



Clinical trial results:

A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of six months treatment with the tyrosine kinase inhibitor of STI571 for the treatment of pulmonary arterial hypertension.

Summary

EudraCT number	2005-005569-12
Trial protocol	GB DE AT
Global end of trial date	31 January 2014

Results information

Result version number	v1 (current)
This version publication date	14 April 2016
First version publication date	14 April 2016

Trial information

Trial identification

Sponsor protocol code	CSTI571E2203
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00477269
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	31 January 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 January 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To assess the safety and tolerability of oral STI571 compared with placebo in patients with pulmonary arterial hypertension.
- To evaluate efficacy of oral STI571 as measured by improvement in 6-minute walk test.

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	23 June 2006
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	United States: 8
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Germany: 30
Worldwide total number of subjects	59
EEA total number of subjects	51

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	52
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fifty-nine subjects were enrolled in the core trial and 22 continued into the extension phase. The original protocol allowed for compassionate use but a DMC recommended a protocol amendment for the extension. When extension phase was implemented, patients had already been treated for up to two years on compassionate use dose.

Pre-assignment

Screening details:

Sixty-one patients were screened and 59 enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Core-STI571

Arm description:

STI571 (Imatinib) was supplied in 100 mg capsules and was to have been administered orally with daily dose starting at 200 mg rising to 400 mg within two weeks. Dose may have been downtitrated from 400 to 200 mg one time during the trial.

Arm type	Experimental
Investigational medicinal product name	Imatinib
Investigational medicinal product code	STI571
Other name	Glivec, Gleevec
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Core study: STI571 was initiated at a dose level of 200 mg (two 100 mg capsules) per day for the first two weeks of treatment. If treatment was well tolerated, an up-titration to 400 mg (four 100 mg capsules) occurred. Patients then continued treatment for the next five months. If 400 mg was not well tolerated, one down-titration during the course of the study was permitted. STI571 was provided as 100 mg capsules, orally taken.

Open label extension: STI571 was provided as 100 mg capsules for oral administration.

Patients were instructed to take the study drug once daily with a meal and a large glass (8 oz/200 mL) of water to to not chew the medication, but to swallow it whole.

Arm title	Core-Placebo
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Arm description:

The appearance of placebo medication was identical to that of active drug.

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

Dosage and administration details:

Placebo matching capsules to be administered the same as the STI571 experimental arm.

Number of subjects in period 1	Core-STI571	Core-Placebo
Started	28	31
Completed	19	23
Not completed	9	8
Adverse event, serious fatal	3	3
Consent withdrawn by subject	-	1
Adverse event, non-fatal	6	4

Period 2

Period 2 title	Extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Extension-STI571
Arm description:	
Open label	
Arm type	Experimental
Investigational medicinal product name	Imatinib
Investigational medicinal product code	STI571
Other name	Glivec, Gleevec
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Open label extension: STI571 was provided as 100 mg capsules for oral administration.

Patients were instructed to take the study drug once daily with a meal and a large glass (8 oz/200 mL) of water to to not chew the medication, but to swallow it whole.

Number of subjects in period 2^[1]	Extension-STI571
Started	22
Completed	9
Not completed	13
Adverse event, serious fatal	4
Unsatisfactory therapeutic effect	2
Adverse event, non-fatal	4

Administrative problems	2
Abnormal laboratory value	1

Notes:

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

Justification: This study was comprised of several treatment phases. Initially the study was a 6 month treatment period in patients with PAH. Once patients completed this phase they were given the opportunity to continue to receive imatinib via compassionate use. After advice from the DSMB, a formal extension phase was launched. Twenty-two patients were receiving imatinib via compassionate use and were enrolled into the extension phase of the study.

Baseline characteristics

Reporting groups

Reporting group title	Core-STI571
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Reporting group description:

STI571 (Imatinib) was supplied in 100 mg capsules and was to have been administered orally with daily dose starting at 200 mg rising to 400 mg within two weeks. Dose may have been downtitrated from 400 to 200 mg one time during the trial.

Reporting group title	Core-Placebo
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Reporting group description:

The appearance of placebo medication was identical to that of active drug.

Reporting group values	Core-STI571	Core-Placebo	Total
Number of subjects	28	31	59
Age categorical			
Units: Subjects			
Adults (18-64 years)	26	26	52
From 65-84 years	2	5	7
Age continuous			
Units: years			
arithmetic mean	44.4	44.2	
standard deviation	± 15.3	± 15.7	-
Gender categorical			
Units: Subjects			
Female	18	22	40
Male	10	9	19

End points

End points reporting groups

Reporting group title	Core-STI571
Reporting group description: STI571 (Imatinib) was supplied in 100 mg capsules and was to have been administered orally with daily dose starting at 200 mg rising to 400 mg within two weeks. Dose may have been downtitrated from 400 to 200 mg one time during the trial.	
Reporting group title	Core-Placebo
Reporting group description: The appearance of placebo medication was identical to that of active drug.	
Reporting group title	Extension-STI571
Reporting group description: Open label	
Subject analysis set title	STI571 Six Min Walk Day 32
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients included in Six Minute Walk Test analysis group on STI571 at Day 32.	
Subject analysis set title	STI571 Six Min Walk Week 8
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients included in Six Minute Walk Test analysis group on STI571 at Week 8.	
Subject analysis set title	STI571 Six Min Walk Week 12
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients included in Six Minute Walk Test analysis group on STI571 at Week 12.	
Subject analysis set title	STI571 Six Min Walk Week 16
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients included in Six Minute Walk Test analysis group on STI571 at Week 16.	
Subject analysis set title	STI571 Six Min Walk Week 20
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients included in Six Minute Walk Test analysis group on STI571 at Week 20.	
Subject analysis set title	STI571 Six Min Walk Week 24
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients included in Six Minute Walk Test analysis group on STI571 at Week 24 (Study Completion).	
Subject analysis set title	Placebo Six Min Walk Day 32
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients included in Six Minute Walk Test analysis group on Placebo at Day 32.	
Subject analysis set title	Placebo Six Min Walk Week 8
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients included in Six Minute Walk Test analysis group on Placebo at Week 8.	
Subject analysis set title	Placebo Six Min Walk Week 12
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients included in Six Minute Walk Test analysis group on Placebo at Week 12.

Subject analysis set title	Placebo Six Min Walk Week 16
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients included in Six Minute Walk Test analysis group on Placebo at Week 16.

Subject analysis set title	Placebo Six Min Walk Week 20
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients included in Six Minute Walk Test analysis group on Placebo at Week 20.

Subject analysis set title	Placebo Six Min Walk Week 24
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients included in Six Minute Walk Test analysis group on Placebo at Week 24 (Study Completion).

Primary: Number of Patients With Adverse Events (AEs), Serious Adverse Events (SAEs) and Death During the Core

End point title	Number of Patients With Adverse Events (AEs), Serious Adverse Events (SAEs) and Death During the Core ^[1]
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End point description:

No statistical analysis provided for Number of Patients With Adverse Events (AEs), Serious Adverse Events (SAEs) and Death During the Core. All patients with all (serious and non -serious) adverse events, and death were reported. See Safety Section.

End point type	Primary
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End point timeframe:

6 months

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: No statistical analysis was planned for this primary outcome measure.

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: Patients				
Patients with AE(s)	27	29		
Death	3	3		
SAE(s)	12	11		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Patients With Adverse Events (AEs), Serious Adverse Events (SAEs) and Death During the Extension

End point title	Number of Patients With Adverse Events (AEs), Serious Adverse Events (SAEs) and Death During the Extension ^[2]
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End point description:

No formal statistical analysis was performed in the extension phase of this study so no analysis data sets were defined. All summaries are based on all patients enrolled. See Safety Section

End point type	Primary
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End point timeframe:

72 months

Notes:

[2] - 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: No statistical analysis was planned for this primary outcome measure.

End point values	Extension-STI571			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Patients				
Any Adverse Event(s)	22			
Death	4			
Serious Adverse Event(s)	16			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline of Six Minute Walk Test - Total Distance Walked

End point title	Change From Baseline of Six Minute Walk Test - Total Distance Walked
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End point description:

The Six Minute Walk test was carried out along a course, measuring at least 20 meters delineated by markers. Patients were instructed to walk at a comfortable speed as far as they could manage in six minutes, resting whenever they needed to. Distance <500 meters suggests considerable exercise limitation; Distance 500-800 meters suggests moderate limitation; Distance >800 meters (with no rests) suggests mild or no limitation.

The intention to treat population (ITT) included all patients who received at least one dose of study medication. Evaluable patients required observations at both baseline and endpoint.

End point type	Primary
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End point timeframe:

Baseline, Day 32, Week 8, Week 12, Week 16, Week 20 and Week 24.

End point values	STI571 Six Min Walk Day 32	STI571 Six Min Walk Week 8	STI571 Six Min Walk Week 12	STI571 Six Min Walk Week 16
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	23	22	19
Units: Meters				
arithmetic mean (standard deviation)	10.2 (± 53.7)	17 (± 55.6)	21 (± 36.2)	25.5 (± 43.1)

End point values	STI571 Six Min Walk Week 20	STI571 Six Min Walk Week 24	Placebo Six Min Walk Day 32	Placebo Six Min Walk Week 8
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	21	27	24
Units: Meters				

arithmetic mean (standard deviation)	38.3 (± 42.5)	22 (± 63.1)	8.2 (± 27.5)	15.5 (± 40.8)
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End point values	Placebo Six Min Walk Week 12	Placebo Six Min Walk Week 16	Placebo Six Min Walk Week 20	Placebo Six Min Walk Week 24
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	21	12
Units: Meters				
arithmetic mean (standard deviation)	7.8 (± 50)	12.1 (± 47.9)	12.8 (± 60.4)	-1 (± 53.3)

Statistical analyses

Statistical analysis title	Six Minute Walk Test - Total Distance Day 32
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Statistical analysis description:

The six minute walk tests at week 24 was analyzed using an analysis of covariance (ANCOVA) model including treatment (STI571 or placebo) as fixed effect and value at baseline as covariate.

For this timepoint the differences between STI571 and placebo was estimated together with the 95% confidence intervals. The analysis was performed on intention to treat population.

Comparison groups	STI571 Six Min Walk Day 32 v Placebo Six Min Walk Day 32
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8772
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.93
upper limit	25.61

Statistical analysis title	Six Min Walk -Total Distance Week 8
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Statistical analysis description:

The six minute walk tests at week 24 was analyzed using an analysis of covariance (ANCOVA) model including treatment (STI571 or placebo) as fixed effect and value at baseline as covariate.

For this timepoint the differences between STI571 and placebo was estimated together with the 95% confidence intervals. The analysis was performed on intention to treat population.

Comparison groups	STI571 Six Min Walk Week 8 v Placebo Six Min Walk Week 8
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9282
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.4
upper limit	29.98

Statistical analysis title	Six Min Walk -Total Distance Week 12
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Statistical analysis description:

The six minute walk tests for all time points was analyzed using an analysis of covariance (ANCOVA) model including treatment (STI571 or placebo) as fixed effect and value at baseline as covariate. For this timepoint the differences between STI571 and placebo was estimated together with the 95% confidence intervals. The analysis was performed on intention to treat population.

Comparison groups	STI571 Six Min Walk Week 12 v Placebo Six Min Walk Week 12
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2877
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	13.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.19
upper limit	40.1

Statistical analysis title	Six Min Walk -Total Distance Week 16
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Statistical analysis description:

The six minute walk tests for all time points was analyzed using an analysis of covariance (ANCOVA) model including treatment (STI571 or placebo) as fixed effect and value at baseline as covariate. For this timepoint the differences between STI571 and placebo was estimated together with the 95% confidence intervals. The analysis was performed on intention to treat population.

Comparison groups	STI571 Six Min Walk Week 16 v Placebo Six Min Walk Week 16
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3392
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	13.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.64
upper limit	41.48

Statistical analysis title	Six Min Walk -Total Distance Week 20
Statistical analysis description:	
The six minute walk tests for all time points was analyzed using an analysis of covariance (ANCOVA) model including treatment (STI571 or placebo) as fixed effect and value at baseline as covariate. For this timepoint the differences between STI571 and placebo was estimated together with the 95% confidence intervals. The analysis was performed on intention to treat population.	
Comparison groups	STI571 Six Min Walk Week 20 v Placebo Six Min Walk Week 20
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1507
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	24.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.28
upper limit	58.05

Statistical analysis title	Six Min Walk -Total Distance Week 24
Statistical analysis description:	
The six minute walk tests for all time points was analyzed using an analysis of covariance (ANCOVA) model including treatment (STI571 or placebo) as fixed effect and value at baseline as covariate. For this timepoint the differences between STI571 and placebo was estimated together with the 95% confidence intervals. The analysis was performed on intention to treat population.	
Comparison groups	STI571 Six Min Walk Week 24 v Placebo Six Min Walk Week 24
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2134
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	21.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.03
upper limit	56.51

Primary: Change From Baseline of Six Minute Walk Test - Number of Stops at Different Time Periods

End point title	Change From Baseline of Six Minute Walk Test - Number of Stops at Different Time Periods
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End point description:

The Six Minute Walk test was carried out along a course, such as a hospital corridor, measuring at least 20 meters delineated by markers. Patients were instructed to walk at a comfortable speed as far as they could manage in six minutes, resting whenever they needed to. If the patient stopped the duration of each stop was recorded.

The intention to treat population (ITT) included all patients who received at least one dose of study medication. Evaluable patients required observations at both baseline and endpoint.

End point type	Primary
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End point timeframe:

Baseline, Day 32, Week 8, Week 12, Week 16, Week 20 and Study completion (Week 24)

End point values	STI571 Six Min Walk Day 32	STI571 Six Min Walk Week 8	STI571 Six Min Walk Week 12	STI571 Six Min Walk Week 16
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	23	22	19
Units: Number of stops				
arithmetic mean (standard deviation)	-0.2 (± 0.7)	-0.2 (± 0.7)	-0.3 (± 0.9)	-0.3 (± 0.8)

End point values	STI571 Six Min Walk Week 20	STI571 Six Min Walk Week 24	Placebo Six Min Walk Day 32	Placebo Six Min Walk Week 8
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	21	27	24
Units: Number of stops				
arithmetic mean (standard deviation)	-0.4 (± 1)	-0.3 (± 0.8)	0.1 (± 0.4)	0 (± 0.4)

End point values	Placebo Six Min Walk Week 12	Placebo Six Min Walk Week 16	Placebo Six Min Walk Week 20	Placebo Six Min Walk Week 24
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	21	12
Units: Number of stops				
arithmetic mean (standard deviation)	0.3 (± 0.9)	0 (± 0.2)	0.3 (± 1)	-0.1 (± 0.5)

Statistical analyses

Statistical analysis title	Six Minute Walk Test-Number of Stops - Day 32
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Statistical analysis description:

Change From Baseline of Six Minute Walk Test - Number of Stops at Different Time Periods
Day 32

Comparison groups	STI571 Six Min Walk Day 32 v Placebo Six Min Walk Day 32
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0166
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.38

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	0.07

Statistical analysis title	Six Minute Walk Test-Number of Stops Week 8
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Statistical analysis description:

Change From Baseline of Six Minute Walk Test - Number of Stops at Different Time Periods Week 8

Comparison groups	STI571 Six Min Walk Week 8 v Placebo Six Min Walk Week 8
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.24
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.14

Statistical analysis title	Six Minute Walk Test-Number of Stops Week 12
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Statistical analysis description:

Change From Baseline of Six Minute Walk Test - Number of Stops at Different Time Periods Week 12

Comparison groups	STI571 Six Min Walk Week 12 v Placebo Six Min Walk Week 12
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0252
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	-0.08

Statistical analysis title	Six Minute Walk Test-Number of Stops Week 16
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Statistical analysis description:

Change From Baseline of Six Minute Walk Test - Number of Stops at Different Time Periods Week 16

Comparison groups	STI571 Six Min Walk Week 16 v Placebo Six Min Walk Week 16
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0755
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.03

Statistical analysis title	Six Minute Walk Test-Number of Stops Week 20
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Statistical analysis description:

Change From Baseline of Six Minute Walk Test - Number of Stops at Different Time Periods
Week 20

Comparison groups	STI571 Six Min Walk Week 20 v Placebo Six Min Walk Week 20
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0297
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	-0.07

Statistical analysis title	Six Minute Walk -Number of Stops Completion
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Statistical analysis description:

Change From Baseline of Six Minute Walk Test - Number of Stops at Different Time Periods
Study Completion

Comparison groups	STI571 Six Min Walk Week 24 v Placebo Six Min Walk Week 24
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1485
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.06

Primary: Change From Baseline of Six Minute Walk Test - Total Duration of Stops at Different Time Periods

End point title	Change From Baseline of Six Minute Walk Test - Total Duration of Stops at Different Time Periods
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End point description:

The Six Minute Walk test was carried out along a course, such as a hospital corridor, measuring at least 20 meters delineated by markers. Patients were instructed to walk at a comfortable speed as far as they could manage in six minutes, resting whenever they needed to. If the patient stopped the duration of each stop was recorded.

The intention to treat population (ITT) included all patients who received at least one dose of study medication. Evaluable patients required observations at both baseline and endpoint.

End point type	Primary
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End point timeframe:

Baseline, Day 32, Week 8, Week 12, Week 16, Week 20 and Study completion (Week 24)

End point values	STI571 Six Min Walk Day 32	STI571 Six Min Walk Week 8	STI571 Six Min Walk Week 12	STI571 Six Min Walk Week 16
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	23	22	19
Units: minutes				
arithmetic mean (standard deviation)	-0.06 (± 0.19)	-0.03 (± 0.1)	-0.03 (± 0.1)	-0.03 (± 0.1)

End point values	STI571 Six Min Walk Week 20	STI571 Six Min Walk Week 24	Placebo Six Min Walk Day 32	Placebo Six Min Walk Week 8
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	21	27	24
Units: minutes				
arithmetic mean (standard deviation)	-0.05 (± 0.15)	-0.02 (± 0.1)	0.12 (± 0.36)	0.07 (± 0.27)

End point values	Placebo Six Min Walk Week 12	Placebo Six Min Walk Week 16	Placebo Six Min Walk Week 20	Placebo Six Min Walk Week 24
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	21	12
Units: minutes				
arithmetic mean (standard deviation)	0.19 (± 0.55)	0.06 (± 0.26)	0.12 (± 0.42)	0.03 (± 0.18)

Statistical analyses

Statistical analysis title	Six Minute Walk Duration of stops [min] - Day 32
Statistical analysis description: Change From Baseline of Six Minute Walk Test -Total duration of stops [min] at Different Time Periods Day 32	
Comparison groups	STI571 Six Min Walk Day 32 v Placebo Six Min Walk Day 32
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0301
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.02

Statistical analysis title	Six Minute Walk Duration of stops [min] Week 8
Statistical analysis description: Change From Baseline of Six Minute Walk Test -Total duration of stops [min] Week 8	
Comparison groups	Placebo Six Min Walk Week 8 v STI571 Six Min Walk Week 8
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1179
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.03

Statistical analysis title	Six Minute Walk Duration of stops [min] Week 12
Statistical analysis description: Change From Baseline of Six Minute Walk Test -Total duration of stops [min]	

Week 12

Comparison groups	STI571 Six Min Walk Week 12 v Placebo Six Min Walk Week 12
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0652
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	0.01

Statistical analysis title

Six Minute Walk Duration of stops [min] Week16

Statistical analysis description:

Change From Baseline of Six Minute Walk Test -Total duration of stops [min]
Week 16

Comparison groups	STI571 Six Min Walk Week 20 v Placebo Six Min Walk Week 16
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1826
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.04

Statistical analysis title

Six Minute Walk Duration of stops [min] Week 20

Statistical analysis description:

Change From Baseline of Six Minute Walk Test -Total duration of stops [min]
Week 20

Comparison groups	STI571 Six Min Walk Week 20 v Placebo Six Min Walk Week 20
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0863
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.03

Statistical analysis title	Six Min Walk Duration of stops [min] Week 24
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Statistical analysis description:

Change From Baseline of Six Minute Walk Test -Total duration of stops [min]
Study Completion

Comparison groups	STI571 Six Min Walk Week 24 v Placebo Six Min Walk Week 24
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1896
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.03

Primary: Change From Baseline of Six Minute Walk Test - Total Distance Walked at week 8

End point title	Change From Baseline of Six Minute Walk Test - Total Distance Walked at week 8
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End point description:

20 meters delineated by markers. Patients were instructed to walk at a comfortable speed as far as they could manage in six minutes, resting whenever they needed to. Distance <500 meters suggests considerable exercise limitation; Distance 500-800 meters suggests moderate limitation; Distance >800 meters (with no rests) suggests mild or no limitation. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type	Primary
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End point timeframe:

Baseline, week 8

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Meters				
arithmetic mean (standard deviation)				
week 8 (n=23,24)	17 (± 55.6)	15.5 (± 40.8)		

Statistical analyses

Statistical analysis title	Six Minute Walk Test - Total Distance at Week 8
Statistical analysis description:	
The six minute walk tests at week 24 was analyzed using an analysis of covariance (ANCOVA) model including treatment (STI571 or placebo) as fixed effect and value at baseline as covariate. For all time-points the differences between STI571 and placebo will be estimated together with the 95% confidence intervals. The analysis will be performed on intention to treat population.	
Comparison groups	Core-STI571 v Core-Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9282
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.4
upper limit	29.98

Secondary: Number of Patients With Pulmonary Hypertension (PAH) Assessed by World Health Organization (WHO) Classification on Physical Activity

End point title	Number of Patients With Pulmonary Hypertension (PAH) Assessed by World Health Organization (WHO) Classification on Physical Activity
End point description:	
PAH assessed according to the WHO classification: Class I Patients with PAH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope. Class II Patients with PAH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope. Class III Patients with PAH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope. Class IV Patients with PAH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity. The intention to treat population (ITT) will include all patients who received at least one dose of study medication.	
End point type	Secondary
End point timeframe:	
Baseline, Day 32, Week 8, Week 12, Week 16, Week 20 and Study completion	

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: Participants				
Baseline: WHO Class IV (n=27,30)	2	1		
Baseline: WHO Class III (n=27,30)	14	22		
Baseline: WHO Class II (n=27,30)	11	7		
Day 32: WHO Class IV (n=27,30)	3	3		
Day 32: WHO Class III (n=27,30)	11	21		
Day 32: WHO Class II (n=27,30)	13	6		
Week 8: WHO Class IV (n=24,27)	3	1		
Week 8: WHO Class III (n=24,27)	9	20		
Week 8: WHO Class II (n=24,27)	12	6		
Week 12: WHO Class IV (n=23,27)	0	1		
Week 12: WHO Class III (n=23,27)	12	17		
Week 12: WHO Class II (n=23,27)	11	9		
Week 16: WHO Class IV (n=22,27)	0	1		
Week 16: WHO Class III (n=22,27)	11	18		
Week 16: WHO Class II (n=22,27)	11	7		
Week 16: WHO Class I (n=22,27)	0	1		
Week 20: WHO Class IV (n=19,24)	0	1		
Week 20: WHO Class III (n=19,24)	10	14		
Week 20: WHO Class II (n=19,24)	8	9		
Week 20: WHO Class I (n=19,24)	1	0		
Week 24: WHO Class IV (n=21,25)	1	2		
Week 24: WHO Class III (n=21,25)	12	13		
Week 24: WHO Class II (n=21,25)	8	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Borg Score-Oxygen Saturation(SaO2) During the Six Minutes Walk Test at Different Time Periods

End point title	Borg Score-Oxygen Saturation(SaO2) During the Six Minutes Walk Test at Different Time Periods
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End point description:

Six Minute Walk test was carried out along a course, such as a hospital corridor, measuring at least 20 meters delineated by markers. During the walk the patient was connected to a portable pulse oximeter via a finger probe. Patients were instructed to walk at a comfortable speed as far as they could manage in six minutes, resting whenever they needed to. The test was terminated if the patient became too distressed or if their SaO2% fell below 60%. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Baseline, Day 32, Week 8, Week 12, Week 16, Week 20 and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: Percentage of Oxygen Saturation				
arithmetic mean (standard deviation)				
Baseline: Resting (n= 28, 29)	94.3 (± 4.6)	93.4 (± 4.7)		
Baseline: End of Test (n= 28, 28)	87.9 (± 12.4)	87.9 (± 8.2)		
Baseline: 2 minutes after end of test (n=26, 26)	93 (± 7)	92 (± 6.2)		
Day 32: Resting (n= 25, 28)	94.5 (± 4)	92.4 (± 6.3)		
Day 32: End of Test (n= 25, 28)	89 (± 11.2)	87.2 (± 12.8)		
Day 32: 2 minutes after end of test (n= 25, 26)	94.8 (± 4.6)	92.7 (± 7.1)		
Week 8: Resting (n= 23, 25)	95.1 (± 3.3)	93.2 (± 6.1)		
Week 8: End of Test (n= 23, 24)	90.9 (± 6.7)	87.9 (± 11.9)		
Week 8: 2 minutes after end of test (n= 23, 23)	94.4 (± 5.3)	93.1 (± 7.8)		
Week 12: Resting (n= 22, 25)	95.1 (± 4.8)	93.9 (± 5.6)		
Week 12: End of Test (n= 20, 24)	89.8 (± 9.2)	89.6 (± 8.9)		
Week 12: 2 minutes after end of test (n= 19, 22)	92.7 (± 8.9)	94.2 (± 5.6)		
Week 16: Resting (n= 19, 24)	95 (± 5)	94.1 (± 5.1)		
Week 16: End of Test (n= 18, 23)	87.9 (± 13.1)	88.1 (± 9.8)		
Week 16: 2 minutes after end of test (n= 19, 19)	94.6 (± 6)	93.3 (± 8)		
Week 20: Resting (n= 19, 22)	94 (± 4.7)	93.7 (± 5)		
Week 20: End of Test (n= 18, 21)	87.5 (± 13.2)	87.6 (± 9.1)		
Week 20: 2 minutes after end of test (n= 19, 21)	93.8 (± 7.1)	93.4 (± 7.4)		
Week 24: Resting (n= 20, 22)	95.5 (± 3.4)	94.3 (± 4.6)		
Week 24: End of Test (n= 20, 21)	89.9 (± 7.1)	89.3 (± 8.4)		
Week 24: 2 minutes after end of test (n= 20, 21)	94.8 (± 4.3)	94.8 (± 3.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Borg Score-Systolic Blood Pressure During the Six Minutes Walk Test at Different Time Periods

End point title	Borg Score-Systolic Blood Pressure During the Six Minutes Walk Test at Different Time Periods
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End point description:

Six Minute Walk test was carried out along a course, such as a hospital corridor, measuring at least 20 meters delineated by markers. During the walk the patient was connected to a portable pulse oximeter via a finger probe. Patients were instructed to walk at a comfortable speed as far as they could manage in six minutes, resting whenever they needed to. Systolic blood pressure (mmHg) were recorded before the test at resting, at the end of the test and two minutes after the end of the test. The intention to treat population (ITT) included all patients who received at least one dose of study medication

End point type	Secondary
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End point timeframe:

Baseline, Day 32, Week 8, Week 12, Week 16, Week 20 and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline: Resting (n= 26, 28)	111.3 (± 14.2)	104.6 (± 13.2)		
Baseline: End of Test (n= 21, 26)	119.9 (± 19.3)	118.3 (± 18)		
Baseline: 2 minutes after end of test (n=25, 27)	120 (± 18.3)	110.4 (± 13.6)		
Day 32: Resting (n= 25, 27)	111.4 (± 9.6)	106 (± 12.3)		
Day 32: End of Test (n= 22, 22)	126.5 (± 17.3)	122.3 (± 18.6)		
Day 32: 2 minutes after end of test (n= 25, 26)	119.6 (± 12.6)	113.8 (± 14.9)		
Week 8: Resting (n= 22, 24)	108.9 (± 12.3)	107.3 (± 13.5)		
Week 8: End of Test (n= 19, 20)	124.6 (± 16.1)	119.9 (± 17.1)		
Week 8: 2 minutes after end of test (n= 23, 24)	115.2 (± 13.6)	114.5 (± 13.7)		
Week 12: Resting (n= 22, 23)	106.5 (± 11.5)	107.7 (± 13.8)		
Week 12: End of Test (n= 17, 19)	122.2 (± 17)	118.8 (± 22.9)		
Week 12: 2 minutes after end of test (n= 20, 22)	115.9 (± 14.2)	115.9 (± 14.9)		
Week 16: Resting (n= 19, 22)	106.7 (± 9.7)	105.7 (± 12.5)		
Week 16: End of Test (n= 15,18)	117.2 (± 12.3)	119.8 (± 13.5)		
Week 16: 2 minutes after end of test (n= 19, 22)	114.6 (± 13.8)	112.6 (± 15.8)		
Week 20: Resting (n= 19, 20)	106.5 (± 7)	109.1 (± 12.1)		
Week 20: End of Test (n= 16,17)	122.4 (± 13.3)	119.9 (± 19.3)		
Week 20: 2 minutes after end of test (n= 19, 20)	115.5 (± 14)	115.1 (± 15.1)		
Week 24: Resting (n= 20, 21)	110.6 (± 15.6)	108.2 (± 15.7)		
Week 24: End of Test (n= 16, 17)	126.9 (± 23.6)	116.8 (± 14.9)		
Week 24: 2 minutes after end of test (n= 20, 19)	118.2 (± 18.6)	111.1 (± 10.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Borg Score-Diastolic Blood Pressure During the Six Minutes Walk Test at Different Time Periods

End point title	Borg Score-Diastolic Blood Pressure During the Six Minutes Walk Test at Different Time Periods
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End point description:

Six Minute Walk test was carried out along a course, such as a hospital corridor, measuring at least 20 meters delineated by markers. During the walk the patient was connected to a portable pulse oximeter via a finger probe. Patients were instructed to walk at a comfortable speed as far as they could manage in six minutes, resting whenever they needed to. Diastolic blood pressure (mmHg) were recorded before the test at resting, at the end of the test and two minutes after the end of the test. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type	Secondary
End point timeframe:	
Baseline, Day 32, Week 8, Week 12, Week 16, Week 20 and Study completion (Week 24)	

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline: Resting (n= 26, 28)	68.2 (± 10.2)	67.9 (± 8.9)		
Baseline: End of Test (n= 21, 26)	75.1 (± 10.8)	69.5 (± 11.9)		
Baseline: 2 minutes after end of test (n=25, 27)	71.6 (± 9.8)	67.9 (± 9.6)		
Day 32: Resting (n= 25, 27)	69.6 (± 10.4)	68.4 (± 8.8)		
Day 32: End of Test (n= 22, 22)	78.2 (± 12.3)	75.2 (± 11.2)		
Day 32: 2 minutes after end of test (n= 25, 26)	72.5 (± 9.1)	70.7 (± 9.4)		
Week 8: Resting (n= 22, 24)	67.7 (± 11.8)	68.8 (± 9)		
Week 8: End of Test (n= 19, 20)	74.8 (± 10.8)	74 (± 10.9)		
Week 8: 2 minutes after end of test (n= 23, 24)	71.2 (± 10.3)	72.2 (± 11.7)		
Week 12: Resting (n= 22, 23)	65.5 (± 8.3)	70.6 (± 11.6)		
Week 12: End of Test (n= 17, 19)	75.6 (± 11.5)	72.4 (± 14.3)		
Week 12: 2 minutes after end of test (n= 20, 22)	73.1 (± 8.9)	72 (± 13.7)		
Week 16: Resting (n= 19, 22)	67.7 (± 9.9)	66.7 (± 7.7)		
Week 16: End of Test (n= 15,18)	72.7 (± 9.2)	76.7 (± 8.6)		
Week 16: 2 minutes after end of test (n= 19, 22)	71.4 (± 11)	70.5 (± 8)		
Week 20: Resting (n= 19, 20)	67.2 (± 8)	69.8 (± 8.8)		
Week 20: End of Test (n= 16,17)	72.9 (± 8.7)	72.9 (± 8.1)		
Week 20: 2 minutes after end of test (n= 19, 20)	71.9 (± 9.2)	72.7 (± 9.8)		
Week 24: Resting (n= 20, 21)	69.7 (± 10.3)	70.7 (± 10.9)		
Week 24: End of Test (n= 16, 17)	74.1 (± 10.7)	72.3 (± 10.9)		
Week 24: 2 minutes after end of test (n= 20, 19)	71.3 (± 10.1)	72.9 (± 9.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Borg Score-Heart Rate (HR) During the Six Minutes Walk Test at Different Time Periods

End point title	Borg Score-Heart Rate (HR) During the Six Minutes Walk Test at Different Time Periods
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End point description:

Six Minute Walk test was carried out along a course, such as a hospital corridor, measuring at least 20 meters delineated by markers. During the walk the patient was connected to a portable pulse oximeter

via a finger probe. Patients were instructed to walk at a comfortable speed as far as they could manage in six minutes, resting whenever they needed to. Heart Rate (bpm) were recorded before the test at resting, at the end of the test and two minutes after the end of the test. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type	Secondary
End point timeframe:	
Baseline, Day 32, Week 8, Week 12, Week 16, Week 20 and Study completion (Week 24)	

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
Baseline: Resting (n= 28, 29)	80.8 (± 13)	87.9 (± 12.7)		
Baseline: End of Test (n= 28, 29)	106.3 (± 23.9)	112.3 (± 20.4)		
Baseline: 2 minutes after end of test (n=26, 26)	84.2 (± 16.9)	94.1 (± 14.6)		
Day 32: Resting (n= 25, 28)	80.7 (± 14.3)	83.6 (± 15.7)		
Day 32: End of Test (n= 25, 28)	108.4 (± 19.1)	113.1 (± 19.5)		
Day 32: 2 minutes after end of test (n= 25, 26)	89.2 (± 17)	90.6 (± 14.1)		
Week 8: Resting (n= 23, 25)	80.3 (± 9.6)	81.1 (± 11.2)		
Week 8: End of Test (n= 23, 24)	109.5 (± 21.4)	110.3 (± 26.4)		
Week 8: 2 minutes after end of test (n= 23, 23)	85.3 (± 15.7)	88.9 (± 13.2)		
Week 12: Resting (n= 22, 25)	76.5 (± 13.2)	85.1 (± 13.2)		
Week 12: End of Test (n= 20, 25)	105.3 (± 26.2)	113 (± 26.5)		
Week 12: 2 minutes after end of test (n= 19, 22)	83.8 (± 17.8)	89.4 (± 15.7)		
Week 16: Resting (n= 19, 24)	76.5 (± 13.2)	84.4 (± 12.9)		
Week 16: End of Test (n= 18, 23)	102.8 (± 25.6)	117.9 (± 24.3)		
Week 16: 2 minutes after end of test (n= 19, 21)	85.8 (± 21)	85.5 (± 14.4)		
Week 20: Resting (n= 19, 22)	75.3 (± 13.8)	80.2 (± 9.6)		
Week 20: End of Test (n= 18,22)	109.2 (± 26.8)	118 (± 24.5)		
Week 20: 2 minutes after end of test (n= 19, 21)	83.3 (± 17.4)	87.3 (± 11.4)		
Week 24: Resting (n= 20, 22)	79.5 (± 13.8)	83.6 (± 8.6)		
Week 24: End of Test (n= 20, 21)	110.2 (± 18.1)	116.8 (± 21.7)		
Week 24: 2 minutes after end of test (n= 20, 21)	87.9 (± 17.5)	88.9 (± 11.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Borg Score Breathlessness During the Six Minutes Walk Test at Different Time Periods

End point title	Borg Score Breathlessness During the Six Minutes Walk Test at Different Time Periods
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End point description:

Borg Score during Six Minute Walk test was carried out along a course, such as a hospital corridor, measuring at least 20 meters delineated by markers. During the walk the patient was connected to a portable pulse oximeter via a finger probe. Patients were instructed to walk at a comfortable speed as far as they could manage in six minutes, resting whenever they needed to. Borg Score of Breathlessness was recorded using the following score of 0 to 10, how breathless do you feel? 0 is nothing at all and 10 is maximal breathlessness. The intention to treat population (ITT) will include all patients who received at least one dose of study medication

End point type	Secondary
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End point timeframe:

Baseline, Day 32, Week 8, Week 12, Week 16, Week 20 and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline: Resting (n= 26, 27)	68.2 (± 10.2)	67.9 (± 8.9)		
Baseline: End of Test (n= 27, 29)	75.1 (± 10.8)	69.5 (± 11.9)		
Baseline: 2 minutes after end of test (n=24, 26)	71.6 (± 9.8)	67.9 (± 9.6)		
Day 32: Resting (n= 25, 27)	69.6 (± 10.4)	68.4 (± 8.8)		
Day 32: End of Test (n= 25, 28)	78.2 (± 12.3)	75.2 (± 11.2)		
Day 32: 2 minutes after end of test (n= 25, 26)	72.5 (± 9.1)	70.7 (± 9.4)		
Week 8: Resting (n= 23, 24)	67.7 (± 11.8)	68.8 (± 9)		
Week 8: End of Test (n= 23, 25)	74.8 (± 10.8)	74 (± 10.9)		
Week 8: 2 minutes after end of test (n= 23, 24)	71.2 (± 10.3)	72.2 (± 11.7)		
Week 12: Resting (n= 22, 24)	65.5 (± 8.3)	70.6 (± 11.6)		
Week 12: End of Test (n= 22, 25)	75.6 (± 11.5)	72.4 (± 14.3)		
Week 12: 2 minutes after end of test (n= 22, 23)	73.1 (± 8.9)	72 (± 13.7)		
Week 16: Resting (n= 19, 23)	67.7 (± 9.9)	66.7 (± 7.7)		
Week 16: End of Test (n= 18, 23)	72.7 (± 9.2)	76.7 (± 8.6)		
Week 16: 2 minutes after end of test (n= 19, 23)	71.4 (± 11)	70.5 (± 8)		
Week 20: Resting (n= 19, 21)	67.2 (± 8)	69.8 (± 8.8)		
Week 20: End of Test (n= 18,22)	72.9 (± 8.7)	72.9 (± 8.1)		
Week 20: 2 minutes after end of test (n= 18, 20)	71.9 (± 9.2)	72.7 (± 9.8)		
Week 24: Resting (n= 20, 21)	69.7 (± 10.3)	70.7 (± 10.9)		
Week 24: End of Test (n= 20, 21)	74.1 (± 10.7)	72.3 (± 10.9)		
Week 24: 2 minutes after end of test (n= 20, 20)	71.3 (± 10.1)	72.9 (± 9.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Pulmonary Artery Pressure (PAP) at Baseline and Study Completion

End point title	Mean Pulmonary Artery Pressure (PAP) at Baseline and Study Completion
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End point description:

The right heart catheter assessment was performed to assess several prognostic hemodynamic variables in pulmonary hypertension, including right Pulmonary Arterial Pressure (PAP). These were assessed when the patient was in a stable hemodynamic rest state (as demonstrated by three consecutive Mean PAP and CO measurements within 10% of each other). PAP was assessed when the patient was breathing ambient air, every 2 minutes whilst breathing Nitric Oxide(NO) (1st and 2nd), 5 min after the end of NO administration, and 15 mins after the end of NO administration. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: Pulmonary Artery Pressure mmHg				
arithmetic mean (standard deviation)				
Baseline breathing ambient air (n=27,28)	61.7 (± 15.6)	59.2 (± 11.6)		
Baseline every 2 mins breathing NO (1st) (n=20,20)	61.6 (± 18.7)	55.7 (± 12)		
Baseline every 2 mins breathing NO (2nd) (n=17,18)	58.1 (± 16.7)	53.3 (± 11.5)		
Baseline 5 mins after NO administration (n=20,14)	60.9 (± 16.2)	56.9 (± 10.8)		
Baseline 15 mins after NO administration(n=19,19)	60.3 (± 16)	56.5 (± 10.3)		
Week 24 breathing ambient air (n=20,22)	52.5 (± 11.4)	55.5 (± 11.6)		
Week 24 every 2 mins breathing NO (1st) (n=10,13)	50.9 (± 17.5)	55.1 (± 13.9)		
Week 24 every 2 mins breathing NO (2nd) (n=9,11)	46.2 (± 18.1)	53.9 (± 14)		
Week 24 5 mins after NO administration (n=10,12)	47 (± 15.8)	57.5 (± 12.8)		
Week 24 15 mins after NO administration (n=10,14)	48.1 (± 13.7)	57.2 (± 12.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Pulmonary Artery Wedge Pressure (PAWP) at Baseline and Study Completion

End point title	Mean Pulmonary Artery Wedge Pressure (PAWP) at Baseline and Study Completion
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End point description:

The right heart catheter assessment was performed to assess several prognostic hemodynamic variables

in pulmonary hypertension, including right Pulmonary Arterial Pressure (PAP). These were assessed when the patient was in a stable hemodynamic rest state (as demonstrated by three consecutive Mean PAP and CO measurements within 10% of each other). PAP was assessed when the patient was breathing ambient air, every 2 minutes whilst breathing Nitric Oxide(NO) (1st and 2nd), 5 min after the end of NO administration, and 15 mins after the end of NO administration. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline breathing ambient air (n=26,28)	9 (± 2.6)	7.6 (± 2.3)		
Baseline every 2 mins breathing NO (1st) (n=20,17)	9.5 (± 2)	7.7 (± 2.9)		
Baseline every 2 mins breathing NO (2nd) (n=17,16)	9.4 (± 2.2)	7.8 (± 3.4)		
Baseline 5 mins after NO administration (n=19,12)	9.5 (± 2.7)	7.8 (± 2.9)		
Baseline 15 mins after NO administration(n=18,17)	9.6 (± 2.4)	8.1 (± 2.6)		
Week 24 breathing ambient air (n=19,22)	8.4 (± 3.2)	8.6 (± 2.8)		
Week 24 every 2 mins breathing NO (1st) (n=9,13)	7.9 (± 3.1)	10.2 (± 3.7)		
Week 24 every 2 mins breathing NO (2nd) (n=9,11)	7 (± 3.4)	10 (± 3.7)		
Week 24 5 mins after NO administration (n=10,12)	7.1 (± 3.1)	10.3 (± 3.3)		
Week 24 15 mins after NO administration (n=10,14)	6.7 (± 2.8)	10.4 (± 3.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Systolic Arterial Pressure (SAP) at Baseline and Study Completion

End point title	Mean Systolic Arterial Pressure (SAP) at Baseline and Study Completion
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End point description:

The right heart catheter assessment was performed to assess several prognostic hemodynamic variables in pulmonary hypertension, including right Pulmonary Arterial Pressure (PAP). These were assessed when the patient was in a stable hemodynamic rest state (as demonstrated by three consecutive Mean PAP and CO measurements within 10% of each other). PAP was assessed when the patient was breathing ambient air, every 2 minutes whilst breathing Nitric Oxide(NO) (1st and 2nd), 5 min after the end of NO administration, and 15 mins after the end of NO administration. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline breathing ambient air (n=26,28)	110.3 (± 19.5)	108.2 (± 15.4)		
Baseline every 2 mins breathing NO (1st) (n=20,19)	108.3 (± 18.9)	106.9 (± 18)		
Baseline every 2 mins breathing NO (2nd) (n=17,17)	109.9 (± 19.1)	105.4 (± 18.1)		
Baseline 5 mins after NO administration (n=21,15)	106 (± 17.7)	107.1 (± 18.6)		
Baseline 15 mins after NO administration(n=19,19)	109.5 (± 20.3)	106.9 (± 16.7)		
Week 24 breathing ambient air (n=20,22)	108 (± 19.8)	106.9 (± 18.8)		
Week 24 every 2 mins breathing NO (1st) (n=10,13)	103.9 (± 17.5)	102.9 (± 20.4)		
Week 24 every 2 mins breathing NO (2nd) (n=9,11)	104.8 (± 18.3)	103.6 (± 19.2)		
Week 24 5 mins after NO administration (n=9,12)	103.4 (± 18.7)	104 (± 20)		
Week 24 15 mins after NO administration (n=10,14)	103.8 (± 21.4)	107.3 (± 18.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Heart Rate (HR) at Baseline and Study Completion

End point title | Mean Heart Rate (HR) at Baseline and Study Completion

End point description:

The right heart catheter assessment was performed to assess several prognostic hemodynamic variables in pulmonary hypertension, including Heart Rate (HR). These were assessed when the patient was in a stable hemodynamic rest state (as demonstrated by three consecutive Mean PAP and CO measurements within 10% of each other). PAP was assessed when the patient was breathing ambient air, every 2 minutes whilst breathing Nitric Oxide(NO) (1st and 2nd), 5 min after the end of NO administration, and 15 mins after the end of NO administration. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type | Secondary

End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
Baseline breathing ambient air (n=27,28)	77.3 (± 7.5)	84.9 (± 13)		
Baseline every 2 mins breathing NO (1st) (n=20,19)	75.9 (± 12.9)	84.4 (± 15.5)		
Baseline every 2 mins breathing NO (2nd) (n=17,17)	75.2 (± 13.6)	83.3 (± 13.2)		
Baseline 5 mins after NO administration (n=19,15)	73.2 (± 10.2)	84.3 (± 13.9)		
Baseline 15 mins after NO administration(n=18,19)	76.2 (± 9)	85.1 (± 13.8)		
Week 24 breathing ambient air (n=20,22)	76.6 (± 8.6)	83 (± 12.8)		
Week 24 every 2 mins breathing NO (1st) (n=9,13)	76.3 (± 10.1)	82.5 (± 15.3)		
Week 24 every 2 mins breathing NO (2nd) (n=8,11)	76.6 (± 10.3)	82.8 (± 16.7)		
Week 24 5 mins after NO administration (n=9,12)	75.7 (± 10.2)	79.3 (± 10.4)		
Week 24 15 mins after NO administration (n=10,14)	73.2 (± 8.3)	82.9 (± 10.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Cardiac Output (CO) at Baseline and Study Completion

End point title	Mean Cardiac Output (CO) at Baseline and Study Completion
End point description:	The right heart catheter assessment was performed to assess several prognostic hemodynamic variables in pulmonary hypertension, including Cardiac Output (CO). These were assessed when the patient was in a stable hemodynamic rest state (as demonstrated by three consecutive Mean PAP and CO measurements within 10% of each other). PAP was assessed when the patient was breathing ambient air, every 2 minutes whilst breathing Nitric Oxide(NO) (1st and 2nd), 5 min after the end of NO administration, and 15 mins after the end of NO administration. The intention to treat population (ITT) included all patients who received at least one dose of study medication.
End point type	Secondary
End point timeframe:	Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: L/min				
arithmetic mean (standard deviation)				
Baseline breathing ambient air (n=27,28)	4.2 (± 1.33)	4.09 (± 1.44)		

Baseline every 2 mins breathing NO (1st) (n=19,20)	4.02 (± 1.32)	4.22 (± 1.64)		
Baseline every 2 mins breathing NO (2nd) (n=17,18)	3.98 (± 1.16)	4.43 (± 1.8)		
Baseline 5 mins after NO administration (n=19,14)	4.2 (± 1.16)	4.71 (± 1.95)		
Baseline 15 mins after NO administration(n=18,19)	3.87 (± 1.03)	4.47 (± 2.15)		
Week 24 breathing ambient air (n=20,22)	4.9 (± 1.21)	4.35 (± 1.57)		
Week 24 every 2 mins breathing NO (1st) (n=10,13)	4.8 (± 1.26)	4.67 (± 2.27)		
Week 24 every 2 mins breathing NO (2nd) (n=9,11)	4.79 (± 1.31)	4.62 (± 2.26)		
Week 24 5 mins after NO administration (n=10,12)	4.63 (± 1.21)	4.65 (± 1.99)		
Week 24 15 mins after NO administration (n=10,14)	4.48 (± 1.21)	4.46 (± 1.98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Pulmonary Vascular Resistance (PVR) at Baseline and Study Completion

End point title	Mean Pulmonary Vascular Resistance (PVR) at Baseline and Study Completion
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End point description:

The right heart catheter assessment was performed to assess several prognostic hemodynamic variables in pulmonary hypertension, including Pulmonary Vascular Resistance (PVR). These were assessed when the patient was in a stable hemodynamic rest state (as demonstrated by three consecutive Mean PAP and CO measurements within 10% of each other). PAP was assessed when the patient was breathing ambient air, every 2 minutes whilst breathing Nitric Oxide(NO) (1st and 2nd), 5 min after the end of NO administration, and 15 mins after the end of NO administration. PVR calculated according to the equation: $PVR = (PAP - PCWP)/CO$. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: dyn*s/cm ⁵				
arithmetic mean (standard deviation)				
Baseline breathing ambient air (n=27,27)	1124.4 (± 460)	1118.3 (± 486.7)		
Baseline every 2 mins breathing NO (1st) (n=19,17)	1180.9 (± 520.8)	1067.9 (± 509.1)		
Baseline every 2 mins breathing NO (2nd) (n=17,16)	1064.6 (± 458.9)	982.8 (± 483.9)		
Baseline 5 mins after NO administration (n=19,11)	1131.5 (± 491.2)	1160.4 (± 510)		

Baseline 15 mins after NO administration(n=18,16)	1181.9 (± 498.7)	1132.9 (± 461)		
Week 24 breathing ambient air (n=19,21)	729.9 (± 230.1)	1017 (± 369.1)		
Week 24 every 2 mins breathing NO (1st) (n=9,14)	706.9 (± 285.5)	1000.6 (± 501.5)		
Week 24 every 2 mins breathing NO (2nd) (n=9,11)	687.4 (± 276.3)	1033.6 (± 546.2)		
Week 24 5 mins after NO administration (n=10,12)	717.2 (± 271.6)	987.8 (± 370.4)		
Week 24 15 mins after NO administration (n=10,14)	776.1 (± 286.8)	1042.5 (± 388.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Systemic Vascular Resistance (SVR) at Baseline and Study Completion

End point title	Mean Systemic Vascular Resistance (SVR) at Baseline and Study Completion
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End point description:

The right heart catheter assessment was performed to assess several prognostic hemodynamic variables in pulmonary hypertension, including Systemic Vascular Resistance (SVR). These were assessed when the patient was in a stable hemodynamic rest state (as demonstrated by three consecutive Mean PAP and CO measurements within 10% of each other). PAP was assessed when the patient was breathing ambient air, every 2 minutes whilst breathing Nitric Oxide(NO) (1st and 2nd), 5 min after the end of NO administration, and 15 mins after the end of NO administration. SVR was calculated according to the equation: $SVR = (Paorta - Right\ atrium) / CO$. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: dyn*s/cm ⁵				
arithmetic mean (standard deviation)				
Baseline breathing ambient air (n=26,26)	1674.4 (± 761.2)	1764.8 (± 481.9)		
Baseline every 2 mins breathing NO (1st) (n=18,15)	1778.2 (± 709.5)	1769.7 (± 457)		
Baseline every 2 mins breathing NO (2nd) (n=16,14)	1807.3 (± 615.1)	1664.7 (± 472)		
Baseline 5 mins after NO administration (n=18,11)	1609.2 (± 593.4)	1666.6 (± 488.6)		
Baseline 15 mins after NO administration(n=17,15)	1976.3 (± 877.5)	1748.4 (± 499.3)		
Week 24 breathing ambient air (n=18,21)	1427.2 (± 446.8)	1667.9 (± 357.8)		
Week 24 every 2 mins breathing NO (1st) (n=9,13)	1344.2 (± 474.8)	1579.3 (± 386.8)		

Week 24 every 2 mins breathing NO (2nd) (n=9,11)	1367.9 (± 601.7)	1592.5 (± 389)		
Week 24 5 mins after NO administration (n=9,12)	1419.7 (± 566.6)	1503.9 (± 305.3)		
Week 24 15 mins after NO administration (n=10,14)	1431.7 (± 524.4)	1629.3 (± 355.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Gas Measurement - PaO2 at Baseline and Study Completion

End point title	Blood Gas Measurement - PaO2 at Baseline and Study Completion
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End point description:

The right heart catheter assessment was performed to assess Blood Gas Measurements in pulmonary hypertension, including PaO2 levels at baseline and Study completion Week 24. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline n=22,21	63.36 (± 14.33)	63.75 (± 12.02)		
Week 24 n=16,17	72.49 (± 14.09)	70.13 (± 16.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Gas Measurement - PvO2 at Baseline and Study Completion

End point title	Blood Gas Measurement - PvO2 at Baseline and Study Completion
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End point description:

The right heart catheter assessment was performed to assess Blood Gas Measurements in pulmonary hypertension, including PvO2 levels at baseline and Study completion Week 24. The intention to treat population (ITT) included all patients who received at least one dose of study medication

End point type	Secondary
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End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline n=14,14	33.16 (± 4.62)	34.7 (± 4.75)		
Week 24 n=11,11	35.56 (± 3.8)	32.65 (± 4.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Gas Measurement - Arterial Saturation at Baseline and Study Completion

End point title	Blood Gas Measurement - Arterial Saturation at Baseline and Study Completion
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End point description:

The right heart catheter assessment was performed to assess Blood Gas Measurements in pulmonary hypertension, including Arterial Saturation levels at baseline and Study completion Week 24. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: Percentage of saturation				
arithmetic mean (standard deviation)				
Baseline n=19,16	87.99 (± 9.19)	91.81 (± 4.05)		
Week 24 n=14,15	92.89 (± 4.5)	91.78 (± 3.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Gas Measurement - Venous Saturation at Baseline and Study Completion

End point title	Blood Gas Measurement - Venous Saturation at Baseline and Study Completion
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End point description:

The right heart catheter assessment was performed to assess Blood Gas Measurements in pulmonary hypertension, including Venous Saturation levels at baseline and Study completion Week 24. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type Secondary

End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: Percentage of saturation				
arithmetic mean (standard deviation)				
Baseline n=17,14	57.96 (± 10.48)	60.84 (± 6.61)		
Week 24 n=13,13	65.11 (± 6.91)	57 (± 9.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Gas Measurement - pH at Baseline and Study Completion

End point title Blood Gas Measurement - pH at Baseline and Study Completion

End point description:

The right heart catheter assessment was performed to assess Blood Gas Measurements in pulmonary hypertension, including pH levels at baseline and Study completion Week 24. The pH scale measures how acidic or basic a substance is. It ranges from 0 to 14. A pH of 7 is neutral. A pH less than 7 is acidic, and a pH greater than 7 is basic. The intention to treat population (ITT) included all patients who received at least one dose of study medication.

End point type Secondary

End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: pH scale				
arithmetic mean (standard deviation)				
Baseline n=24,23	7.43 (± 0.04)	7.44 (± 0.05)		
Week 24 n=17,17	7.44 (± 0.05)	7.46 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Gas Measurement - PaCO₂ at Baseline and Study Completion

End point title	Blood Gas Measurement - PaCO ₂ at Baseline and Study Completion
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End point description:

The right heart catheter assessment was performed to assess Blood Gas Measurements in pulmonary hypertension, including PaCO₂ levels at baseline and Study completion Week 24. The intention to treat population (ITT) included all patients who received at least one dose of study medication

End point type	Secondary
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End point timeframe:

Baseline, and Study completion (Week 24)

End point values	Core-STI571	Core-Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline n=23,21	32.7 (± 4.4)	30.02 (± 4.76)		
Week 24 n=16,17	33.36 (± 5.11)	30.23 (± 3.55)		

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Core - STI571
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Reporting group description:

STI571 (Imatinib) was supplied in 100 mg capsules and was to have been administered orally with daily dose starting at 200 mg rising to 400 mg within two weeks. Dose may have been downtitrated from 400 to 200 mg one time during the trial.

Reporting group title	Extension - STI571
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Reporting group description:

Open label.

Reporting group title	Core - Placebo
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Reporting group description:

The appearance of placebo medication was identical to that of active drug.

Serious adverse events	Core - STI571	Extension - STI571	Core - Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 28 (42.86%)	16 / 22 (72.73%)	11 / 31 (35.48%)
number of deaths (all causes)	3	4	3
number of deaths resulting from adverse events	0	0	1
Vascular disorders			
Arterial rupture			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Surgical and medical procedures			
Tonsillectomy			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Catheter related complication			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 28 (0.00%)	7 / 22 (31.82%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 28 (0.00%)	0 / 22 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea at rest			

subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary artery aneurysm			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	2 / 28 (7.14%)	1 / 22 (4.55%)	3 / 31 (9.68%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Subdural haematoma			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 22 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	2 / 28 (7.14%)	0 / 22 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 28 (0.00%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 28 (0.00%)	0 / 22 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Right ventricular failure			
subjects affected / exposed	1 / 28 (3.57%)	1 / 22 (4.55%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	2 / 28 (7.14%)	1 / 22 (4.55%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 28 (7.14%)	3 / 22 (13.64%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal haemorrhage			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal polyp			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung infection			
subjects affected / exposed	0 / 28 (0.00%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 22 (4.55%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Core - STI571	Extension - STI571	Core - Placebo
Total subjects affected by non-serious adverse events subjects affected / exposed	26 / 28 (92.86%)	21 / 22 (95.45%)	25 / 31 (80.65%)
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 28 (7.14%)	0 / 22 (0.00%)	3 / 31 (9.68%)
occurrences (all)	2	0	4
Haematoma			
subjects affected / exposed	1 / 28 (3.57%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Hypotension			
subjects affected / exposed	0 / 28 (0.00%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 22 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Chest pain			
subjects affected / exposed	1 / 28 (3.57%)	1 / 22 (4.55%)	3 / 31 (9.68%)
occurrences (all)	1	2	3
Chest discomfort			
subjects affected / exposed	2 / 28 (7.14%)	4 / 22 (18.18%)	3 / 31 (9.68%)
occurrences (all)	2	7	4
Exercise tolerance decreased			
subjects affected / exposed	1 / 28 (3.57%)	0 / 22 (0.00%)	2 / 31 (6.45%)
occurrences (all)	1	0	2
Fatigue			
subjects affected / exposed	3 / 28 (10.71%)	3 / 22 (13.64%)	4 / 31 (12.90%)
occurrences (all)	3	4	4
General physical health deterioration			

subjects affected / exposed	1 / 28 (3.57%)	3 / 22 (13.64%)	0 / 31 (0.00%)
occurrences (all)	1	3	0
Oedema			
subjects affected / exposed	1 / 28 (3.57%)	8 / 22 (36.36%)	0 / 31 (0.00%)
occurrences (all)	2	16	0
Oedema peripheral			
subjects affected / exposed	7 / 28 (25.00%)	9 / 22 (40.91%)	5 / 31 (16.13%)
occurrences (all)	13	14	7
Pyrexia			
subjects affected / exposed	2 / 28 (7.14%)	4 / 22 (18.18%)	0 / 31 (0.00%)
occurrences (all)	2	7	0
Pain			
subjects affected / exposed	0 / 28 (0.00%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 28 (7.14%)	7 / 22 (31.82%)	6 / 31 (19.35%)
occurrences (all)	2	9	6
Dyspnoea			
subjects affected / exposed	2 / 28 (7.14%)	3 / 22 (13.64%)	5 / 31 (16.13%)
occurrences (all)	2	6	6
Nasal congestion			
subjects affected / exposed	2 / 28 (7.14%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	2	2	0
Oropharyngeal pain			
subjects affected / exposed	0 / 28 (0.00%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Rhinitis allergic			
subjects affected / exposed	0 / 28 (0.00%)	3 / 22 (13.64%)	0 / 31 (0.00%)
occurrences (all)	0	3	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 28 (3.57%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Insomnia			

subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	4 / 22 (18.18%) 4	0 / 31 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	4 / 22 (18.18%) 4	0 / 31 (0.00%) 0
Investigations			
Blood amylase increased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	0 / 31 (0.00%) 0
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	3 / 22 (13.64%) 4	1 / 31 (3.23%) 1
Blood potassium decreased subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 4	6 / 22 (27.27%) 7	0 / 31 (0.00%) 0
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	3 / 22 (13.64%) 5	0 / 31 (0.00%) 0
Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	1 / 31 (3.23%) 1
Brain natriuretic peptide increased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	3 / 22 (13.64%) 5	0 / 31 (0.00%) 0
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	3 / 22 (13.64%) 4	1 / 31 (3.23%) 1
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	0 / 31 (0.00%) 0
Lipase increased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	0 / 31 (0.00%) 0
Platelet count decreased			

subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	1 / 22 (4.55%) 1	0 / 31 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	4 / 22 (18.18%) 4	0 / 31 (0.00%) 0
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 22 (0.00%) 0	2 / 31 (6.45%) 2
Cardiac disorders Cardiac failure subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	0 / 31 (0.00%) 0
Palpitations subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 9	4 / 22 (18.18%) 7	4 / 31 (12.90%) 5
Pericardial effusion subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	1 / 31 (3.23%) 1
Tachycardia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	0 / 31 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 4	5 / 22 (22.73%) 6	3 / 31 (9.68%) 3
Headache subjects affected / exposed occurrences (all)	10 / 28 (35.71%) 14	4 / 22 (18.18%) 4	6 / 31 (19.35%) 10
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	3 / 22 (13.64%) 6	0 / 31 (0.00%) 0
Ear and labyrinth disorders Tinnitus			

subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	3 / 22 (13.64%) 3	0 / 31 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 4	8 / 22 (36.36%) 12	4 / 31 (12.90%) 4
Eye disorders Eye swelling subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 4	1 / 22 (4.55%) 1	0 / 31 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 4	0 / 22 (0.00%) 0	0 / 31 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	2 / 22 (9.09%) 3	1 / 31 (3.23%) 1
Ascites subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	4 / 22 (18.18%) 4	1 / 31 (3.23%) 1
Constipation subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	2 / 22 (9.09%) 2	2 / 31 (6.45%) 2
Diarrhoea subjects affected / exposed occurrences (all)	6 / 28 (21.43%) 10	9 / 22 (40.91%) 12	3 / 31 (9.68%) 3
Dyspepsia subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3	4 / 22 (18.18%) 5	2 / 31 (6.45%) 3
Gastritis subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 3	0 / 31 (0.00%) 0
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 22 (0.00%) 0	3 / 31 (9.68%) 3
Vomiting			

subjects affected / exposed occurrences (all)	6 / 28 (21.43%) 10	3 / 22 (13.64%) 3	1 / 31 (3.23%) 1
Nausea subjects affected / exposed occurrences (all)	14 / 28 (50.00%) 17	8 / 22 (36.36%) 11	5 / 31 (16.13%) 5
Skin and subcutaneous tissue disorders			
Dry skin subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	0 / 31 (0.00%) 0
Alopecia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	0 / 31 (0.00%) 0
Periorbital oedema subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 4	0 / 22 (0.00%) 0	0 / 31 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 5	0 / 22 (0.00%) 0	3 / 31 (9.68%) 4
Rash subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3	3 / 22 (13.64%) 4	0 / 31 (0.00%) 0
Swelling face subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	2 / 22 (9.09%) 2	0 / 31 (0.00%) 0
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	4 / 22 (18.18%) 4	0 / 31 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 6	3 / 22 (13.64%) 6	0 / 31 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 4	3 / 22 (13.64%) 3	0 / 31 (0.00%) 0
Back pain			

subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 4	2 / 22 (9.09%) 3	4 / 31 (12.90%) 4
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	0 / 31 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3	1 / 22 (4.55%) 2	3 / 31 (9.68%) 3
Myalgia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	5 / 22 (22.73%) 6	1 / 31 (3.23%) 1
Infections and infestations			
Bacteriuria subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	0 / 31 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 5	1 / 31 (3.23%) 1
Cystitis subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	1 / 31 (3.23%) 1
Gastrointestinal infection subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	5 / 22 (22.73%) 10	1 / 31 (3.23%) 1
Helicobacter infection subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 22 (9.09%) 2	0 / 31 (0.00%) 0
Herpes simplex subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	0 / 22 (0.00%) 0	1 / 31 (3.23%) 1
Oral candidiasis subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	0 / 22 (0.00%) 0	0 / 31 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 28 (21.43%) 6	14 / 22 (63.64%) 30	8 / 31 (25.81%) 9

Sinusitis			
subjects affected / exposed	1 / 28 (3.57%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Respiratory tract infection			
subjects affected / exposed	6 / 28 (21.43%)	11 / 22 (50.00%)	1 / 31 (3.23%)
occurrences (all)	7	50	2
Urinary tract infection			
subjects affected / exposed	0 / 28 (0.00%)	7 / 22 (31.82%)	0 / 31 (0.00%)
occurrences (all)	0	9	0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 22 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	1 / 28 (3.57%)	4 / 22 (18.18%)	2 / 31 (6.45%)
occurrences (all)	1	5	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2006	Additional biomarker assessments for Brain Natriuretic Peptide (BNP) and specialist assessments (multiple inert gas elimination technique and blood gases) were to be conducted in at least one of the participating centers. The amendment also clarified and corrected inconsistencies in the protocol text and updated the names and contact details of responsible study personnel.
15 June 2006	Right Heart Catheterization procedure could have been performed within one month of the patient receiving the first dose rather than at the baseline visit. A Data Safety Monitoring Board was to be implemented to address the recommendations of the German national regulatory authority, BfArM which was requested during the protocol approval process. Patient diary cards were issued to patients for monitoring of weight. Additional criteria for patient withdrawal from study which included reduction/down-titration in dose was added. An interim analysis was planned of the first 30 patients that completed 3 months of treatment to provide an interim risk-benefit evaluation based on blinded data. No formal statistical testing will be applied.
19 September 2006	Documentation of the procedure for reporting Serious Adverse events at the Austrian site (Site 003) was added. This new site was set up after finalization of the study protocol.
15 February 2007	Following review of the IND submission the FDA requested that further information concerning the methodology used for genotyping of the exploratory biomarker samples and gene expression be included. Additional text has been added to sections 7.6.1 Genetic polymorphism and 7.6.2 Gene expression in peripheral blood cells.
01 October 2007	An interim analysis was added for patients who had completed at least 2 months treatment for a blinded analysis of the Six Minute Walk Test and hemodynamic parameter data. Exclusion Criteria was modified to exclude any pre-existing condition associated with chronic hypoxia that may have contributed to the severity of Pulmonary Arterial Hypertension.
12 March 2008	The study design was modified to include an extension period for follow up safety (two years) which formalized the compassionate use that had been available for patients. This was recommended by the Data Safety Monitoring Board to monitor the safety of long term use of imatinib. The results from the extension study were reported independently from the results of the core study.
19 May 2008	The completion of the clinical phase of the core study enabled un-blinding of all data. Due to the open-label design of the extension study, the ongoing safety review (previously performed in the core study by the independent Data Safety Monitoring Committee) was performed by Novartis until the final study results were available. This review of SAE reports was continued (to be reported as per the core study) to ensure oversight of safety in the extension study. However, if the core study was found to be positive then an external (to Novartis) expert, independent of the study, was to review SAE reports. Simplifications to the data collected in the CRF were made, with the remaining data only maintained as source documents. The Week 1 visit, as well as weeks 2 and 3 visits, became optional for those patients already receiving compassionate Glivec.

09 December 2008	The duration of this extension study was increased to 5 years or until STI571 was approved and marketed for this patient population. It emerged that thyroid disorders may result from the use of imatinib, therefore, monitoring of thyroid stimulating hormone was included at each visit. Right heart catheterization was removed. Since the safety profile of this drug in this population has been better established with completion of the core study, the visit frequency for safety monitoring was reduced to every 6 months.
03 April 2009	Amendment 12 was rejected by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK based on the study end being until STI571 was approved for treating pulmonary arterial hypertension and this not being an acceptable scientific endpoint. This was changed to a duration of 5 years..
23 June 2009	This protocol was amended following review by the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) to define the function of the data safety monitoring board. A Data Safety Monitoring Board (DSMB) was formed to review the data collected in the extension study. The DSMB reviewed serious adverse events every 3 months until the study was completed and reviewed all available safety data every six months in relation to the benefit of STI571 in pulmonary arterial hypertension. If any new safety concerns arose with prolonged dosing, a Novartis review board or the DSMB determined whether any changes were required to the protocol.
18 April 2013	Due to the submission of a marketing authorization for STI571, an interim CSR to the extension study was written to enable accurate reporting of data. This amendment detailed the interim access to data required for the CSR. Advice received from the Data Safety Monitoring Board suggested closer monitoring of patient's Echocardiograms. This included making the Echocardiogram assessments mandatory every 6 months. The protocol was changed to reflect this requirement.
06 May 2013	The protocol was amended to revise the information on concomitant use of imatinib and oral Vitamin K antagonists in PAH patients. This was 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. The risk of subdural hematoma was increased in patients taking imatinib and oral Vitamin K antagonists concomitantly. This amendment will increase this extension period from 5 to 6 years. This extension will provide drug to patients who continue to benefit until a new study is started into which the patients can be enrolled (CQT1571A2304).
26 June 2013	The protocol was amended to revise information on concomitant use of imatinib and oral vitamin K antagonists in PAH patients. The concomitant use of imatinib and oral vitamin K antagonists was no longer permitted in the study. This was based on health authority feedback which advised that patients must be discontinued if they were receiving concomitant oral vitamin K antagonist therapy. To comply with this request, Novartis amended the study protocol accordingly and added additional discontinuation criterion.
14 August 2013	The protocol was amended to revise information on further extension of the trial from 5 years to 6 years. This additional extension was not approved by the German health authority and was not applicable to German sites. This amendment detailed the areas of the protocol that were not applicable to Germany.

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.

Novartis withdrew marketing for QTI571 filed in US, Europe, Japan, and Switzerland in 2012 for the treatment of PAH following discussion with the FDA and CHMP. Core study was completed, Novartis terminated extension study in PAH on 20 Nov 2013.

Notes: