Clinical trial results:
Prospective, Multi-center, Double-blind, Randomized, Active-controlled, Triple-dummy, Parallel-group, Group-sequential, Adaptive Phase 3 Clinical Study to Compare the Efficacy and Safety of Macitentan and Tadalafil Monotherapies With the Corresponding Fixed Dose Combination in Subjects With Pulmonary Arterial Hypertension (PAH), Followed by an Open-label Treatment Period With Macitentan and Tadalafil Fixed Dose Combination Therapy

Summary

EudraCT number	2014-004786-25
Trial protocol	DE PL ES BG IT
Global end of trial date	27 September 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	AC-077A301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03904693
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.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	27 September 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the effect of the macitentan 10 milligrams (mg) and tadalafil 40 mg as a fixed dose combination (M/T FDC) vs macitentan 10 mg alone on pulmonary vascular resistance (PVR) at end of double-blind treatment (EDBT) in participants with symptomatic World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) who were PAH-specific treatment-naive or were currently treated with an endothelin receptor antagonists (ERA) as monotherapy and to evaluate the effect of the M/T FDC vs tadalafil 40 mg alone on PVR at EDBT in participants with symptomatic WHO Group 1 PAH who are PAH-specific treatment-naive or were currently treated with a phosphodiesterase type-5 inhibitor (PDE-5i) as monotherapy.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2019
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	South Africa: 6
Country: Number of subjects enrolled	China: 23
Country: Number of subjects enrolled	Japan: 8
Country: Number of subjects enrolled	Malaysia: 13
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Türkiye: 17
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Spain: 8

Worldwide total number of subjects	186
EEA total number of subjects	43

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)	148
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 187 participants were enrolled and randomised, of whom 186 received treatment. Of these, 170 completed the treatment, and 177 completed the double-blind (DB) period. Among them, 169 entered the open-label (OL) extension and received treatment; 135 completed the treatment, and 144 participants completed the study.

Period 1

Period 1 title	DB Treatment Period (Week 1 to Week 16)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg

Arm description:

During double-blind treatment period, participants who were either treatment-naive or on a predefined stable dose of endothelin receptor antagonist (ERA), received one tablet of macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg, orally, once daily at Weeks 1 and 2 (titration phase). From Week 3 to 16 (maintenance phase), participants continued to receive one tablet of macitentan 10 mg and two tablets placebo tablet matching to tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.

Arm type	Active comparator
Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	ACT-064992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet of macitentan 10 mg orally, once daily at Weeks 1 and 2 (titration phase) and from Week 3 to 16 (maintenance phase).

Investigational medicinal product name	Placebo matching to M/T FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet of placebo matching to M/T FDC, orally, once daily from Week 3 to 16 (maintenance phase).

Investigational medicinal product name	Placebo matching to Tadalafil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received two tablets of placebo matching to tadalafil 20 mg, orally, once daily at Weeks 1 and 2 (titration phase) and from Week 3 to 16 (maintenance phase).

Arm title	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg)

Arm description:

During DB treatment period, participants who were either treatment-naive or on a predefined stable dose of phosphodiesterase type-5 inhibitor (PDE-5i), received one tablet (two tablets if already on allowable dose at baseline) of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (titration phase). Participants further received two tablets of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg, orally, once daily at Week 2 (titration phase). From Week 3 to 16 (maintenance phase), participants received two tablets of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and one tablet of placebo matching to M/T FDC, orally, once daily.

Arm type	Active comparator
Investigational medicinal product name	Tadalafil 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet (two tablets if already on allowable dose at baseline) of tadalafil 20 mg, orally, once daily at Week 1 (titration phase). Participants further received two tablets of tadalafil 20 mg, orally, once daily at Week 2 (titration phase) and from Week 3 to 16 (maintenance phase).

Investigational medicinal product name	Placebo matching to M/T FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet of placebo matching to M/T FDC, orally, once daily from Week 3 to 16 (maintenance phase).

Investigational medicinal product name	Placebo matching to Macitentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet of placebo matching to macitentan 10 mg, orally, once daily at Week 1 and Week 2 (titration phase) and from Week 3 to 16 (maintenance phase).

Arm title	DB: Treatment-naive/Prior ERA/ PDE-5i Strata: M/T FDC

Arm description:

During double-blind treatment period, participants who were either treatment-naive or on a predefined stable dose of ERA or PDE-5i, received one tablet of macitentan 10 mg along with one tablet of tadalafil 20 mg and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (uptitration phase). Participants further received one tablet of macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily at Week 2 (uptitration phase). From Week 3 to 16 (maintenance phase), participants received one tablet of placebo matching to macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg and one tablet of macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.

Arm type	Experimental
Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	ACT-064992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet of macitentan 10 mg orally, once daily at Weeks 1 and 2 (titration phase).

Investigational medicinal product name	Tadalafil 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet of tadalafil 20 mg, orally, once daily at Week 1 (uptitration phase). Participants further received two tablets of tadalafil 20 mg, orally, once daily at Week 2 (uptitration phase).

Investigational medicinal product name	M/T FDC
Investigational medicinal product code	ACT-064992D
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet of M/T FDC, orally, once daily from Week 3 to 16 (maintenance phase).

Investigational medicinal product name	Placebo matching to Macitentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet of placebo matching to macitentan 10 mg, orally, once daily from Week 3 to 16 (maintenance phase).

Investigational medicinal product name	Placebo matching to Tadalafil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (uptitration phase). From Week 3 to 16 (maintenance phase), participants received two tablets of placebo matching to tadalafil 20 mg, orally, once daily.

Number of subjects in period 1	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg)	DB: Treatment-naive/Prior ERA/ PDE-5i Strata: M/T FDC
Started	35	44	107
Naive and Prior ERA Strata: M/T FDC	0 [1]	0 [2]	70 [3]
Naive and Prior PDE-5i Strata: M/T FDC	0 [4]	0 [5]	86 [6]
Completed	35	43	99
Not completed	0	1	8
Adverse event, serious fatal	-	-	2
Consent withdrawn by subject	-	1	4
Physician decision	-	-	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only reported subjects were planned to be included in the milestone.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only reported subjects were planned to be included in the milestone.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only reported subjects were planned to be included in the milestone.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only reported subjects were planned to be included in the milestone.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only reported subjects were planned to be included in the milestone.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only reported subjects were planned to be included in the milestone.

Period 2

Period 2 title	OL Treatment Period (Week 17 to Week189)
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	OL: Treatment-naive and Prior ERA Strata: M/T FDC

Arm description:

After completion of DB phase, participants who were either treatment-naive or on a predefined stable dose of ERA and received macitentan monotherapy during DB phase entered open label (OL) phase. During the OL phase participants received one tablet of macitentan 10 mg along with one tablet of tadalafil 20 mg and one tablet of placebo matching tadalafil 20 mg, orally, once daily for first 7 days (Week 17, titration phase). Subsequently participants received two tablets of tadalafil 20 mg along with one tablet of macitentan 10 mg, orally, once daily for 7 days (Week 18, titration phase). From Weeks 19 to 183 (maintenance phase), participants continued to receive one tablet of M/T FDC, orally, once daily.

Arm type	Active comparator
Investigational medicinal product name	M/T FDC
Investigational medicinal product code	ACT-064992D
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the OL phase participants received one tablet of M/T FDC, orally, once daily from Weeks 19 to 183 (maintenance phase).

Investigational medicinal product name	Placebo matching Tadalafil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the OL phase participants received one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 17 (titration phase).

Investigational medicinal product name	Tadalafil 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the OL phase participants received one tablet of tadalafil 20 mg orally, once daily at Week 17 and Week 18 (titration phase).

Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	ACT-064992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the OL phase participants received one tablet of macitentan 10 mg orally, once daily at Week 17 and Week 18 (titration phase).

Arm title	OL: Treatment-naive and Prior PDE-5i Strata: M/T FDC

Arm description:

After completion of DB phase, participants who were either treatment-naive or on a predefined stable dose of PDE-5i and received tadalafil monotherapy during DB phase entered OL phase. During the OL phase participants received one tablet of macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily for the first 2 weeks (Week 17 and Week 18; titration phase). From Weeks 19 to 183 (maintenance phase), participants continued to receive one tablet of M/T FDC, orally, once daily.

Arm type	Active comparator
Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	ACT-064992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the OL phase participants received one tablet of macitentan 10 mg, orally, once daily for first 2 weeks (week 17 and Week 18; titration phase).

Investigational medicinal product name	Tadalafil 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the OL phase participants received two tablet of tadalafil 20 mg, orally, once daily for first 2 weeks (week 17 and Week 18; titration phase).

Investigational medicinal product name	M/T FDC
Investigational medicinal product code	ACT-064992D
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the OL phase participants received one tablet of M/T FDC, orally, once daily from Weeks 19 to 183 (maintenance phase).

Arm title	OL: Treatment-naive and Prior ERA/ PDE-5i Strata: M/T FDC

Arm description:

After completion of DB phase, participants who were either treatment-naive or on a predefined stable

dose of ERA or PDE-5i and received M/T FDC during DB phase entered OL phase. During the OL phase participants received one tablet macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily for 2 weeks (Week 17 and Week 18; titration phase). From Weeks 19 to 183 (maintenance phase), participants continued to receive one tablet of M/T FDC, orally, once daily.

Arm type	Experimental
Investigational medicinal product name	M/T FDC
Investigational medicinal product code	ACT-064992D
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the OL phase participants received one tablet of M/T FDC, orally, once daily from Weeks 19 to 183 (maintenance phase).

Investigational medicinal product name	Tadalafil 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the OL phase participants received two tablet of tadalafil 20 mg, orally, once daily for first 2 weeks (week 17 and Week 18; titration phase).

Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	ACT-064992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the OL phase participants received one tablet of macitentan 10 mg, orally, once daily for first 2 weeks (week 17 and Week 18; titration phase).

Number of subjects in period 2[7]	OL: Treatment-naive and Prior ERA Strata: M/T FDC	OL: Treatment-naive and Prior PDE-5i Strata: M/T FDC	OL: Treatment-naive and Prior ERA/ PDE-5i Strata: M/T FDC
Started	35	43	91
Completed	30	38	76
Not completed	5	5	15
Adverse event, serious fatal	-	-	5
Consent withdrawn by subject	2	4	7
Adverse event, non-fatal	2	-	-
Initiated prohibited medication	1	-	-
Technical problems	-	-	1
Family problems	-	-	1
Noncompliance with study drug	-	1	-
Lost to follow-up	-	-	1

Notes:

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

Justification: Only reported subjects were planned to be included in the current period.

Baseline characteristics

Reporting groups	
Reporting group title	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg
Reporting group description:	
During double-blind treatment period, participants who were either treatment-naive or on a predefined stable dose of endothelin receptor antagonist (ERA), received one tablet of macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg, orally, once daily at Weeks 1 and 2 (titration phase). From Week 3 to 16 (maintenance phase), participants continued to receive one tablet of macitentan 10 mg and two tablets placebo tablet matching to tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.	
Reporting group title	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg)
Reporting group description:	
During DB treatment period, participants who were either treatment-naive or on a predefined stable dose of phosphodiesterase type-5 inhibitor (PDE-5i), received one tablet (two tablets if already on allowable dose at baseline) of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (titration phase). Participants further received two tablets of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg, orally, once daily at Week 2 (titration phase). From Week 3 to 16 (maintenance phase), participants received two tablets of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and one tablet of placebo matching to M/T FDC, orally, once daily.	
Reporting group title	DB: Treatment-naive/Prior ERA/ PDE-5i Strata: M/T FDC
Reporting group description:	
During double-blind treatment period, participants who were either treatment-naive or on a predefined stable dose of ERA or PDE-5i, received one tablet of macitentan 10 mg along with one tablet of tadalafil 20 mg and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (uptitration phase). Participants further received one tablet of macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily at Week 2 (uptitration phase). From Week 3 to 16 (maintenance phase), participants received one tablet of placebo matching to macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg and one tablet of macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.	

Reporting group values	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg)	DB: Treatment-naive/Prior ERA/ PDE-5i Strata: M/T FDC
Number of subjects	35	44	107
Age Categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	51.3	53.1	48.7
standard deviation	± 15.85	± 13.66	± 15.78
Gender categorical			
Units: Subjects			
Male	6	10	25
Female	29	34	82

Reporting group values	Total		
Number of subjects	186		
Age Categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Male	41		
Female	145		

End points reporting groups

Reporting group title	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg

Reporting group description:

During double-blind treatment period, participants who were either treatment-naive or on a predefined stable dose of endothelin receptor antagonist (ERA), received one tablet of macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg, orally, once daily at Weeks 1 and 2 (titration phase). From Week 3 to 16 (maintenance phase), participants continued to receive one tablet of macitentan 10 mg and two tablets placebo tablet matching to tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.

Reporting group title	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg)

Reporting group description:

During DB treatment period, participants who were either treatment-naive or on a predefined stable dose of phosphodiesterase type-5 inhibitor (PDE-5i), received one tablet (two tablets if already on allowable dose at baseline) of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (titration phase). Participants further received two tablets of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg, orally, once daily at Week 2 (titration phase). From Week 3 to 16 (maintenance phase), participants received two tablets of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and one tablet of placebo matching to M/T FDC, orally, once daily.

Reporting group title	DB: Treatment-naive/Prior ERA/ PDE-5i Strata: M/T FDC

Reporting group description:

During double-blind treatment period, participants who were either treatment-naive or on a predefined stable dose of ERA or PDE-5i, received one tablet of macitentan 10 mg along with one tablet of tadalafil 20 mg and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (uptitration phase). Participants further received one tablet of macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily at Week 2 (uptitration phase). From Week 3 to 16 (maintenance phase), participants received one tablet of placebo matching to macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg and one tablet of macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.

Reporting group title	OL: Treatment-naive and Prior ERA Strata: M/T FDC

Reporting group description:

After completion of DB phase, participants who were either treatment-naive or on a predefined stable dose of ERA and received macitentan monotherapy during DB phase entered open label (OL) phase. During the OL phase participants received one tablet of macitentan 10 mg along with one tablet of tadalafil 20 mg and one tablet of placebo matching tadalafil 20 mg, orally, once daily for first 7 days (Week 17, titration phase). Subsequently participants received two tablets of tadalafil 20 mg along with one tablet of macitentan 10 mg, orally, once daily for 7 days (Week 18, titration phase). From Weeks 19 to 183 (maintenance phase), participants continued to receive one tablet of M/T FDC, orally, once daily.

Reporting group title	OL: Treatment-naive and Prior PDE-5i Strata: M/T FDC

Reporting group description:

After completion of DB phase, participants who were either treatment-naive or on a predefined stable dose of PDE-5i and received tadalafil monotherapy during DB phase entered OL phase. During the OL phase participants received one tablet of macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily for the first 2 weeks (Week 17 and Week 18; titration phase). From Weeks 19 to 183 (maintenance phase), participants continued to receive one tablet of M/T FDC, orally, once daily.

Reporting group title	OL: Treatment-naive and Prior ERA/ PDE-5i Strata: M/T FDC

Reporting group description:

After completion of DB phase, participants who were either treatment-naive or on a predefined stable dose of ERA or PDE-5i and received M/T FDC during DB phase entered OL phase. During the OL phase participants received one tablet macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily for 2 weeks (Week 17 and Week 18; titration phase). From Weeks 19 to 183 (maintenance phase), participants continued to receive one tablet of M/T FDC, orally, once daily.

Subject analysis set title	DB: Treatmentnaive And Prior ERA Strata: M/T FDC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

During double-blind treatment period, participants who were either treatment-naive or on a predefined stable dose of ERA, received one tablet of macitentan 10 mg along with one tablet of tadalafil 20 mg

and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (uptitration phase). Participants further received one tablet of macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily at Week 2 (uptitration phase). From Week 3 to 16 (maintenance phase), participants received one tablet of placebo matching to macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg and one tablet of macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.

Subject analysis set title	DB: Treatment-naive And Prior PDE-5i Strata: M/T FDC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

During double-blind treatment period, participants who were either treatment-naive or on a predefined stable dose of PDE-5i, received one tablet of macitentan 10 mg along with one tablet of tadalafil 20 mg and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (uptitration phase). Participants further received one tablet of macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily at Week 2 (uptitration phase). From Week 3 to 16 (maintenance phase), participants received one tablet of placebo matching to macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg and one tablet of macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.

Primary: Change in Pulmonary Vascular Resistance (PVR) Expressed as the Ratio of Geometric Means of End of Double-blind Treatment (EDBT) to Baseline

End point title	Change in Pulmonary Vascular Resistance (PVR) Expressed as the Ratio of Geometric Means of End of Double-blind Treatment (EDBT) to Baseline[1]

End point description:

Change in PVR expressed as the ratio of geometric means of EDBT to baseline were reported. The full analysis set (FAS) included all randomised participants who received at least one dose of study treatment (for participants on FDC, at least one dose of either macitentan or tadalafil). Treatment-naive participants randomised to both macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC) arms (ERA and PDE-5i strata) were counted twice as per planned analysis.

End point type	Primary

End point timeframe:

Baseline, EDBT (up to 16 weeks)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be analysed for specified baseline arms only.

End point values	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg)	DB: Treatmentnaive And Prior ERA Strata: M/T FDC	DB: Treatment-naive And Prior PDE-5i Strata: M/T FDC
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	35	44	70	86
Units: Ratio				
geometric mean (confidence interval 95%)	0.77 (0.69 to 0.87)	0.78 (0.72 to 0.84)	0.55 (0.50 to 0.60)	0.56 (0.52 to 0.60)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg v DB: Treatmentnaive And Prior ERA Strata: M/T FDC

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.82

Statistical analysis title	Statistical Analysis 2
Comparison groups	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg) v DB: Treatment-naive And Prior PDE-5i Strata: M/T FDC
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.8

Secondary: Change From Baseline to EDBT in 6-minutes Walking Distance (6MWD)

End point title	Change From Baseline to EDBT in 6-minutes Walking Distance (6MWD)[2]

End point description:

Change from baseline to EDBT in 6MWD were reported. 6MWD was measured by 6-minute walk test (6MWT). The test measured the distance an individual was able to walk over a total of six minutes on a hard, flat surface with no obstacles. The goal was for the individual to walk as far as possible in 6 minutes. The FAS included all randomised participants who received at least one dose of study treatment (for participants on FDC, at least one dose of either macitentan or tadalafil). Treatment-naive participants randomised to both M/T FDC arms (ERA and PDE-5i strata) were counted twice as per planned analysis.

End point type	Secondary

End point timeframe:

Baseline, EDBT (Week 16)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be analysed for specified baseline arms only.

End point values	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg)	DB: Treatmentnaive And Prior ERA Strata: M/T FDC	DB: Treatment-naive And Prior PDE-5i Strata: M/T FDC
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	35	44	70	86
Units: Meters				
arithmetic mean (standard deviation)	38.5 (± 70.42)	15.9 (± 45.04)	52.9 (± 88.23)	43.4 (± 78.03)

Statistical analyses

Statistical analysis title	Statistical Analysis 4
Comparison groups	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg) v DB: Treatment-naive And Prior PDE-5i Strata: M/T FDC
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0591
Method	ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	25.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	51.59

Statistical analysis title	Statistical Analysis 3
Comparison groups	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg v DB: Treatmentnaive And Prior ERA Strata: M/T FDC
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3802
Method	ANCOVA
Parameter estimate	Geometric Mean Ratio
Point estimate	16.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17
upper limit	49.08

Secondary: Change From Baseline in Pulmonary Arterial Hypertension Symptoms

and Impact (PAH-SYMPACT) in Cardiopulmonary Symptom Domain Scores to EDBT

End point title	Change From Baseline in Pulmonary Arterial Hypertension Symptoms and Impact (PAH-SYMPACT) in Cardiopulmonary Symptom Domain Scores to EDBT[3]

End point description:

PAH-SYMPACT was a pulmonary arterial hypertension (PAH)-specific patient-reported outcomes questionnaire that consists of 11 symptoms items, 11 impacts items and 1 item on oxygen use. The symptom items were divided into cardiopulmonary and cardiovascular domains, and the impact items were divided into physical and emotional/cognitive domains. Cardiopulmonary symptoms contain 6 items; shortness of breath, fatigue, lack of energy, swelling in ankles or legs, swelling in stomach area, and cough. Scores for the individual items were reported on a 5-point Likert scale, ranging from 0 (no symptom at all) to 4 (very severe symptoms), with higher scores indicated greater symptom severity. The PAH-SYMPACT symptoms analysis set included all participants included in the FAS for whom at least one baseline value of symptoms domain was provided. Treatment-naive participants randomised to both M/T FDC arms (ERA and PDE-5i strata) were counted twice as per planned analysis.

End point type	Secondary

End point timeframe:

Baseline, EDBT (Week 16)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data was planned to be analysed for specified baseline arms only.

End point values	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg)	DB: Treatmentnaive And Prior ERA Strata: M/T FDC	DB: Treatment-naive And Prior PDE-5i Strata: M/T FDC
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	33	42	66	81
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.14 (± 0.478)	-0.13 (± 0.554)	-0.20 (± 0.394)	-0.15 (± 0.404)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pulmonary Arterial Hypertension Symptoms and Impact (PAH-SYMPACT) in Cardiovascular Symptom Domain Scores to EDBT

End point title	Change From Baseline in Pulmonary Arterial Hypertension Symptoms and Impact (PAH-SYMPACT) in Cardiovascular Symptom Domain Scores to EDBT[4]

End point description:

PAHSYMPACT is a PAH-specific patient-reported outcomes questionnaire that consists of 11 symptoms items, 11 impacts items and 1 item on oxygen use. The symptom items were divided into cardiopulmonary and cardiovascular domains, and the impact items were divided into physical and emotional/cognitive domains. Cardiovascular symptoms contain 5 items; heart palpitations (heart fluttering), rapid heartbeat, chest pain, chest tightness, and lightheadedness. Scores for the individual items were reported on a 5-point Likert scale, ranging from 0 (no symptom at all) to 4 (very severe symptom), with higher scores indicated greater symptom severity. The PAH-SYMPACT symptoms analysis set included all participants included in the FAS for whom at least one baseline value of symptoms domain was provided. Treatment-naive participants randomised to both M/T FDC arms (ERA and PDE-5i strata) were counted twice as per planned analysis.

End point type	Secondary

End point timeframe:

Baseline, EDBT (Week 16)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be analysed for specified baseline arms only.

End point values	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg)	DB: Treatmentnaive And Prior ERA Strata: M/T FDC	DB: Treatment-naive And Prior PDE-5i Strata: M/T FDC
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	33	42	66	81
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.14 (± 0.473)	-0.18 (± 0.612)	-0.15 (± 0.349)	-0.10 (± 0.318)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Absence of Worsening in World Health Organization (WHO) Functional Class (FC) From Baseline at EDBT

End point title	Percentage of Participants With Absence of Worsening in World Health Organization (WHO) Functional Class (FC) From Baseline at EDBT[5]

End point description:

Percentage of participants with absence of worsening in FC from baseline at EDBT were reported. Study was adaptive with 2 stages: Stage 1 and Stage 2. WHO functional classification (FC), PAH range from Class I (no limitation in physical activity, no dyspnea or fatigue, chest pain, or near syncope with normal activity), Class II (slight limitation of physical activity), Class III (marked limitation of physical activity), Class IV (cannot perform a physical activity without any symptoms, dyspnea and/or fatigue at rest). The FAS included all randomised participants who received at least one dose of study treatment (for participants on FDC, at least one dose of either macitentan or tadalafil). Treatment-naive participants randomised to both M/T FDC arms (ERA and PDE-5i strata) were counted twice as per planned analysis. Here, 'N' (overall number of participants analysed) signifies the number of participants evaluable and "n" number of participants evaluable for specified category.

End point type	Secondary

End point timeframe:

At Week 16 (EDBT)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be analysed for specified baseline arms only.

End point values	DB: Treatment-naive/Prior ERA Strata (S): Macitentan 10mg	DB: Treatment-naive/Prior PDE-5i S :Tadalafil 20 mg(2*20 mg)	DB: Treatmentnaive And Prior ERA Strata: M/T FDC	DB: Treatment-naive And Prior PDE-5i Strata: M/T FDC
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	18	22	38	47
Units: Percentage of participants				

number (not applicable)				
Stage: 1 : Class I (n=18, 22, 47, 38)	5.6	4.5	5.3	12.8
Stage: I : Class II (n=18, 38, 22, 47)	55.6	63.6	57.9	59.6
Stage: I : Class III (n=18, 38, 22, 47, 38)	38.9	31.8	23.7	25.5
Stage: I : Class IV (n=18, , 38, 22, 47)	0	0	0	0
Stage: 1 : Missing (n=18, , 38, 22, 47)	0	13.2	13.2	2.1
Stage: 2 : Class I (n=17, 32, 22, 39)	11.8	9.1	9.4	7.7
Stage: 2 : Class II (n=17, 32, 22, 39)	52.9	54.5	75.0	61.5
Stage: 2 : Class III (n=17, 32, 22, 39)	35.3	36.4	15.6	25.6
Stage: 2 : Class IV (n=17, 32, 22, 39)	0	0	0	0
Stage: 2 : Missing (n=17, 32, 22, 39)	0	0	0	5.1

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

DB phase: From Day 1 to Week 16; OL phase: From Week 16 up to 35 days after last dose (Week 189)

Adverse event reporting additional description:

DB: all treated. OL: combination safety set: participants in M/T FDC in DB and received M/T FDC in DB and those who received M/T FDC in OL. Treatment naive participants in both M/T FDC arms (ERA/PDE-5i strata) counted twice per planned analysis. For participants treated with M/T FDC in DB, combined data from DB and OL was analyzed in OL period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	DB: Treatment-naive and Prior ERA Strata: Macitentan 10 mg

Reporting group description:

During double-blind (DB) treatment period, participants who were either treatment-naive or on a predefined stable dose of endothelin receptor antagonist (ERA), received one tablet of macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg, orally, once daily at Weeks 1 and 2 (titration phase). From Week 3 to 16 (maintenance phase), participants continued to receive one tablet of macitentan 10 mg and two tablets placebo tablet matching to tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.

Reporting group title	DB: Treatment-naive And Prior ERA Strata: M/T FDC

Reporting group description:

During DB treatment period, participants who were either treatment-naive or on a predefined stable dose of ERA, received one tablet of macitentan 10 mg along with one tablet of tadalafil 20 mg and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (uptitration phase). Participants further received one tablet of macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily at Week 2 (uptitration phase). From Week 3 to 16 (maintenance phase), participants received one tablet of placebo matching to macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg and one tablet of macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.

Reporting group title	DB:Treatment-naive/PriorPDE-5i Strata:Tadalafil 20mg(2*20 mg)

Reporting group description:

During double-blind treatment period, participants who were either treatment-naive or on a predefined stable dose of phosphodiesterase type-5 inhibitor (PDE-5i), received one tablet (two tablets if already on allowable dose at baseline) of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (titration phase). Participants further received two tablets of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg, orally, once daily at Week 2 (titration phase). From Week 3 to 16 (maintenance phase), participants received two tablets of tadalafil 20 mg along with one tablet of placebo matching to macitentan 10 mg and one tablet of placebo matching to M/T FDC, orally, once daily.

Reporting group title	DB: Treatment-naive And Prior PDE-5i strata: M/T FDC

Reporting group description:

During DB treatment period, participants who were either treatment-naive or on a predefined stable dose of PDE-5i, received one tablet of macitentan 10 mg along with one tablet of tadalafil 20 mg and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (uptitration phase). Participants further received one tablet of macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily at Week 2 (uptitration phase). From Week 3 to 16 (maintenance phase), participants received one tablet of placebo matching to macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg and one tablet of macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.

Reporting group title	DB: Treatment-naive and Prior ERA/ PDE-5i Strata: M/T FDC

Reporting group description:

During DB treatment period, participants who were either treatment-naive or on a predefined stable

dose of ERA or PDE-5i, received one tablet of macitentan 10 mg along with one tablet of tadalafil 20 mg and one tablet of placebo matching to tadalafil 20 mg, orally, once daily at Week 1 (uptitration phase). Participants further received one tablet of macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily at Week 2 (uptitration phase). From Week 3 to 16 (maintenance phase), participants received one tablet of placebo matching to macitentan 10 mg along with two tablets of placebo matching to tadalafil 20 mg and one tablet of macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), orally, once daily.

Reporting group title	OL: Treatment-naive and Prior ERA Strata: M/T FDC

Reporting group description:

After completion of DB phase, participants who were either treatment-naive or on a predefined stable dose of ERA and received macitentan monotherapy during DB phase entered open label (OL) phase. During the OL phase participants received one tablet of macitentan 10 mg along with one tablet of tadalafil 20 mg and one tablet of placebo matching tadalafil 20 mg, orally, once daily for first 7 days (Week 17, titration phase). Subsequently participants received two tablets of tadalafil 20 mg along with one tablet of macitentan 10 mg, orally, once daily for 7 days (Week 18, titration phase). From Weeks 19 to 183 (maintenance phase), participants continued to receive one tablet of M/T FDC, orally, once daily.

Reporting group title	OL: Treatment-naive and Prior PDE-5i Strata: M/T FDC

Reporting group description:

After completion of DB phase, participants who were either treatment-naive or on a predefined stable dose of PDE-5i and received tadalafil monotherapy during DB phase entered OL phase. During the OL phase participants received one tablet of macitentan 10 mg along with two tablets of tadalafil 20 mg, orally, once daily for the first 2 weeks (Week 17 and Week 18; titration phase). From Weeks 19 to 183 (maintenance phase), participants continued to receive one tablet of M/T FDC, orally, once daily.

Reporting group title	DB + OL: Treatment-naive and Prior ERA/ PDE-5i Strata: M/T FDC

Reporting group description:

During DB phase, participants who were either treatment-naive or on predefined stable dose of ERA/PDE-5i, received macitentan 10mg with tadalafil 20mg and placebo matching to tadalafil 20mg orally once daily(QD) at Week 1(uptitration phase). Participants received one tablet of macitentan 10mg with two tablets of tadalafil 20mg orally QD at Week 2 (uptitration phase). From Week 3-16 (maintenance phase), participants received one tablet of placebo matching to macitentan 10mg and two tablets matching to tadalafil 20mg and one tablet of M/T FDC orally once daily. After completion of DB phase, participants who were either treatment-naive or on a predefined stable dose of ERA/PDE-5i and received M/T FDC during DB phase entered OL phase. During OL phase participants received one tablet macitentan 10mg along with two tablets of tadalafil 20mg orally QD at Weeks 17,18 (titration phase). From Weeks 19-183 (maintenance phase), participants continued with one tablet of M/T FDC orally QD.

Serious adverse events	DB: Treatment-naive and Prior ERA Strata: Macitentan 10 mg	DB: Treatment-naive And Prior ERA Strata: M/T FDC	DB:Treatment-naive/PriorPDE-5i Strata:Tadalafil 20mg(2*20 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 35 (8.57%)	11 / 70 (15.71%)	4 / 44 (9.09%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Prostate Cancer			

subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Mucinous Cystadenocarcinoma Ovary			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Breast Cancer			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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			
Chest Pain			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Fatigue			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Peripheral Swelling			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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
Swelling Face			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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

Reproductive system and breast disorders			
Endometrial Hyperplasia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Endometriosis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Intermenstrual Bleeding			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Ovarian Cyst Ruptured			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Uterine Polyp			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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
Autoimmune Lung Disease			

subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Asthma			
subjects affected / exposed	1 / 35 (2.86%)	0 / 70 (0.00%)	0 / 44 (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
Hypoxia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Respiratory Failure			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Pulmonary Veno-Occlusive Disease			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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
Pulmonary Arterial Hypertension			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Pneumothorax			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Injury, poisoning and procedural complications			
Jaw Fracture			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Humerus Fracture			

subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Femur Fracture			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Overdose			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Patella Fracture			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Subdural Haematoma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 35 (2.86%)	0 / 70 (0.00%)	0 / 44 (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
Cor Pulmonale			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Coronary Artery Disease			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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			

subjects affected / exposed	0 / 35 (0.00%)	2 / 70 (2.86%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial Flutter			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Atrial Fibrillation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Left Ventricular Failure			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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
Palpitations			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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
Sinus Node Dysfunction			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Supraventricular Tachycardia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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			
Epilepsy			

subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Cerebral Infarction			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Horner's Syndrome			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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
Migraine			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Blood and lymphatic system disorders			
Normochromic Anaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Anaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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
Eye disorders			
Retinal Vein Occlusion			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Gastrointestinal disorders			

Colitis Ischaemic			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Gastritis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Haemorrhoids			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Hiatus Hernia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Tongue Cyst			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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
Subileus			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Oesophageal Ulcer			

subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Polyp			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Varices Oesophageal			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Hepatobiliary disorders			
Hepatic Cirrhosis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Portal Hypertension			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Glomerulonephritis Membranous			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Renal Impairment			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Musculoskeletal and connective tissue			

disorders			
Greater Trochanteric Pain Syndrome			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Arthritis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Systemic Scleroderma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Osteonecrosis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Cellulitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Abscess Bacterial			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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

Covid-19 Pneumonia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 70 (1.43%)	0 / 44 (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
Diverticulitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Covid-19			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Gastroenteritis Clostridial			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Influenza			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (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
Parainfluenzae Virus Infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Pneumonia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 70 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Viral			

subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Rhinovirus Infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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
Staphylococcal Bacteraemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (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	DB: Treatment-naive And Prior PDE-5i strata: M/T FDC	DB: Treatment-naive and Prior ERA/ PDE-5i Strata: M/T FDC	OL: Treatment-naive and Prior ERA Strata: M/T FDC
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 86 (13.95%)	15 / 107 (14.02%)	10 / 35 (28.57%)
number of deaths (all causes)	2	3	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Prostate Cancer			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Mucinous Cystadenocarcinoma Ovary			

subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Breast Cancer			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Fatigue			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Peripheral Swelling			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Swelling Face			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Reproductive system and breast disorders			
Endometrial Hyperplasia			

subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Intermenstrual Bleeding			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Ovarian Cyst Ruptured			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Uterine Polyp			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Dyspnoea			
subjects affected / exposed	2 / 86 (2.33%)	2 / 107 (1.87%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune Lung Disease			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			

subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Hypoxia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Pulmonary Veno-Occlusive Disease			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Pulmonary Arterial Hypertension			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Injury, poisoning and procedural complications			
Jaw Fracture			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Humerus Fracture			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Femur Fracture			

subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Overdose			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Patella Fracture			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Subdural Haematoma			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Cor Pulmonale			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Coronary Artery Disease			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Cardiac Failure			
subjects affected / exposed	1 / 86 (1.16%)	2 / 107 (1.87%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial Flutter			

subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Atrial Fibrillation			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Left Ventricular Failure			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Right Ventricular Failure			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Node Dysfunction			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Supraventricular Tachycardia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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			
Epilepsy			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Cerebral Infarction			

subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Hemiparesis			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Horner's Syndrome			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Migraine			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Blood and lymphatic system disorders			
Normochromic Anaemia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Anaemia			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Eye disorders			
Retinal Vein Occlusion			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Gastrointestinal disorders			
Colitis Ischaemic			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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

Gastritis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Haemorrhoids			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus Hernia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Tongue Cyst			
subjects affected / exposed	0 / 86 (0.00%)	1 / 107 (0.93%)	0 / 35 (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
Subileus			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal Ulcer			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Large Intestine Polyp			

subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices Oesophageal			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Hepatobiliary disorders			
Hepatic Cirrhosis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Portal Hypertension			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Glomerulonephritis Membranous			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Renal Impairment			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Musculoskeletal and connective tissue disorders			
Greater Trochanteric Pain Syndrome			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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

Arthritis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Systemic Scleroderma			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 107 (0.93%)	0 / 35 (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
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	2 / 35 (5.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Abscess Bacterial			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19 Pneumonia			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Diverticulitis			

subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (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
Gastroenteritis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Gastroenteritis Clostridial			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Influenza			
subjects affected / exposed	0 / 86 (0.00%)	1 / 107 (0.93%)	0 / 35 (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
Parainfluenzae Virus Infection			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Pneumonia Viral			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Rhinovirus Infection			

subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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
Staphylococcal Bacteraemia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	0 / 35 (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	OL: Treatment-naive and Prior PDE-5i Strata: M/T FDC	DB + OL: Treatment-naive and Prior ERA/ PDE-5i Strata: M/T FDC	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 43 (30.23%)	39 / 107 (36.45%)	
number of deaths (all causes)	2	9	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	0 / 43 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucinous Cystadenocarcinoma Ovary			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer			

subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Swelling			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling Face			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial Hyperplasia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			

subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermenstrual Bleeding			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Cyst Ruptured			
subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Polyp			
subjects affected / exposed	1 / 43 (2.33%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 43 (0.00%)	4 / 107 (3.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Autoimmune Lung Disease			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	0 / 43 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulmonary Veno-Occlusive Disease			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Arterial Hypertension			
subjects affected / exposed	0 / 43 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Jaw Fracture			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			

subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella Fracture			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor Pulmonale			
subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	0 / 43 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial Flutter			
subjects affected / exposed	1 / 43 (2.33%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			

subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Failure			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 43 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Ventricular Failure			
subjects affected / exposed	1 / 43 (2.33%)	4 / 107 (3.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus Node Dysfunction			
subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			

subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Horner's Syndrome			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Normochromic Anaemia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal Vein Occlusion			
subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis Ischaemic			
subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus Hernia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue Cyst			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Ulcer			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Polyp			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices Oesophageal			

subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic Cirrhosis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal Hypertension			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis Membranous			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Impairment			
subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Greater Trochanteric Pain Syndrome			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Systemic Scleroderma			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Bacterial			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 Pneumonia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Covid-19			

subjects affected / exposed	0 / 43 (0.00%)	5 / 107 (4.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Clostridial			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Influenza			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae Virus Infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 43 (2.33%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Viral			
subjects affected / exposed	1 / 43 (2.33%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus Infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Upper Respiratory Tract Infection			

subjects affected / exposed	1 / 43 (2.33%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Bacteraemia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DB: Treatment-naive and Prior ERA Strata: Macitentan 10 mg	DB: Treatment-naive And Prior ERA Strata: M/T FDC	DB:Treatment-naive/PriorPDE-5i Strata:Tadalafil 20mg(2*20 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 35 (45.71%)	49 / 70 (70.00%)	31 / 44 (70.45%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 35 (5.71%)	3 / 70 (4.29%)	0 / 44 (0.00%)
occurrences (all)	2	3	0
Hypotension			
subjects affected / exposed	0 / 35 (0.00%)	5 / 70 (7.14%)	0 / 44 (0.00%)
occurrences (all)	0	5	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 35 (2.86%)	2 / 70 (2.86%)	1 / 44 (2.27%)
occurrences (all)	1	2	1
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 35 (0.00%)	2 / 70 (2.86%)	3 / 44 (6.82%)
occurrences (all)	0	2	4
Pyrexia			
subjects affected / exposed	0 / 35 (0.00%)	2 / 70 (2.86%)	0 / 44 (0.00%)
occurrences (all)	0	3	0

Peripheral Swelling			
subjects affected / exposed	1 / 35 (2.86%)	6 / 70 (8.57%)	0 / 44 (0.00%)
occurrences (all)	2	6	0
Oedema Peripheral			
subjects affected / exposed	4 / 35 (11.43%)	9 / 70 (12.86%)	5 / 44 (11.36%)
occurrences (all)	4	11	6
Respiratory, thoracic and mediastinal disorders			
Nasal Congestion			
subjects affected / exposed	0 / 35 (0.00%)	3 / 70 (4.29%)	0 / 44 (0.00%)
occurrences (all)	0	3	0
Dyspnoea			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	2 / 44 (4.55%)
occurrences (all)	0	1	2
Cough			
subjects affected / exposed	1 / 35 (2.86%)	5 / 70 (7.14%)	2 / 44 (4.55%)
occurrences (all)	1	5	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood Glucose Increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Haemoglobin Decreased			
subjects affected / exposed	0 / 35 (0.00%)	3 / 70 (4.29%)	0 / 44 (0.00%)
occurrences (all)	0	4	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 35 (2.86%)	1 / 70 (1.43%)	2 / 44 (4.55%)
occurrences (all)	3	1	2
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 35 (17.14%)	12 / 70 (17.14%)	6 / 44 (13.64%)
occurrences (all)	7	16	6
Dizziness			

subjects affected / exposed	1 / 35 (2.86%)	2 / 70 (2.86%)	1 / 44 (2.27%)
occurrences (all)	1	2	1
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	1 / 35 (2.86%)	2 / 70 (2.86%)	1 / 44 (2.27%)
occurrences (all)	1	2	1
Leukopenia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Anaemia			
subjects affected / exposed	0 / 35 (0.00%)	6 / 70 (8.57%)	0 / 44 (0.00%)
occurrences (all)	0	8	0
Gastrointestinal disorders			
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 35 (2.86%)	0 / 70 (0.00%)	1 / 44 (2.27%)
occurrences (all)	1	0	1
Haemorrhoids			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 35 (0.00%)	5 / 70 (7.14%)	3 / 44 (6.82%)
occurrences (all)	0	5	4
Vomiting			
subjects affected / exposed	0 / 35 (0.00%)	3 / 70 (4.29%)	2 / 44 (4.55%)
occurrences (all)	0	3	3
Gastritis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 35 (0.00%)	4 / 70 (5.71%)	6 / 44 (13.64%)
occurrences (all)	0	4	7
Dyspepsia			

subjects affected / exposed	0 / 35 (0.00%)	4 / 70 (5.71%)	3 / 44 (6.82%)
occurrences (all)	0	4	3
Musculoskeletal and connective tissue disorders			
Pain in Extremity			
subjects affected / exposed	0 / 35 (0.00%)	2 / 70 (2.86%)	4 / 44 (9.09%)
occurrences (all)	0	2	4
Myalgia			
subjects affected / exposed	0 / 35 (0.00%)	5 / 70 (7.14%)	2 / 44 (4.55%)
occurrences (all)	0	5	2
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Back Pain			
subjects affected / exposed	1 / 35 (2.86%)	5 / 70 (7.14%)	4 / 44 (9.09%)
occurrences (all)	1	5	6
Arthralgia			
subjects affected / exposed	2 / 35 (5.71%)	2 / 70 (2.86%)	4 / 44 (9.09%)
occurrences (all)	2	2	4
Infections and infestations			
Sinusitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	1 / 44 (2.27%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	1 / 35 (2.86%)	1 / 70 (1.43%)	0 / 44 (0.00%)
occurrences (all)	1	1	0
Covid-19			
subjects affected / exposed	2 / 35 (5.71%)	1 / 70 (1.43%)	2 / 44 (4.55%)
occurrences (all)	2	1	2
Suspected Covid-19			
subjects affected / exposed	0 / 35 (0.00%)	0 / 70 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Urinary Tract Infection			
subjects affected / exposed	0 / 35 (0.00%)	2 / 70 (2.86%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Upper Respiratory Tract Infection			

subjects affected / exposed	0 / 35 (0.00%)	2 / 70 (2.86%)	0 / 44 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 70 (1.43%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	1 / 35 (2.86%)	4 / 70 (5.71%)	1 / 44 (2.27%)
occurrences (all)	1	4	1

Non-serious adverse events	DB: Treatment-naive And Prior PDE-5i strata: M/T FDC	DB: Treatment-naive and Prior ERA/ PDE-5i Strata: M/T FDC	OL: Treatment-naive and Prior ERA Strata: M/T FDC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 86 (67.44%)	72 / 107 (67.29%)	28 / 35 (80.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
Vascular disorders			
Flushing			
subjects affected / exposed	3 / 86 (3.49%)	3 / 107 (2.80%)	0 / 35 (0.00%)
occurrences (all)	3	3	0
Hypotension			
subjects affected / exposed	4 / 86 (4.65%)	7 / 107 (6.54%)	1 / 35 (2.86%)
occurrences (all)	4	7	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 86 (2.33%)	3 / 107 (2.80%)	0 / 35 (0.00%)
occurrences (all)	2	3	0
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 86 (2.33%)	3 / 107 (2.80%)	0 / 35 (0.00%)
occurrences (all)	2	3	0
Pyrexia			
subjects affected / exposed	4 / 86 (4.65%)	4 / 107 (3.74%)	0 / 35 (0.00%)
occurrences (all)	6	6	0
Peripheral Swelling			

subjects affected / exposed	6 / 86 (6.98%)	6 / 107 (5.61%)	1 / 35 (2.86%)
occurrences (all)	6	6	1
Oedema Peripheral			
subjects affected / exposed	12 / 86 (13.95%)	14 / 107 (13.08%)	1 / 35 (2.86%)
occurrences (all)	15	18	1
Respiratory, thoracic and mediastinal disorders			
Nasal Congestion			
subjects affected / exposed	3 / 86 (3.49%)	4 / 107 (3.74%)	1 / 35 (2.86%)
occurrences (all)	3	4	1
Dyspnoea			
subjects affected / exposed	2 / 86 (2.33%)	2 / 107 (1.87%)	0 / 35 (0.00%)
occurrences (all)	2	2	0
Cough			
subjects affected / exposed	6 / 86 (6.98%)	6 / 107 (5.61%)	2 / 35 (5.71%)
occurrences (all)	6	6	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Investigations			
Blood Glucose Increased			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Haemoglobin Decreased			
subjects affected / exposed	8 / 86 (9.30%)	8 / 107 (7.48%)	4 / 35 (11.43%)
occurrences (all)	9	9	5
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 86 (2.33%)	3 / 107 (2.80%)	1 / 35 (2.86%)
occurrences (all)	2	3	1
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 86 (16.28%)	18 / 107 (16.82%)	3 / 35 (8.57%)
occurrences (all)	16	23	4
Dizziness			

subjects affected / exposed	3 / 86 (3.49%)	3 / 107 (2.80%)	2 / 35 (5.71%)
occurrences (all)	3	3	3
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	2 / 86 (2.33%)	2 / 107 (1.87%)	0 / 35 (0.00%)
occurrences (all)	2	2	0
Leukopenia			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Thrombocytopenia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	3
Anaemia			
subjects affected / exposed	6 / 86 (6.98%)	8 / 107 (7.48%)	4 / 35 (11.43%)
occurrences (all)	7	10	5
Gastrointestinal disorders			
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	3 / 35 (8.57%)
occurrences (all)	1	1	3
Haemorrhoids			
subjects affected / exposed	0 / 86 (0.00%)	1 / 107 (0.93%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Nausea			
subjects affected / exposed	4 / 86 (4.65%)	6 / 107 (5.61%)	1 / 35 (2.86%)
occurrences (all)	4	6	1
Vomiting			
subjects affected / exposed	4 / 86 (4.65%)	4 / 107 (3.74%)	0 / 35 (0.00%)
occurrences (all)	4	4	0
Gastritis			
subjects affected / exposed	2 / 86 (2.33%)	2 / 107 (1.87%)	3 / 35 (8.57%)
occurrences (all)	2	2	3
Diarrhoea			
subjects affected / exposed	5 / 86 (5.81%)	5 / 107 (4.67%)	0 / 35 (0.00%)
occurrences (all)	5	5	0
Dyspepsia			

subjects affected / exposed	4 / 86 (4.65%)	4 / 107 (3.74%)	0 / 35 (0.00%)
occurrences (all)	4	4	0
Musculoskeletal and connective tissue disorders			
Pain in Extremity			
subjects affected / exposed	2 / 86 (2.33%)	3 / 107 (2.80%)	1 / 35 (2.86%)
occurrences (all)	2	3	1
Myalgia			
subjects affected / exposed	4 / 86 (4.65%)	6 / 107 (5.61%)	5 / 35 (14.29%)
occurrences (all)	4	6	6
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 86 (0.00%)	1 / 107 (0.93%)	2 / 35 (5.71%)
occurrences (all)	0	2	2
Back Pain			
subjects affected / exposed	3 / 86 (3.49%)	5 / 107 (4.67%)	2 / 35 (5.71%)
occurrences (all)	3	5	3
Arthralgia			
subjects affected / exposed	4 / 86 (4.65%)	4 / 107 (3.74%)	3 / 35 (8.57%)
occurrences (all)	4	4	3
Infections and infestations			
Sinusitis			
subjects affected / exposed	1 / 86 (1.16%)	1 / 107 (0.93%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Nasopharyngitis			
subjects affected / exposed	3 / 86 (3.49%)	3 / 107 (2.80%)	2 / 35 (5.71%)
occurrences (all)	3	3	3
Covid-19			
subjects affected / exposed	2 / 86 (2.33%)	2 / 107 (1.87%)	7 / 35 (20.00%)
occurrences (all)	2	2	9
Suspected Covid-19			
subjects affected / exposed	0 / 86 (0.00%)	0 / 107 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Urinary Tract Infection			
subjects affected / exposed	0 / 86 (0.00%)	2 / 107 (1.87%)	2 / 35 (5.71%)
occurrences (all)	0	2	2
Upper Respiratory Tract Infection			

subjects affected / exposed	1 / 86 (1.16%)	2 / 107 (1.87%)	5 / 35 (14.29%)
occurrences (all)	1	2	5
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 86 (2.33%)	2 / 107 (1.87%)	3 / 35 (8.57%)
occurrences (all)	2	2	4
Hyperuricaemia			
subjects affected / exposed	4 / 86 (4.65%)	4 / 107 (3.74%)	0 / 35 (0.00%)
occurrences (all)	4	4	0

Non-serious adverse events	OL: Treatment-naive and Prior PDE-5i Strata: M/T FDC	DB + OL: Treatment-naive and Prior ERA/ PDE-5i Strata: M/T FDC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 43 (88.37%)	89 / 107 (83.18%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 43 (0.00%)	4 / 107 (3.74%)	
occurrences (all)	0	4	
Hypotension			
subjects affected / exposed	1 / 43 (2.33%)	9 / 107 (8.41%)	
occurrences (all)	1	10	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 43 (0.00%)	7 / 107 (6.54%)	
occurrences (all)	0	9	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 43 (2.33%)	3 / 107 (2.80%)	
occurrences (all)	1	3	
Pyrexia			
subjects affected / exposed	5 / 43 (11.63%)	7 / 107 (6.54%)	
occurrences (all)	5	11	
Peripheral Swelling			

subjects affected / exposed	0 / 43 (0.00%)	7 / 107 (6.54%)	
occurrences (all)	0	7	
Oedema Peripheral			
subjects affected / exposed	5 / 43 (11.63%)	16 / 107 (14.95%)	
occurrences (all)	7	21	
Respiratory, thoracic and mediastinal disorders			
Nasal Congestion			
subjects affected / exposed	2 / 43 (4.65%)	6 / 107 (5.61%)	
occurrences (all)	2	6	
Dyspnoea			
subjects affected / exposed	7 / 43 (16.28%)	5 / 107 (4.67%)	
occurrences (all)	7	5	
Cough			
subjects affected / exposed	5 / 43 (11.63%)	11 / 107 (10.28%)	
occurrences (all)	5	12	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 107 (1.87%)	
occurrences (all)	0	2	
Investigations			
Blood Glucose Increased			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences (all)	0	0	
Haemoglobin Decreased			
subjects affected / exposed	1 / 43 (2.33%)	13 / 107 (12.15%)	
occurrences (all)	1	16	
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 43 (6.98%)	7 / 107 (6.54%)	
occurrences (all)	4	7	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 43 (4.65%)	23 / 107 (21.50%)	
occurrences (all)	2	31	
Dizziness			

subjects affected / exposed	1 / 43 (2.33%)	6 / 107 (5.61%)	
occurrences (all)	1	6	
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	2 / 43 (4.65%)	6 / 107 (5.61%)	
occurrences (all)	2	7	
Leukopenia			
subjects affected / exposed	0 / 43 (0.00%)	3 / 107 (2.80%)	
occurrences (all)	0	3	
Thrombocytopenia			
subjects affected / exposed	1 / 43 (2.33%)	2 / 107 (1.87%)	
occurrences (all)	1	2	
Anaemia			
subjects affected / exposed	5 / 43 (11.63%)	13 / 107 (12.15%)	
occurrences (all)	5	17	
Gastrointestinal disorders			
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	0 / 43 (0.00%)	3 / 107 (2.80%)	
occurrences (all)	0	3	
Nausea			
subjects affected / exposed	1 / 43 (2.33%)	8 / 107 (7.48%)	
occurrences (all)	1	11	
Vomiting			
subjects affected / exposed	2 / 43 (4.65%)	9 / 107 (8.41%)	
occurrences (all)	5	10	
Gastritis			
subjects affected / exposed	0 / 43 (0.00%)	4 / 107 (3.74%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	2 / 43 (4.65%)	7 / 107 (6.54%)	
occurrences (all)	2	7	
Dyspepsia			

subjects affected / exposed	1 / 43 (2.33%)	4 / 107 (3.74%)	
occurrences (all)	2	6	
Musculoskeletal and connective tissue disorders			
Pain in Extremity			
subjects affected / exposed	1 / 43 (2.33%)	6 / 107 (5.61%)	
occurrences (all)	1	6	
Myalgia			
subjects affected / exposed	2 / 43 (4.65%)	7 / 107 (6.54%)	
occurrences (all)	2	7	
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 43 (0.00%)	1 / 107 (0.93%)	
occurrences (all)	0	2	
Back Pain			
subjects affected / exposed	2 / 43 (4.65%)	7 / 107 (6.54%)	
occurrences (all)	2	7	
Arthralgia			
subjects affected / exposed	3 / 43 (6.98%)	8 / 107 (7.48%)	
occurrences (all)	5	8	
Infections and infestations			
Sinusitis			
subjects affected / exposed	1 / 43 (2.33%)	2 / 107 (1.87%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	2 / 43 (4.65%)	7 / 107 (6.54%)	
occurrences (all)	8	11	
Covid-19			
subjects affected / exposed	10 / 43 (23.26%)	25 / 107 (23.36%)	
occurrences (all)	11	26	
Suspected Covid-19			
subjects affected / exposed	0 / 43 (0.00%)	0 / 107 (0.00%)	
occurrences (all)	0	0	
Urinary Tract Infection			
subjects affected / exposed	4 / 43 (9.30%)	6 / 107 (5.61%)	
occurrences (all)	4	7	
Upper Respiratory Tract Infection			

subjects affected / exposed	6 / 43 (13.95%)	5 / 107 (4.67%)	
occurrences (all)	6	7	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 43 (2.33%)	4 / 107 (3.74%)	
occurrences (all)	1	4	
Hyperuricaemia			
subjects affected / exposed	0 / 43 (0.00%)	4 / 107 (3.74%)	
occurrences (all)	0	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2019	The purpose of this amendment was to meet 1. eligibility criteria for hemodynamics will be confirmed by the central reading, 2. change the objective of the evaluation of PAH symptoms and their impact on participant's life from secondary to "other" objective, 3. update frequency of liver function test monitoring, 4. update plan for follow-up of participants who prematurely discontinue study treatment.
28 February 2020	The purpose of this amendment was to implement updated guidelines for the right heart catheterization and 6-minute walk test (6MWT) procedures in order to facilitate alignment in Right heart catheterization (RHC) and 6MWT procedures and data collection across all Actelion trials.
17 July 2020	The purpose of this amendment was to update an exclusion criteria and concomitant therapy section pertaining to newly identified drug-drug interactions (DDI) between macitentan and fluconazole (a dual moderate inhibitor of CYP3A4 and CYP2C9) from a pre-clinical study on implications of role of CYP2C9 in the metabolism of macitentan.
20 October 2020	The purpose of this amendment was to move the cardiopulmonary and cardiovascular domain scores of the Pulmonary Arterial Hypertension Symptoms and Impact (PAH-SYMPACT) from exploratory endpoints to secondary endpoints following discussion with the Food and Drug Administration (FDA).
27 April 2021	The purpose of this amendment was to change the requirements on the minimum number of participants in each stratum (that is, treatment-naive, prior endothelin receptor antagonists [ERA]; prior- Phosphodiesterase type-5 inhibitor [PDE5i]) at the interim and final analyses.
21 November 2022	The purpose of this amendment was to capture participant experience while on one tablet of macitentan 10 mg and tadalafil 40 mg fixed-dose combination (M/T FDC), a semi- structured qualitative interview sub study was assessed the participant's experience with study treatment, with regard to satisfaction with treatment regimen and adherence to treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported