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Sponsor

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Generic Drug Name

Imatinib

Therapeutic Area of Trial

Pulmonary arterial hypertension

Approved Indication

- Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP), blast crisis (BC), accelerated phase (AP), and CP after failure of interferon-α (IFN).
- Relapsed or refractory Ph+ acute lymphoblastic leukemia (ALL)
- Hypereosinophilic syndrome (HES)
- Chronic eosinophilic leukemia (CEL)
- Myelodysplastic/myeloproliferative diseases (MDS/MPD)
- Aggressive systemic mastocytosis (ASM)
- KIT (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)
- Adjuvant treatment of adult patients following resection of KIT (CD117)-positive GIST
- Dermatofibrosarcoma protuberans (DFSP).

Protocol Number

CQTI571A2102

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

Study Phase

Phase I

Study Start/End Dates

20 Apr 2011 to 24 Dec 2012

The study was terminated prior to achieving the recruitment target due to a change in the development program for QTI571 in PAH. At the time of termination, all subjects had either completed or discontinued the study.

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Study Design/Methodology

Non-randomized, multiple dosing, three treatment periods, open-label, single sequence single group study to evaluate the effect of two doses of QTI571 on the pharmacokinetics of co-administered drugs sildenafil and bosentan in PAH patients.

Eligible patients entered three treatment periods: 1) 8 days treatment of bosentan 125 mg b.i.d and sildenafil t.i.d, 2) 14 days concomitant treatment of QTI571 200 mg q.d, bosentan 125 mg b.i.d and sildenafil t.i.d, 3) 14 days concomitant treatment of QTI571 400 mg q.d, bosentan 125 mg b.i.d and sildenafil t.i.d.

PK samples were collected prior to treatment 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), United Kingdom (1), United States (2)

Publication

N/A

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

Oral tablets of 200 mg or 400 mg QTI571 (imatinib) once each morning. Bosentan and sildenafil were sourced locally.

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 “back-transformed” to the original scale, giving, for each dose level of QTI571, the ratio of QTI571 + co-administered sildenafil and bosentan relative to the co-administered drugs alone (sildenafil + bosentan).

Adverse events were summarized by the number and percentage of subjects who had any adverse event (AE), who had an AE in each body system, and who had each individual AE.

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Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Pulmonary arterial hypertension (PAH) patients in 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 WHO Diagnostic Group 1 such as congenital large or small unrepaired systemic to pulmonary shunts, portal hypertension, 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.

Participant Flow

	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 Characteristics

		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%)

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Outcome Measures

Primary Outcome Results

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 sildenafil 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	9.82	1.36	(1.14, 1.62)
	Test 2	17	12.30	1.70	(1.43, 2.03)
	Ref	17	7.22		
Cmax (ng/mL)	Test 1	17	3.14	1.28	(1.03, 1.61)
	Test 2	17	3.81	1.56	(1.24, 1.95)
	Ref	17	2.44		

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.

N-Desmethyl Sildenafil not dose normalized.

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Safety Results

Adverse Events by System Organ Class

	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)
System organ class				
Gastrointestinal disorders	2 (9.5)	6 (31.6)	8 (44.4)	12 (57.1)
Nervous system disorders	3 (14.3)	3 (15.8)	3 (16.7)	9 (42.9)
Cardiac disorders	2 (9.5)	1 (5.3)	3 (16.7)	6 (28.6)
General disorders and administration site conditions	3 (14.3)	1 (5.3)	3 (16.7)	6 (28.6)
Infections and infestations	0 (0.0)	3 (15.8)	3 (16.7)	6 (28.6)
Investigations	1 (4.8)	2 (10.5)	4 (22.2)	6 (28.6)
Blood and lymphatic system disorders	2 (9.5)	1 (5.3)	3 (16.7)	5 (23.8)
Metabolism and nutrition disorders	2 (9.5)	1 (5.3)	2 (11.1)	5 (23.8)
Musculoskeletal and connective tissue disorders	1 (4.8)	3 (15.8)	3 (16.7)	5 (23.8)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (10.5)	3 (16.7)	5 (23.8)
Eye disorders	0 (0.0)	2 (10.5)	2 (11.1)	4 (19.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (5.3)	3 (16.7)	3 (14.3)
Psychiatric disorders	1 (4.8)	0 (0.0)	1 (5.6)	2 (9.5)
Renal and urinary disorders	1 (4.8)	0 (0.0)	1 (5.6)	2 (9.5)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)
Endocrine disorders	1 (4.8)	0 (0.0)	0 (0.0)	1 (4.8)
Injury, poisoning and procedural complications	1 (4.8)	0 (0.0)	0 (0.0)	1 (4.8)
Vascular disorders	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.8)

AEs are arranged in descending order of frequency (in All subject group) and by system organ class.

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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 (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.

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)

Other Relevant Findings

N/A

Date of Clinical Trial Report

14 Aug 2013

Date Inclusion on Novartis Clinical Trial Results Database

25 Sep, 2013

Date of Latest Update