Clinical trial results:
An extension study to CQTI571A2301 to evaluate the long-term safety, tolerability and efficacy of oral QTI571 (imatinib) in the treatment of severe pulmonaryarterial hypertension: IMPRES Extension.

Summary

EudraCT number	2009-018167-26
Trial protocol	AT ES DE BE GB IT FR
Global end of trial date	16 April 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	16 August 2015

Trial information

Trial identification

Sponsor protocol code	CQTI571A2301E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01117987
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111,

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	16 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2014
Global end of trial reached?	Yes
Global end of trial date	16 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of QTI571

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2010
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	Belgium: 1
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	144
EEA total number of subjects	63

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)	125
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The following screening procedures were performed within 2 weeks of extension study enrollment (first drug assignment):
- Screening safety laboratories, electrocardiogram (ECG) and 6MWD performed at Visit 1 if not performed in the previous 4 weeks.
- Echocardiogram was performed at Visit 1 if not performed in the previous 8 weeks.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Core Imatinib

Arm description:

Depending on the participants randomized treatment in the core study, CQTI571A2301 (NCT00902174), and their completion status in the core study, participants received imatinib at 200 mg qd, 400 mg qd, or 200 mg qd with an increase to 400 mg qd after 2 weeks, if tolerated.

Arm type	Experimental
Investigational medicinal product name	Imatinib
Investigational medicinal product code	QTI571
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants, who received imatinib 200 mg in the core study, CQTI571A2301 (NCT00902174), and completed the core study, received imatinib 200 mg every day (qd) in the extension. Participants, who were randomized to receive imatinib 400 mg in the core study and completed the core study, received imatinib 400 mg qd in the extension. Participants, who terminated early from the core study or who were randomized to placebo and completed the core study, started the extension with imatinib 200 mg qd. After 2 weeks, the dose was increased to 400 mg qd if tolerated.

Arm title	Core Placebo

Arm description:

Depending on the participants randomized treatment in the core study, CQTI571A2301 (NCT00902174), and their completion status in the core study, participants received imatinib at 200 mg qd, 400 mg qd, or 200 mg qd with an increase to 400 mg qd after 2 weeks, if tolerated.

Arm type	Experimental
Investigational medicinal product name	Imatinib
Investigational medicinal product code	QTI571
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

To preserve the blind of the core study until the core study CQTI571A2301 was completed, participants received a blinded study drug package containing a 70-tablet bottle of imatinim and 70-tablet bottle of matching placebo

Number of subjects in period 1	Core Imatinib	Core Placebo
Started	66	78
Completed	5	4
Not completed	61	74
Adverse event, serious fatal	5	10
Consent withdrawn by subject	5	10
Subject no longer requires study drug	1	-
Adverse event, non-fatal	19	26
Protocol deviation	-	1
Administrative problems	25	22
Lost to follow-up	1	1
Abnormal test procedure result	2	-
Lack of efficacy	3	4

Baseline characteristics

Reporting groups	
Reporting group title	Core Imatinib
Reporting group description:	
Depending on the participants randomized treatment in the core study, CQTI571A2301 (NCT00902174), and their completion status in the core study, participants received imatinib at 200 mg qd, 400 mg qd, or 200 mg qd with an increase to 400 mg qd after 2 weeks, if tolerated.	
Reporting group title	Core Placebo
Reporting group description:	
Depending on the participants randomized treatment in the core study, CQTI571A2301 (NCT00902174), and their completion status in the core study, participants received imatinib at 200 mg qd, 400 mg qd, or 200 mg qd with an increase to 400 mg qd after 2 weeks, if tolerated.	

Reporting group values	Core Imatinib	Core Placebo	Total
Number of subjects	66	78	144
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	53	72	125
From 65-84 years	13	6	19
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	49.3	45.7	
standard deviation	± 15.52	± 13.31	-
Gender, Male/Female Units: Participants			
Female	57	63	120
Male	9	15	24

End points

End points reporting groups

Reporting group title	Core Imatinib
Reporting group description:	
Depending on the participants randomized treatment in the core study, CQTI571A2301 (NCT00902174), and their completion status in the core study, participants received imatinib at 200 mg qd, 400 mg qd, or 200 mg qd with an increase to 400 mg qd after 2 weeks, if tolerated.	
Reporting group title	Core Placebo
Reporting group description:	
Depending on the participants randomized treatment in the core study, CQTI571A2301 (NCT00902174), and their completion status in the core study, participants received imatinib at 200 mg qd, 400 mg qd, or 200 mg qd with an increase to 400 mg qd after 2 weeks, if tolerated.	

Primary: Number of participants with adverse events, serious adverse events and deaths

End point title	Number of participants with adverse events, serious adverse events and deaths[1]
End point description:	
Adverse event monitoring was conducted throughout the study.	
End point type	Primary
End point timeframe:	
204 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: statistical analysis not prespecified for this outcome measure.

End point values	Core Imatinib	Core Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	78		
Units: Participants				
Adverse events (non-serious and serious)	62	76		
Serious adverse events	40	53		
Deaths	6	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from core study baseline in Six-Minute Walk Distance (6MWD)

End point title	Change from core study baseline in Six-Minute Walk Distance (6MWD)
End point description:	
A six minute walk test (6MWT) was performed in accordance with the guidleines of the American Thoracic Society (2002).	
End point type	Secondary

End point timeframe:

core study baseline, extension baseline, 12 weeks, 24 weeks, 48 weeks, 72 weeks, 96 weeks, 120 weeks, 144 weeks, 156 weeks, 204 weeks

End point values	Core Imatinib	Core Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	78		
Units: meters				
arithmetic mean (standard deviation)				
Extension baseline (n=61,77)	42.98 (± 55.209)	4.91 (± 62.629)		
Week 12 (n=58,57)	48.75 (± 60.887)	16.25 (± 64.992)		
Week 24 (n=54,53)	44.71 (± 45.506)	19.34 (± 71.675)		
Week 48 (n=47,42)	45.81 (± 72.15)	29.18 (± 65.198)		
Week 72 (n=40,39)	49.54 (± 76.019)	56.46 (± 111.13)		
Week 96 (n=38,35)	66.64 (± 71.08)	41.03 (± 54.495)		
Week 120 (n=32,29)	83.19 (± 67.855)	37.43 (± 60.087)		
Week 144 (n=27,21)	67.7 (± 64)	39.45 (± 79.356)		
Week 156 (n=21,18)	72.6 (± 67.972)	30.17 (± 66.856)		
Week 204 (n=4,3)	96.88 (± 42.048)	4.5 (± 25.608)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with incidence of clinical worsening events

End point title	Percentage of participants with incidence of clinical worsening events

End point description:

Clinical worsening events included death, overnight hospitalization for worsening of PAH, worsening of World Health Organization (WHO) functional class by at least one level (drop in WHO), 15% decrease in the 6MWD as compared to baseline confirmed by two 6MWTs at two consecutive study visits (6MWD reduction), and drop in WHO & 6MWD reduction. Some participants have fulfilled more than one criterion. Therefore, the sum of individual components may be higher than the total number of participants with clinical worsening.

End point type	Secondary

End point timeframe:

204 weeks

End point values	Core Imatinib	Core Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	78		
Units: Percentage of participants				
number (not applicable)				
Total participants with clinical worsening	50	46.2		
Death (all deaths)	7.6	12.8		
Hospitalization for worsening of PAH	33.3	28.2		
Drop in WHO	24.2	19.2		
6MWD reduction	12.1	19.2		
Drop in WHO and 6MWD reduction	1.5	3.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Placebo tablets

Reporting group description:

Placebo tablets

Reporting group title	Imatinib 100mg tablets

Reporting group description:

Imatinib 100mg tablets

Serious adverse events	Placebo tablets	Imatinib 100mg tablets	
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 78 (67.95%)	40 / 66 (60.61%)	
number of deaths (all causes)	10	5	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
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	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Arteriovenous fistula			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 78 (1.28%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Craniotomy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain death			

subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device leakage			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exercise tolerance decreased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			

subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 78 (3.85%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoeic attack			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute respiratory failure			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 78 (6.41%)	4 / 66 (6.06%)	
occurrences causally related to treatment / all	1 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 78 (2.56%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 78 (1.28%)	3 / 66 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			

subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	8 / 78 (10.26%)	6 / 66 (9.09%)	
occurrences causally related to treatment / all	3 / 10	1 / 8	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 78 (2.56%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 78 (2.56%)	3 / 66 (4.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary hypertension			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			

subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood potassium increased			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophil percentage increased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematocrit decreased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular pressure increased			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
N-terminal prohormone brain natriuretic peptide			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Complications of transplanted lung			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone contusion			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
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 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
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	3 / 78 (3.85%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			

subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			

subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 78 (2.56%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cor pulmonale			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	8 / 78 (10.26%)	5 / 66 (7.58%)	
occurrences causally related to treatment / all	1 / 8	2 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Supraventricular tachycardia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	2 / 78 (2.56%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	7 / 78 (8.97%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
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			
Anaemia			
subjects affected / exposed	2 / 78 (2.56%)	3 / 66 (4.55%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agranulocytosis			

subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	0 / 78 (0.00%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 78 (3.85%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Astigmatism			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal erosion			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital oedema			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal adhesions			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			

subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 78 (0.00%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 78 (3.85%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 78 (2.56%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 78 (2.56%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	2 / 78 (2.56%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroedema			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Telangiectasia			

subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Lupus nephritis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 78 (2.56%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 78 (2.56%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Bursitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic sclerosis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (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	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Device related infection			
subjects affected / exposed	3 / 78 (3.85%)	5 / 66 (7.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycobacterial infection			

subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 78 (3.85%)	3 / 66 (4.55%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pyelonephritis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 78 (3.85%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	2 / 78 (2.56%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 78 (1.28%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 66 (1.52%)	
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	Placebo tablets	Imatinib 100mg tablets	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 78 (92.31%)	55 / 66 (83.33%)	
Vascular disorders			
Flushing			
subjects affected / exposed	5 / 78 (6.41%)	2 / 66 (3.03%)	
occurrences (all)	6	2	
Hypotension			
subjects affected / exposed	3 / 78 (3.85%)	6 / 66 (9.09%)	
occurrences (all)	3	10	
General disorders and administration site conditions			

Face oedema			
subjects affected / exposed	4 / 78 (5.13%)	1 / 66 (1.52%)	
occurrences (all)	4	1	
Chest discomfort			
subjects affected / exposed	4 / 78 (5.13%)	2 / 66 (3.03%)	
occurrences (all)	5	2	
Asthenia			
subjects affected / exposed	2 / 78 (2.56%)	4 / 66 (6.06%)	
occurrences (all)	2	4	
Fatigue			
subjects affected / exposed	11 / 78 (14.10%)	9 / 66 (13.64%)	
occurrences (all)	12	12	
Pyrexia			
subjects affected / exposed	5 / 78 (6.41%)	9 / 66 (13.64%)	
occurrences (all)	6	13	
Oedema peripheral			
subjects affected / exposed	32 / 78 (41.03%)	21 / 66 (31.82%)	
occurrences (all)	48	40	
Non-cardiac chest pain			
subjects affected / exposed	4 / 78 (5.13%)	4 / 66 (6.06%)	
occurrences (all)	5	4	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	4 / 78 (5.13%)	3 / 66 (4.55%)	
occurrences (all)	4	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 78 (14.10%)	16 / 66 (24.24%)	
occurrences (all)	12	25	
Dyspnoea			
subjects affected / exposed	6 / 78 (7.69%)	10 / 66 (15.15%)	
occurrences (all)	6	12	
Hypoxia			
subjects affected / exposed	4 / 78 (5.13%)	2 / 66 (3.03%)	
occurrences (all)	4	2	
Epistaxis			

subjects affected / exposed	6 / 78 (7.69%)	6 / 66 (9.09%)	
occurrences (all)	9	7	
Nasal congestion			
subjects affected / exposed	2 / 78 (2.56%)	5 / 66 (7.58%)	
occurrences (all)	2	5	
Oropharyngeal pain			
subjects affected / exposed	1 / 78 (1.28%)	8 / 66 (12.12%)	
occurrences (all)	1	17	
Pulmonary arterial hypertension			
subjects affected / exposed	4 / 78 (5.13%)	2 / 66 (3.03%)	
occurrences (all)	4	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 78 (6.41%)	2 / 66 (3.03%)	
occurrences (all)	5	2	
Investigations			
Weight decreased			
subjects affected / exposed	3 / 78 (3.85%)	5 / 66 (7.58%)	
occurrences (all)	3	5	
Blood creatinine increased			
subjects affected / exposed	3 / 78 (3.85%)	4 / 66 (6.06%)	
occurrences (all)	4	5	
Weight increased			
subjects affected / exposed	4 / 78 (5.13%)	4 / 66 (6.06%)	
occurrences (all)	6	7	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 78 (1.28%)	4 / 66 (6.06%)	
occurrences (all)	1	5	
Fall			
subjects affected / exposed	1 / 78 (1.28%)	4 / 66 (6.06%)	
occurrences (all)	1	4	
Ligament sprain			
subjects affected / exposed	4 / 78 (5.13%)	0 / 66 (0.00%)	
occurrences (all)	4	0	
Cardiac disorders			

Tachycardia			
subjects affected / exposed	4 / 78 (5.13%)	4 / 66 (6.06%)	
occurrences (all)	5	5	
Pericardial effusion			
subjects affected / exposed	4 / 78 (5.13%)	0 / 66 (0.00%)	
occurrences (all)	4	0	
Palpitations			
subjects affected / exposed	4 / 78 (5.13%)	4 / 66 (6.06%)	
occurrences (all)	4	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 78 (6.41%)	9 / 66 (13.64%)	
occurrences (all)	10	13	
Headache			
subjects affected / exposed	24 / 78 (30.77%)	12 / 66 (18.18%)	
occurrences (all)	27	26	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	7 / 78 (8.97%)	6 / 66 (9.09%)	
occurrences (all)	7	6	
Anaemia			
subjects affected / exposed	8 / 78 (10.26%)	5 / 66 (7.58%)	
occurrences (all)	9	6	
Iron deficiency anaemia			
subjects affected / exposed	6 / 78 (7.69%)	5 / 66 (7.58%)	
occurrences (all)	7	5	
Leukopenia			
subjects affected / exposed	9 / 78 (11.54%)	1 / 66 (1.52%)	
occurrences (all)	19	1	
Eye disorders			
Periorbital oedema			
subjects affected / exposed	23 / 78 (29.49%)	11 / 66 (16.67%)	
occurrences (all)	32	15	
Conjunctival haemorrhage			
subjects affected / exposed	5 / 78 (6.41%)	2 / 66 (3.03%)	
occurrences (all)	9	3	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	3 / 78 (3.85%)	4 / 66 (6.06%)	
occurrences (all)	3	4	
Abdominal pain			
subjects affected / exposed	5 / 78 (6.41%)	6 / 66 (9.09%)	
occurrences (all)	6	8	
Abdominal pain upper			
subjects affected / exposed	5 / 78 (6.41%)	2 / 66 (3.03%)	
occurrences (all)	7	2	
Constipation			
subjects affected / exposed	5 / 78 (6.41%)	3 / 66 (4.55%)	
occurrences (all)	5	3	
Abdominal discomfort			
subjects affected / exposed	5 / 78 (6.41%)	2 / 66 (3.03%)	
occurrences (all)	6	2	
Nausea			
subjects affected / exposed	39 / 78 (50.00%)	21 / 66 (31.82%)	
occurrences (all)	58	31	
Gastritis			
subjects affected / exposed	4 / 78 (5.13%)	0 / 66 (0.00%)	
occurrences (all)	4	0	
Dyspepsia			
subjects affected / exposed	4 / 78 (5.13%)	3 / 66 (4.55%)	
occurrences (all)	5	4	
Diarrhoea			
subjects affected / exposed	27 / 78 (34.62%)	18 / 66 (27.27%)	
occurrences (all)	36	31	
Vomiting			
subjects affected / exposed	25 / 78 (32.05%)	14 / 66 (21.21%)	
occurrences (all)	34	29	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 78 (5.13%)	3 / 66 (4.55%)	
occurrences (all)	4	3	
Rash			

subjects affected / exposed	13 / 78 (16.67%)	7 / 66 (10.61%)	
occurrences (all)	13	8	
Pruritus			
subjects affected / exposed	6 / 78 (7.69%)	1 / 66 (1.52%)	
occurrences (all)	6	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 78 (5.13%)	6 / 66 (9.09%)	
occurrences (all)	4	9	
Arthralgia			
subjects affected / exposed	12 / 78 (15.38%)	5 / 66 (7.58%)	
occurrences (all)	17	6	
Muscle spasms			
subjects affected / exposed	12 / 78 (15.38%)	8 / 66 (12.12%)	
occurrences (all)	15	15	
Musculoskeletal pain			
subjects affected / exposed	2 / 78 (2.56%)	4 / 66 (6.06%)	
occurrences (all)	2	4	
Pain in extremity			
subjects affected / exposed	5 / 78 (6.41%)	6 / 66 (9.09%)	
occurrences (all)	6	10	
Myalgia			
subjects affected / exposed	4 / 78 (5.13%)	2 / 66 (3.03%)	
occurrences (all)	4	2	
Infections and infestations			
Device related infection			
subjects affected / exposed	4 / 78 (5.13%)	0 / 66 (0.00%)	
occurrences (all)	8	0	
Influenza			
subjects affected / exposed	2 / 78 (2.56%)	5 / 66 (7.58%)	
occurrences (all)	2	6	
Nasopharyngitis			
subjects affected / exposed	24 / 78 (30.77%)	17 / 66 (25.76%)	
occurrences (all)	59	54	
Pneumonia			

subjects affected / exposed	4 / 78 (5.13%)	1 / 66 (1.52%)	
occurrences (all)	4	1	
Bronchitis			
subjects affected / exposed	8 / 78 (10.26%)	1 / 66 (1.52%)	
occurrences (all)	16	2	
Upper respiratory tract infection			
subjects affected / exposed	11 / 78 (14.10%)	6 / 66 (9.09%)	
occurrences (all)	13	9	
Respiratory tract infection			
subjects affected / exposed	7 / 78 (8.97%)	3 / 66 (4.55%)	
occurrences (all)	12	5	
Urinary tract infection			
subjects affected / exposed	8 / 78 (10.26%)	3 / 66 (4.55%)	
occurrences (all)	12	4	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	4 / 78 (5.13%)	2 / 66 (3.03%)	
occurrences (all)	6	3	
Fluid overload			
subjects affected / exposed	4 / 78 (5.13%)	1 / 66 (1.52%)	
occurrences (all)	6	1	
Decreased appetite			
subjects affected / exposed	4 / 78 (5.13%)	2 / 66 (3.03%)	
occurrences (all)	4	2	
Hypokalaemia			
subjects affected / exposed	10 / 78 (12.82%)	5 / 66 (7.58%)	
occurrences (all)	14	5	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 78 (0.00%)	5 / 66 (7.58%)	
occurrences (all)	0	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2010	Amendment 1: The protocol was amended to allow for additional safety monitoring, provide necessary clarifications and ensure alignment with the core protocol CQTI571A2301. To implement additional safety monitoring, three additional visits were added to the protocol changing the 6- month interval visits to 3-month intervals.
19 July 2010	Amendment 2: The protocol was amended to clarify the exclusion criterion for male and female contraception requirements and to specify an end date for the study.
26 July 2011	Amendment 3: The protocol was amended to unblind patients and site staff to the QTI571 dose strength and allow for patients to administer open-label study medication. This planned amendment followed the database lock and unblinding of the treatment assignments in the core protocol CQTI571A2301. Prior to this amendment, extension study medication was supplied in a blinded fashion to patients to prevent knowledge of the QTI571 dose level. This was done in order to maintain the blinding of the core protocol CQTI571A2301. Following this database lock, it is no longer necessary to have patients administer placebo study medication and maintain blinding in the extension study. In addition, the requirements for restarting study drug after a drop in platelets was amended. At the request of the French Health Authority, a specific country requirement was added, wherein, patients in this country can only resume when platelet count is above 75,000/mm3, even though the baseline count may have been lower. This requirement was implemented globally however has come to be overly restrictive for many patients in other countries whose platelet count was below the restart requirement at baseline. Since this requirement was only specific to France, the protocol will now allow patients in other countries to be restarted on drug when the platelet count has returned to baseline levels if less than 75,000/mm3 at study start.
20 March 2012	Amendment 4: The protocol was amended to obtain survival follow-up information on extension patients and core protocol CQTI571A2301 patients who did not enroll in the extension study. This information is being collected for additional safety monitoring of all patients involved in the core and extension trials. Survival follow-up information will be collected every six months after the patients' last study visit for up to 3 years up until the time of study database lock for this extension protocol.
25 July 2012	Amendment 5: The protocol was amended to clarify the process for the collection of survival follow-up information from subjects in the United States only, as per local regulations. This information is being collected for additional safety monitoring of all patients involved in the core and extension trials. Survival follow-up information will be collected every six months after the patients' last study visit for up to 3 years up until the time of study database lock for this extension protocol. Local regulations in the United States also permit obtaining publically available survival information without patient consent. Survival information will be collected from public databases, in the United States only, for subjects whose consent can not be obtained.
06 December 2012	Amendment 6: The protocol was amended to update language regarding the packaging of the study drug by removing the specifics of open-label study drug provided in 140-tablet bottles. This change will allow for alternative packaging to be used in this study. In addition text was deleted if not pertinent to a section, referred to in previous sections or not relevant to provide in the protocol.

11 January 2013	Amendment 7: The protocol was amended to extend the study duration by one additional year, thereby changing the overall study duration to four years for the approximate 74 ongoing patients out of 144 patients enrolled. This extension in study duration will consist of two additional visits of 6-month frequency with reduced assessments. A physical exam, echocardiogram, and dipstick urine test will not be required as part of the new study visits. Additionally, NTproBNP lab assessment, six-minute walk test and Borg Scale will be performed at one of the 2 new study visits only. Following 3 years of study treatment with imatinib, patients are considered stable and echocardiography will not be required except for the final study visit. The echocardiogram should be performed as clinically indicated as part of standard of care. The assessment schedule and other relevant protocol sections have been updated accordingly. Extending the study by one additional year will allow patients to continue to participate in this extension study and avoid treatment interruption. The protocol stated co-medications that are inhibitors, inducers or substrates of CYP3A4 and CYP2D6 should be used with caution. A statement was added in this amendment to also avoid grapefruit juice and other foods that inhibit CYP3A4 while taking imatinib as these foods may increase the plasma concentration of imatinib.
24 April 2013	Amendment 8: The protocol was amended to revise the information on concomitant use of imatinib and oral vitamin K antagonists in PAH patients. This is based on updated information on the risk of bleeding events, especially subdural hematoma, and the need for these events to receive careful evaluation in PAH patients – as the risk of subdural hematoma is increased in patients taking imatinib and oral vitamin K antagonists concomitantly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In 2013,Novartis discontinued the development program of imatinib in pulmonary arterial hypertension (PAH) due to requirement of regulatory authorities for additional data to secure marketing approval in PAH;all global extension studies were closed

Notes: