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Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

Imatinib

Trial Indication(s)

Pulmonary arterial hypertension

Protocol Number

CQTI571A2102

Protocol Title

A non-randomized, multiple dose, three treatment period, open-label, single sequence, single group study to evaluate the pharmacokinetic effect of two doses of QTI571 (imatinib) on the co-administered drugs sildenafil and bosentan in pulmonary arterial hypertension (PAH) patients

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

20-Apr-2011 to 25-Oct-2012

Reason for Termination

The study was terminated prior to achieving the recruitment target due to a change in the development program for QTI571 in PAH. Patients who completed the study and were eligible for the extension study were enrolled into the extension study.

Study Design/Methodology

This was a non-randomized, multiple dosing, three treatment periods, open-label, single sequence, single group study to evaluate the effect of two doses (200 mg and 400 mg) ofQTI571 on the pharmacokinetics of co-administered drugs sildenafil and bosentan in PAH patients.
The study consisted of an up to 43 days screening period, three treatment periods followed by a study completion evaluation which occurred at the end of treatment Period 3.
During Treatment Period 1, bosentan (125 mg b.i.d) and sildenafil (t.i.d) were administered for 8 days. This was followed by Treatment Period 2 where QTI571 (200 mg q.d), bosentan (125 mg b.i.d) and sildenafil (t.i.d) were administered concomitantly for 2 weeks, and Treatment Period 3 where QTI571 (400 mg q.d), bosentan (125 mg b.i.d) and sildenafil (t.i.d) were administered concomitantly for a further 2 weeks.
PK samples were collected prior to dosing on Day 1 of Treatment Period 1 and at multiple time points at the end of each Treatment Period for assessments of QTI571, bosentan and sildenafil and their active metabolites.

Centers

8 centers in 7 countries: Australia (1), Belgium (1), Germany (1), Italy (1), Lithuania (1), UK (1), and United States (2)

Objectives:

Primary objective

- To investigate the effect of two dose levels of QTI571 on the pharmacokinetics of the coadministered drugs sildenafil and bosentan at steady-state in patients with pulmonary arterial hypertension

Secondary objectives

- To evaluate the safety and tolerability of QTI571 and the co-administered drugs sildenafil and bosentan at pharmacokinetic steady state in patients with pulmonary arterial hypertension
- To evaluate the pharmacokinetics of QTI571 and its active metabolite at steady-state in patients with pulmonary arterial hypertension

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational drug imatinib were prepared by Novartis and supplied to the Investigator as 100 mg film-coated tablets as open label bulk supply.

Statistical Methods

Statistical evaluation of the effect of co-administration of QTI571 (at two doses (200 and 400 mg) on the pharmacokinetics of sidenafil and bosentan was performed on dose normalized AUCtau and Cmax of bosentan, sildenafil and their metabolites (hydroxy bosentan and N-desmethyl sildenafil) [Comparing (sildenafil+bosentan) vs (sildenafil+bosentan)+200 mg QTI571] and [(sildenafil+bosentan) vs (sildenafil+bosentan)+400 mg QTI571].
A mixed effects linear model was fitted to the log-transformed PK parameters. This model included treatment (i.e. dose of QTI571) as a fixed effect, and subject as a random effect (note that treatment and period are aliased and hence period effects were considered as ignorable for this analysis). Estimates for the treatment differences (test vs. reference) and associated 90% confidence intervals were obtained from the above model. These estimates and confidence intervals was then be backtransformed" to the original scale, giving, for each dose level of QTI571, the ratio of QTI571 + coadministered sildenafil and bosentan relative to the co-administered drugs alone (sildenafil +bosentan).
An interim analysis of the PK data were conducted in order to guide internal decision making processes and assist in activities related to submission of QTI571 for market authorization in the indication of PAH

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Participants with Pulmonary arterial hypertension (PAH) in World Health Organization (WHO) Diagnostic Group 1, with pulmonary vascular resistance > 800 dyne*sec*cm^-5,
- On stable doses of bosentan and sildenafil

Exclusion Criteria:

- Other diagnosis of PAH in World Health Organization (WHO) Diagnostic Group 1 such as congenital large or small unrepaired systemic to pulmonary shunts, portal hypertension, Human Immunodeficiency Virus (HIV) infection, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic teleangiectasia, hemoglobinopathies, myeloproliferative disorders, veno-occlusive pulmonary disease
- Significant lung diseases not related to PAH
- Significant cardiovascular system disorders, hematological system disorders, liver insufficiency
- Significant diseases in other organ system.

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Participant Flow Table

Subject disposition - n (%) of subjects (Safety analysis set)

	All subjects N=21 n (%)
Subjects	
Completed	17 (80.95)
Discontinued	4 (19.05)
Main cause of discontinuation	
Adverse Event(s)	2 (9.52)
Subject withdrew consent	1 (4.76)
Protocol deviation	1 (4.76)

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Baseline Charactristics

Demographic summary (Safety analysis set)

		All subjects N=21
Age (years)	Mean (SD)	54.4 (13.44)
	Median	52.0
	Range	25 – 73
Sex - n(%)	Male	6 (28.6%)
	Female	15 (71.4%)
Race - n(%)	Caucasian	20 (95.2%)
	Black	1 (4.8%)
Ethnicity - n(%)	Other	21 (100.0%)
Weight (kg)	Mean (SD)	78.17 (17.60)
	Median	76.00
	Range	50.2 - 120.4
Height (cm)	Mean (SD)	164.2 (9.76)
	Median	160.0
	Range	148 – 185
BMI (kg/m2)	Mean (SD)	28.96 (5.98)
	Median	27.50
	Range	20.9 - 47.0
PAH duration (years)	Mean (SD)	3.76 (3.27)
	Median	3.00
	Range	0.2 - 12.3
WHO classification - n(%)	Class II	6 (28.6%)
	Class III	15 (71.4%)

Primary Outcome Result(s)

Geometric mean ratio and 90% confidence intervals for dose normalized bosentan PK variables before and after QTI571 Administrations

Parameter (unit)	Treatment	N	Adjusted geometric means	Ratio (Test/ Reference)	90% CI for ratio
AUCtau (hr*ng/mL)	Test 1	17	109.29	1.17	(1.03, 1.33)
	Test 2	17	130.59	1.40	(1.23, 1.59)
	Ref	17	93.28		
Cmax (ng/mL)	Test 1	17	21.76	1.00	(0.82, 1.21)
	Test 2	17	23.43	1.07	(0.88, 1.31)
	Ref	17	21.86		

Reference: co-administered drugs (sildenafil + bosentan)

Test 1: co-administered drugs (sildenafil + bosentan) + QTI571 200 mg

Test 2: co-administered drugs (sildenafil + bosentan) + QTI571 400 mg

Log-transformed dose normalized PK parameters of AUCtau and Cmax was analyzed using a linear mixed effect model, with treatment as fixed effect and subject as random effect.

Geometric mean ratio and 90% confidence intervals for dose normalized hydroxyl bosentan PK variables before and after QTI571 administrations

Parameter (unit)	Treatment	N	Adjusted geometric means	Ratio (Test/ Reference)	90% CI for ratio
AUCtau (hr*ng/mL)	Test 1	17	23.28	1.07	(0.95, 1.20)
	Test 2	17	28.73	1.32	(1.17, 1.48)
	Ref	17	21.80		
Cmax (ng/mL)	Test 1	17	3.37	1.01	(0.86, 1.20)
	Test 2	17	4.22	1.27	(1.07, 1.50)
	Ref	17	3.33		

Reference: co-administered drugs (sildenafil + bosentan)

Test 1: co-administered drugs (sildenafil + bosentan) + QTI571 200 mg

Test 2: co-administered drugs (sildenafil + bosentan) + QTI571 400 mg

Log-transformed dose normalized PK parameters of AUCtau and Cmax was analyzed using a linear mixed effect model, with treatment as fixed effect and subject as random effect.

Secondary Outcome Result(s)

Refer to Safety Result section for secondary outcome result.

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Safety Results

Adverse events overall and by system organ class - n (%) of subjects

	bosentan + sildenafil N=21	QTI571 (200 mg q.d) + bosentan + sildenafil N=19	QTI571 (400 mg q.d) + bosentan + sildenafil N=18	All subjects N=21
Subjects with AE(s)	10 (47.6)	9 (47.4)	16 (88.9)	19 (90.5)
Preferred term				
Diarrhea	1 (4.8)	5 (26.3)	2 (11.1)	7 (33.3)
Nausea	1 (4.8)	4 (21.1)	2 (11.1)	7 (33.3)
Blood potassium decreased*	1 (4.8)	1 (5.3)	4 (22.2)	6 (28.6)
Edema peripheral	2 (9.5)	1 (5.3)	3 (16.7)	5 (23.8)
Vomiting	0 (0.0)	1 (5.3)	4 (22.2)	5 (23.8)
Anemia	1 (4.8)	1 (5.3)	3 (16.7)	4 (19.0)
Headache	1 (4.8)	2 (10.5)	1 (5.6)	4 (19.0)
Dizziness	3 (14.3)	0 (0.0)	0 (0.0)	3 (14.3)
Abdominal discomfort	0 (0.0)	1 (5.3)	1 (5.6)	2 (9.5)
Back pain	0 (0.0)	2 (10.5)	0 (0.0)	2 (9.5)
Cough	0 (0.0)	1 (5.3)	1 (5.6)	2 (9.5)
Decreased appetite	0 (0.0)	1 (5.3)	1 (5.6)	2 (9.5)
Dry mouth	0 (0.0)	1 (5.3)	1 (5.6)	2 (9.5)
Iron deficiency	1 (4.8)	0 (0.0)	1 (5.6)	2 (9.5)
Muscle spasms	0 (0.0)	0 (0.0)	2 (11.1)	2 (9.5)
Pain in extremity	1 (4.8)	2 (10.5)	1 (5.6)	2 (9.5)
Periorbital edema	0 (0.0)	1 (5.3)	1 (5.6)	2 (9.5)
Rash	0 (0.0)	0 (0.0)	2 (11.1)	2 (9.5)
Renal failure	1 (4.8)	0 (0.0)	1 (5.6)	2 (9.5)
Rhinitis	0 (0.0)	1 (5.3)	1 (5.6)	2 (9.5)
Urinary tract infection	0 (0.0)	0 (0.0)	2 (11.1)	2 (9.5)

*"blood potassium decreased' and 'hypokalemia' are considered as 'blood potassium decreased' in all summary tables of AE.

Arranged in descending order of frequency (in All Subjects group) and by preferred term.

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Adverse events overall and specific events in greater or equal 5% of all subjects - n (%) of subjects

	Bosentan + sildenafil N=21	QTI571 (200mg q.d) + bosentan + sildenafil N=19	QTI571 (400mg q.d) + bosentan + sildenafil N=18	All subjects N=21
Subjects with AE(s)	3 (14.3)	6 (31.6)	13 (72.2)	16 (76.2)
Preferred term				
Diarrhea	1 (4.8)	4 (21.1)	2(11.1)	7 (33.3)
Nausea	1 (4.8)	4 (21.1)	2 (11.1)	7 (33.3)
Vomiting	0 (0.0)	1 (5.3)	3 (16.7)	4 (19.0)
Headache	1 (4.8)	2 (10.5)	0 (0.0)	3 (14.3)
Abdominal discomfort	0 (0.0)	1 (5.3)	1(5.6)	2 (9.5)
Blood potassium decreased	0 (0.0)	1 (5.3)	1(5.6)	2 (9.5)
Decreased appetite	0 (0.0)	1 (5.3)	1 (5.6)	2 (9.5)
Dry mouth	0 (0.0)	1 (5.3)	1 (5.6)	2 (9.5)
Muscle spasms	0 (0.0)	0 (0.0)	2 (11.1)	2 (9.5)
Edema peripheral	0 (0.0)	0 (0.0)	2 (11.1)	2 (9.5)
Renal failure	1 (4.8)	0 (0.0)	1 (5.6)	2 (9.5)
Abdominal pain	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)
Anemia	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)
Ascites	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)
Blood creatinine increased	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)
Eyelid edema	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)
Fatigue	1 (4.8)	0 (0.0)	0 (0.0)	1 (4.8)
Head discomfort	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)
Myalgia	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)
Periorbital edema	0 (0.0)	1 (5.3)	0 (0.0)	1 (4.8)
Rash	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)
Rhinitis	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)

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Serious Adverse Events and Deaths

	Novartis product
No. (%) of subjects studied	21 (100)
No. (%) of subjects with AE(s)	19 (90.5)
Number (%) of subjects with serious or other significant events	n (%)
Death	0 (0.0)
SAE(s)	2 (9.5)
Discontinued due to SAE(s)	2 (9.5)

Conclusion:

• PK evaluation

Concomitant administration of bosentan and sildenafil with 400 mg QTI571 led to an increase in mean dose normalized bosentan exposure (AUCtau) without significant changes in the metabolite/bosentan AUC ratio. The observed effects of QT571 on the pharmacokinetics of sildenafil and bosentan are in line with expectations based on their respective in vitro metabolization profiles.

• Safety

The majority of the subjects (90.5%) had at least one AE during the study, most of which were mild to moderate in severity. More patients experienced AEs when receiving the higher dose of QTI571 (400mg).

All three study medications were found to be safe in this patient population. No new safety signals emerged from this study.

Date of Clinical Trial Report

19-Jul-2013