Clinical trial results:
An Open-label Extension Study of UT-15C in Subjects with Pulmonary Arterial Hypertension - A Long-term Follow-up to Protocol TDE PH-310

Summary

EudraCT number	2012-000098-21
Trial protocol	GB DE NL AT FR IT SE BE DK GR PL
Global end of trial date	12 August 2021

Results information

Result version number	v1 (current)
This version publication date	08 June 2022
First version publication date	08 June 2022

Trial information

Trial identification

Sponsor protocol code	TDE-PH-311

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01560637
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	United Therapeutics Corporation
Sponsor organisation address	55 TW Alexander Dr, Research Triangle Park, United States, 27709
Public contact	Global Medical Information, United Therapeutics Global Medical Information, 1 919-485-8350, clinicaltrials@unither.com
Scientific contact	Regulatory Department, United Therapeutics Regulatory Department, 1 919-485-8350, RTPRegulatory@unither.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	02 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 August 2021
Global end of trial reached?	Yes
Global end of trial date	12 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to provide UT-15C extended-release tablets for eligible subjects who participated in TDE-PH-310 (A Phase III, International, Multi-center, Randomized, Double-blind, Placebo-controlled, Clinical Worsening Study of UT-15C in Subjects with Pulmonary Arterial Hypertension Receiving Background Oral Monotherapy).

Protection of trial subjects:

The study protocol, protocol amendments, and Informed Consent Forms (ICFs) were submitted for review and approval to each site's Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRBs/IECs were organized and functioned in accordance with the US Code of Federal Regulations (CFR; Title 21 CFR, Part 56) and/or applicable local regulations.

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance.

Each subject enrolled in the study was provided with information related to the clinical study, including specifics related to subject participation. This was documented in a written ICF that was approved by the same IRB/IEC responsible for approval of the protocol at the clinical study site. Each ICF included the elements required by the Food and Drug Administration regulations in 21 CFR Part 50. Informed consent was obtained from each subject prior to initiating any study-specific procedures in accordance with Title 21 CFR, Part 50 and ICH E6 GCP guidance. A copy of the signed ICF was given to the subject and the original was retained in the study site's records.

Background therapy:

Subjects could receive a PDE5-I or an sGC stimulator or an ERA as background PAH therapy.

Evidence for comparator: -

Actual start date of recruitment	29 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	China: 128
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 3

Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Brazil: 40
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Chile: 14
Country: Number of subjects enrolled	India: 31
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Mexico: 76
Country: Number of subjects enrolled	Singapore: 12
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Taiwan: 20
Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	470
EEA total number of subjects	44

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)	398
From 65 to 84 years	72
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects participated in the parent study, TDE-PH-310, and met the definition of clinical worsening (as specified in TDE-PH-310), remained on study drug, was compliant with study procedures and assessments during TDE-PH-310, or was currently enrolled in that study at the time the study was discontinued by the Sponsor.

Pre-assignment

Screening details:

To have been eligible for the present TDE-PH-311, participants in TDE-PH-310 either 1) met the definition of clinical worsening (as specified in the TDE PH 310 protocol), and remained on study drug while compliant with study procedures and assessments during TDE PH 310, or 2) were enrolled in that study at the time it was discontinued

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	UT-15C
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Treprostinil diolamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once all entry criteria were met, placebo- or oral treprostinil-treated subjects from TDE PH 310 were administered oral treprostinil as follows. For subjects who received placebo in TDE-PH-310, dosing of oral treprostinil in TDE-PH-311 was initiated and optimized as in that study, including all safety monitoring and telephone contact. That is, the first dose of oral treprostinil (0.125 mg) was taken at the site by the subject immediately (~10 minutes) after consuming food. Oral dosing of treprostinil continued at 0.125 mg TID (every 6 to 8 hours) immediately after consuming food. Subjects were instructed to take the appropriate number of tablets based upon their prescribed dose. During the first 4 weeks, each dose of oral treprostinil was adjusted in 0.125-mg increments no more than every 24 hours as clinically indicated. Subsequent doses could be adjusted in 0.125- or 0.25-mg increments every 24 hours as necessary to achieve the optimal clinical response. No maximum dose.

Number of subjects in period 1	UT-15C
Started	470
Completed	272
Not completed	198
Adverse event, serious fatal	69
Consent withdrawn by subject	24
Adverse event, non-fatal	63
Progressive Disease	20

Lost to follow-up	8
Reason not Specified	6
Protocol deviation	8

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	470	470	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	398	398	
From 65-84 years	72	72	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	47.2		
standard deviation	± 15.1	-	
Gender categorical Units: Subjects			
Female	374	374	
Male	96	96	
Etiology of PAH Units: Subjects			
Idiopathic/Heritable PAH	299	299	
Collagen Vascular Disease	114	114	
HIV Infection	8	8	
Congenital Heart Defect	38	38	
Other	11	11	
Background PAH Therapy at Randomization in Parent Study Units: Subjects			
PDE5-I Alone or sGC Stimulator Alone	348	348	
ERA Alone	122	122	
6MWD Category at Baseline Units: Subjects			
≤440 meters	286	286	
>440 m	176	176	
Not Applicable	8	8	
WHO Functional Class at Baseline Units: Subjects			
WHO FC I	41	41	

WHO FC II	226	226	
WHO FC III	182	182	
WHO FC IV	21	21	
6MWD at Baseline			
Units: meters			
arithmetic mean	392.0		
standard deviation	± 128.1	-	
Time since PAH Diagnosis			
Units: years			
arithmetic mean	3.16		
standard deviation	± 2.69	-	

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received oral treprostinil in TDE-PH-311 are included in the Safety Population

Reporting group values	Safety Population		
Number of subjects	470		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	398		
From 65-84 years	72		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	47.2		
standard deviation	± 15.1		
Gender categorical			
Units: Subjects			
Female	374		
Male	96		
Etiology of PAH			
Units: Subjects			
Idiopathic/Heritable PAH	299		
Collagen Vascular Disease	114		
HIV Infection	8		
Congenital Heart Defect	38		
Other	11		
Background PAH Therapy at Randomization in Parent Study			
Units: Subjects			

PDE5-I Alone or sGC Stimulator Alone	348		
ERA Alone	122		
6MWD Category at Baseline Units: Subjects			
≤440 meters	286		
>440 m	176		
Not Applicable			
WHO Functional Class at Baseline Units: Subjects			
WHO FC I	41		
WHO FC II	226		
WHO FC III	182		
WHO FC IV	21		
6MWD at Baseline Units: meters			
arithmetic mean	392.0		
standard deviation	± 128.1		
Time since PAH Diagnosis Units: years			
arithmetic mean	3.16		
standard deviation	± 2.69		

End points

End points reporting groups

Reporting group title	UT-15C
Reporting group description: -	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received oral treprostinil in TDE-PH-311 are included in the Safety Population	

Primary: Continued access

End point title	Continued access
End point description:	
The primary objective of this study was to provide or continue to provide oral treprostinil extended-release tablets for eligible subjects who participated in TDE-PH-310.	
End point type	Primary
End point timeframe:	
From Baseline to EOS	

End point values	UT-15C	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	470	470		
Units: n (%)				
number (not applicable)				
Received Oral Treprostinil in TDE-PH-310	212	212		
Received Placebo in TDE-PH-311	258	258		

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
Data is summarized in tables and listings only.	
Comparison groups	UT-15C v Safety Population
Number of subjects included in analysis	940
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0
Method	NA
Parameter estimate	NA
Point estimate	0

Confidence interval	
level	Other: 0 %
sides	1-sided
upper limit	100

Notes:

[1] - No statistical analyses were performed. Data summarized in tables and listings only.

Secondary: 6MWD

End point title	6MWD

End point description:

Change in 6MWD from Baseline to Week 48

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	UT-15C	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	341	341		
Units: meters				
arithmetic mean (standard deviation)	20.1 (± 79.6)	20.1 (± 79.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Borg Dyspnea Score

End point title	Borg Dyspnea Score

End point description:

Change in Borg Dyspnea Score from Baseline to Week 48

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	UT-15C	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	341	341		
Units: Units on a Scale				
arithmetic mean (standard deviation)	-0.49 (± 1.92)	-0.49 (± 1.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: WHO Functional Class

End point title	WHO Functional Class

End point description:

Change in WHO Functional Class from Baseline to Week 48

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	UT-15C	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	362	362		
Units: Units on a Scale				
arithmetic mean (standard deviation)	-0.2 (± 0.6)	-0.2 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma NT-proBNP

End point title	Plasma NT-proBNP

End point description:

Change in plasma NT-proBNP from Baseline to Week 48

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	UT-15C	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	322	322		
Units: pg/mL				
arithmetic mean (standard deviation)	-179.23 (± 1968.99)	-179.23 (± 1968.99)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were captured from the time the ICF was signed. All AEs were followed until resolution, until they were judged by the Investigator to no longer be clinically significant, or for up to 30 days if the AE extended beyond the final visit.

Adverse event reporting additional description:

Any AEs that were ongoing at the study termination visit from the parent study were recorded as continuing AEs in this open-label study. All SAEs were followed until resolution, death, or the subject was lost to follow-up, even if they were ongoing more than 30 days after completion of the final visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Adverse Events - Safety Population

Reporting group description:

All subjects who received oral treprostinil in TDE-PH-311 are included in the Safety Population.

Serious adverse events	Adverse Events - Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	206 / 470 (43.83%)		
number of deaths (all causes)	74		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Breast cancer			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diffuse large B-cell lymphoma			

subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hepatic cancer recurrent				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatocellular carcinoma				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Lung neoplasm malignant				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant pleural effusion				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian adenoma				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
POEMS syndrome				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypotension				
subjects affected / exposed	6 / 470 (1.28%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 0			
Shock				

subjects affected / exposed	3 / 470 (0.64%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	2 / 470 (0.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	3 / 470 (0.64%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	2 / 470 (0.43%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	2 / 470 (0.43%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	2 / 470 (0.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
Asthenia			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Chest discomfort				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sudden cardiac death				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Reproductive system and breast disorders				
Breast mass				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibrocystic breast disease				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Intermenstrual bleeding				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fluid collection				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary hypertension				
subjects affected / exposed	57 / 470 (12.13%)			
occurrences causally related to treatment / all	7 / 79			
deaths causally related to treatment / all	1 / 1			
Respiratory failure				
subjects affected / exposed	8 / 470 (1.70%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 2			
Dyspnoea				
subjects affected / exposed	7 / 470 (1.49%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	5 / 470 (1.06%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	3 / 470 (0.64%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			

Haemoptysis				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Acute pulmonary oedema				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory distress syndrome				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary arterial hypertension				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				

subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Catheterisation cardiac			
subjects affected / exposed	2 / 470 (0.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coagulation time prolonged			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	2 / 470 (0.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Accidental overdose				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Arteriovenous fistula site haemorrhage				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intentional overdose				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Splenic rupture				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				

subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Right ventricular failure			
subjects affected / exposed	22 / 470 (4.68%)		
occurrences causally related to treatment / all	1 / 27		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	19 / 470 (4.04%)		
occurrences causally related to treatment / all	5 / 25		
deaths causally related to treatment / all	2 / 9		
Cardiac arrest			
subjects affected / exposed	4 / 470 (0.85%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Cardiogenic shock			
subjects affected / exposed	4 / 470 (0.85%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Atrial fibrillation			
subjects affected / exposed	3 / 470 (0.64%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	3 / 470 (0.64%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	3 / 470 (0.64%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cor pulmonale			

subjects affected / exposed	3 / 470 (0.64%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	3 / 470 (0.64%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Atrioventricular block complete				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Right ventricular dysfunction				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				

subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Acute right ventricular failure				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic valve incompetence				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block second degree				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure chronic				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cor pulmonale acute				

subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulseless electrical activity				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tricuspid valve incompetence				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Syncope				
subjects affected / exposed	4 / 470 (0.85%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Brain injury				

subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coma				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolic encephalopathy				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				

subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 470 (1.06%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 470 (0.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Anaemia of malignant disease			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erythropenia			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemolytic anaemia			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Iron deficiency anaemia			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Amaurosis			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine ophthalmopathy			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 470 (1.28%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 470 (0.64%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Vomiting			
subjects affected / exposed	3 / 470 (0.64%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 470 (0.43%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	2 / 470 (0.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Abdominal distension				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute abdomen				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulum				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric polyps				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric varices haemorrhage				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				

subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis haemorrhagic				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal polyp haemorrhage				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal vascular malformation haemorrhagic				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				

subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Portal hypertensive gastropathy				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis acute				
subjects affected / exposed	5 / 470 (1.06%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Acute hepatic failure				

subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Biliary tract disorder				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congestive hepatopathy				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic cirrhosis				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hepatitis				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver injury				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subcapsular hepatic haematoma				

subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 470 (0.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Purpura			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	7 / 470 (1.49%)		
occurrences causally related to treatment / all	2 / 8		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	2 / 470 (0.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Chronic kidney disease			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glomerulonephritis acute			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lupus nephritis			

subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal vasculitis			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scleroderma renal crisis			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary bladder polyp			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	4 / 470 (0.85%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Systemic lupus erythematosus			
subjects affected / exposed	3 / 470 (0.64%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

Osteonecrosis				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sjogren's syndrome				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Muscle atrophy				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	32 / 470 (6.81%)			
occurrences causally related to treatment / all	5 / 39			
deaths causally related to treatment / all	1 / 1			
Septic shock				
subjects affected / exposed	9 / 470 (1.91%)			
occurrences causally related to treatment / all	1 / 9			
deaths causally related to treatment / all	0 / 4			
Gastroenteritis				
subjects affected / exposed	6 / 470 (1.28%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	5 / 470 (1.06%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	5 / 470 (1.06%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Urinary tract infection				
subjects affected / exposed	5 / 470 (1.06%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	3 / 470 (0.64%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	3 / 470 (0.64%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
COVID-19 pneumonia				
subjects affected / exposed	3 / 470 (0.64%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Bronchitis				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peritonitis				

subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Upper respiratory tract infection				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial translocation				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis infective				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea infectious				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Enteritis infectious				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gangrene				

subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of bronchiectasis				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis listeria				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Ophthalmic herpes zoster				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia influenzal				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sialoadenitis				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				

subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Fluid overload				
subjects affected / exposed	3 / 470 (0.64%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	2 / 470 (0.43%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Gout				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	1 / 470 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperuricaemia				

subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypervolaemia			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 470 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Adverse Events - Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	450 / 470 (95.74%)		
Investigations			
Weight decreased			
subjects affected / exposed	25 / 470 (5.32%)		
occurrences (all)	25		
Vascular disorders			
Flushing			
subjects affected / exposed	201 / 470 (42.77%)		
occurrences (all)	204		
Hypotension			
subjects affected / exposed	36 / 470 (7.66%)		
occurrences (all)	42		
Cardiac disorders			
Palpitations			
subjects affected / exposed	74 / 470 (15.74%)		
occurrences (all)	81		
Right ventricular failure			
subjects affected / exposed	39 / 470 (8.30%)		
occurrences (all)	54		

Cardiac failure			
subjects affected / exposed	26 / 470 (5.53%)		
occurrences (all)	34		
Nervous system disorders			
Headache			
subjects affected / exposed	328 / 470 (69.79%)		
occurrences (all)	348		
Dizziness			
subjects affected / exposed	120 / 470 (25.53%)		
occurrences (all)	131		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	51 / 470 (10.85%)		
occurrences (all)	55		
Thrombocytopenia			
subjects affected / exposed	17 / 470 (3.62%)		
occurrences (all)	19		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	85 / 470 (18.09%)		
occurrences (all)	98		
Fatigue			
subjects affected / exposed	64 / 470 (13.62%)		
occurrences (all)	68		
Chest pain			
subjects affected / exposed	45 / 470 (9.57%)		
occurrences (all)	54		
Asthenia			
subjects affected / exposed	34 / 470 (7.23%)		
occurrences (all)	38		
Pyrexia			
subjects affected / exposed	24 / 470 (5.11%)		
occurrences (all)	24		
Gastrointestinal disorders			
Abdominal distension			

subjects affected / exposed	35 / 470 (7.45%)		
occurrences (all)	38		
Diarrhoea			
subjects affected / exposed	311 / 470 (66.17%)		
occurrences (all)	354		
Nausea			
subjects affected / exposed	188 / 470 (40.00%)		
occurrences (all)	197		
Vomiting			
subjects affected / exposed	147 / 470 (31.28%)		
occurrences (all)	161		
Abdominal pain			
subjects affected / exposed	40 / 470 (8.51%)		
occurrences (all)	43		
Abdominal pain upper			
subjects affected / exposed	38 / 470 (8.09%)		
occurrences (all)	40		
Gastrooesophageal reflux disease			
subjects affected / exposed	36 / 470 (7.66%)		
occurrences (all)	37		
Abdominal discomfort			
subjects affected / exposed	30 / 470 (6.38%)		
occurrences (all)	30		
Dyspepsia			
subjects affected / exposed	28 / 470 (5.96%)		
occurrences (all)	30		
Colitis			
subjects affected / exposed	25 / 470 (5.32%)		
occurrences (all)	29		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	113 / 470 (24.04%)		
occurrences (all)	131		
Pulmonary hypertension			

subjects affected / exposed	103 / 470 (21.91%)		
occurrences (all)	147		
Cough			
subjects affected / exposed	72 / 470 (15.32%)		
occurrences (all)	76		
Epistaxis			
subjects affected / exposed	24 / 470 (5.11%)		
occurrences (all)	26		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	40 / 470 (8.51%)		
occurrences (all)	41		
Musculoskeletal and connective tissue disorders			
Pain in jaw			
subjects affected / exposed	103 / 470 (21.91%)		
occurrences (all)	106		
Myalgia			
subjects affected / exposed	78 / 470 (16.60%)		
occurrences (all)	82		
Pain in extremity			
subjects affected / exposed	78 / 470 (16.60%)		
occurrences (all)	90		
Arthralgia			
subjects affected / exposed	57 / 470 (12.13%)		
occurrences (all)	69		
Back pain			
subjects affected / exposed	41 / 470 (8.72%)		
occurrences (all)	45		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	116 / 470 (24.68%)		
occurrences (all)	160		
Nasopharyngitis			
subjects affected / exposed	61 / 470 (12.98%)		
occurrences (all)	85		
Pneumonia			

subjects affected / exposed	50 / 470 (10.64%)		
occurrences (all)	59		
Bronchitis			
subjects affected / exposed	31 / 470 (6.60%)		
occurrences (all)	41		
Urinary tract infection			
subjects affected / exposed	30 / 470 (6.38%)		
occurrences (all)	37		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	50 / 470 (10.64%)		
occurrences (all)	56		
Decreased appetite			
subjects affected / exposed	41 / 470 (8.72%)		
occurrences (all)	43		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2012	• Added that AEs extending beyond the final visit were followed for up to 30 days. • Clarified timing of subject contact to assess death and/or AEs following the last study visit. • Updated Guidelines and Definitions for Recording AEs (Section 15.4) to reflect current data capture conventions for AEs.
13 June 2012	• Duration of contraceptive use for WOCBP following last dose of study drug was expanded to 30 days. • Pregnancy reporting procedures were updated. • Updated Guidelines and Definitions for Recording AEs (Section 15.4) to reflect current data capture conventions for AEs regarding action taken.
05 December 2012	• Dosing was changed from twice daily (BID) to TID. • Results of an additional open-label study were added to better understand TID dosing pharmacokinetics. • Clinical laboratory assessments updated to be assessed at all Follow-up Visits. • Timing of TID dosing following meals was updated. • Exercise capacity (6MWD and Borg dyspnea score) timing changed to following the last study dose. • Added that site personnel will be unblinded to treatment assignments following the Study Termination assessments for TDE-PH-310. • Removed caloric requirements for meals preceding the 6MWT.
10 March 2014	• Clarified the logistics of dosing every 6 to 8 hours TID, including the intake of only a partial meal prior to study drug administration. • Updated newly approved PAH therapies and background data for oral treprostinil. • Updated estimated study duration to 4 years. • Clarified abstinence in inclusion criterion to align with regulatory agency review. • Allowed subjects who temporarily used a prostacyclin (28 days or less) to be included in the study. • Method for recording and reporting AEs associated with progression of PAH was clarified. • Storage temperature of study drug updated to be consistent with study drug labels.
09 January 2015	• Reduced sample size based on the amendment to TDE-PH-310.
29 September 2016	• Increased the number of subjects enrolled from approximately 610 subjects to up to 850 subjects. • Added clarification that clinical worsening events in TDE-PH-310 include cases of morbidity or mortality. • Updated the number of subjects that have been treated with Remodulin from 7000 to 17,000. • Added Uptravi® (Actelion Pharmaceuticals US, Inc.) as an approved pharmacotherapy for PAH. • Information regarding TDE-PH-304 was revised to include data from the 01 September 2015 data cut.

13 July 2018	• Added exploratory objectives for optional evaluation of pharmacogenomics. • Increased the estimated study duration from 4 years to approximately 6 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported