaining original copies of ECG and RHC tracings were added. • The guidance for PAH medication dose hold prior to efficacy assessments was updated for oral treprostinil, from 10 to 4 hours, to reflect 3 times daily dosing.
01 October 2015	• Updated Cover Page contact information • Updated information for completed studies of GS-4997 • Moved Section 3.6 Pharmacokinetic Assessments to Section 6.3.3, where it was more appropriate • Clarified inclusion exclusion criteria 8 and 11 and added exclusion criterion 32 • Further defined which concomitant medications were allowed or prohibited and provided timeframes for such • Updated Cover Page contact information • Updated information for completed studies of GS-4997 • Moved Section 3.6 Pharmacokinetic Assessments to Section 6.3.3, where it was more appropriate • Clarified inclusion exclusion criteria 8 and 11 and added exclusion criterion 32 • Further defined which concomitant medications were allowed or prohibited and provided timeframes for such

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported