NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

QBW276

Trial Indication(s)

Cystic Fibrosis

Protocol Number

CQBW276X2201

Protocol Title

A randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of inhaled QBW276 in patients with cystic fibrosis

Clinical Trial Phase

Phase 2

Phase of Drug Development

II

Study Start/End Dates

Study Start Date: September 2017 (Actual)
Primary Completion Date: April 2018 (Actual)
Study Completion Date: April 2018 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a randomized, 3-cohort study planned to be conducted in patients with cystic fibrosis.

Cohorts 1 and 2 were designed to be a randomized, double-blind, placebo-controlled, parallel arm multiple ascending dose study of the safety, tolerability, PK and preliminary efficacy of inhaled QBW276 over 1 week (Cohort 1) and 2 weeks (Cohort 2) in patients with CF regardless of their genotype. The primary objective for Cohorts 1 and 2 was to assess PK, safety and tolerability in CF

Centers

4 centers in 2 countries: Germany(2), United States(2)

Objectives:

Primary Objective: Cohorts 1 and 2

To assess the safety, tolerability and pharmacokinetics (PK) of multiple doses of inhaled QBW276 and its metabolites over 1 or 2 weeks of treatment in patients with cystic fibrosis (CF)

Primary Objective: Cohort 3

To evaluate the pharmacodynamic response to multiple doses of inhaled QBW276 in lung function (percent of predicted Forced Expiratory Volume in 1 second (FEV 1)) over 4 weeks of treatment compared with placebo in patients with CF that are homozygous for the F508del mutation.

Secondary Objective: Cohorts 1 and 2

To evaluate the pharmacodynamic response to multiple doses of inhaled QBW276 on change in lung function (percent of predicted FEV1 and (lung clearance index) (LCI)) in patients with CF To assess the safety, tolerability, PK and PD of multiple doses of inhaled QBW276 and its metabolites over 4 weeks of treatment in patients with CF who are homozygous for the F508del mutation.

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

The investigational drug QBW276 1.5 mg strength and matching placebo capsules were prepared by Novartis and supplied to the Investigator in blister packs. Novartis also supplied the Concept1 inhalation devices to the Investigator.

Statistical Methods

The primary variable was the occurrence of an adverse event for cohort 1 and cohort 2 and the PK parameters measurements. All information obtained on adverse events were listed by cohort, treatment and patient. For each cohort, adverse events were counted within each cohort/dose-level, by treatment received and corresponding percentages were tabulated. All other safety assessments including ECG, vital signs and laboratory data were listed by cohort, treatment, patient, and visit/time and if ranges wereavailable abnormalities (and relevant orthostatic changes) were flagged. Summary statistics were provided by treatment and visit/time.

Drug concentrations were listed by treatment, patient and visit/sampling time point. Descriptive summary statistics were provided by treatment and visit/sampling time point. Summary statistics included mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below the lower limit of quantification (LLOQ) were treated as zero in summary statistics. A geometric mean were not required to be reported if the dataset included zero values.

Pharmacokinetic parameters in Cohorts 1 and 2 were calculated and were listed by treatment and patient. Descriptive summary statistics included mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this was Tmax where median, minimum and maximum were presented. Individual concentration-time profiles and mean profiles with SD bars were presented for Day 1 and Day 7 or 14 in Cohorts 1 and 2

Absolute and change from baseline for all spirometry and LCI parameters were listed by cohort, treatment, patient and visit/time and summarized by treatment group and dose level graphically and in tables. Exploratory analysis of changes in these endpoints was performed, such as stratification of LCI results based on baseline FEV_1 > 80% of predicted and responder analyses.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Cohorts 1 and 2 = any genotype on any standard of care treatment
- Cohort 3 = F508del homozygotes on standard of care at that time
- FEV□between 40 and 100%
- LCI2.5 ≥ 8 if FEV□is more than 80%

Exclusion Criteria:
- Adrenal or electrolyte abnormalities
- Lung transplant
- Autonomic dysfunction (e.g. recurrent episodes of fainting, palpitations, etc.)

Participant Flow Table

Overall Study

	Cohort 1 QBW276	Cohort 2 QBW276	Placebo	Total
Arm/Group Description	QBW276 3mg bid	QBW276 6mg bid	Placebo to QBW276 dose 3mg bid Cohort 1, and Placebo to QBW276 dose 6mg bid Cohort 2.	
Started	6	6	4	16
Completed	6	6	4	16
Not Completed	0	0	0	0

Baseline Characteristics

	Cohort 1 QBW276	Cohort 2 QBW276	Placebo	Total
Arm/Group Description	QBW276 3mg bid	QBW276 6mg bid	Placebo to QBW276 dose 3mg bid Cohort 1, and Placebo to QBW276 dose 6mg bid Cohort 2.	
Number of Participants [units: participants]	6	6	4	16
Age Continuous (units: Years) Mean ± Standard Deviation				
	36.5±7.66	34.8±8.06	28.8±11.53	33.9±8.83

Sex: Female, Male (units:) Count of Participants (Not Applicable)				
Female	0	3	0	3
Male	6	3	4	13
Race (NIH/OMB) (units:) Count of Participants (Not Applicable)				
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	0	0	0
White	6	6	4	16
More than one race	0	0	0	0
Unknown or Not Reported	0	0	0	0

Summary of Efficacy

Primary Outcome Result(s)

Cohorts 1 and 2: Safety Assessments, incidence of Treatment-Emergent Adverse Events [Safety and Tolerability]).

(Time Frame: Cohort 1: day 1-7; Cohort 2: day 1-14)

	Cohort 1 QBW276	**Cohort 2 QBW276**	**Placebo**

Arm/Group Description	QBW276 3mg bid	QBW276 6mg bid	Placebo to QBW276 dose 3mg bid Cohort 1, and Placebo to QBW276 dose 6mg bid Cohort 2.
Number of Participants Analyzed [units: participants]	6	6	4
Cohorts 1 and 2: Safety Assessments, incidence of Treatment-Emergent Adverse Events [Safety and Tolerability]). (units: Participants)			
Death	0	0	0
Serious AE	0	0	0
Subjects with at least one AE	2	6	0

Cohorts 1 and 2: Pharmacokinetics (Cmax) of QBW276, QBP545, and QBV697 in plasma

(Time Frame: Cohort 1: day 1, 7; Cohort 2: day 1, 14)

	Cohort 1 QBW276	Cohort 1 QBP545	Cohort 1 QBV697	Cohort 2 QBW276	Cohort 2 QBP545	Cohort 2 QBV697
Arm/Group Description	QBW276 3mg bid	formation of metabolites QBP545	formation of metabolites QBV697	QBW276 6mg bid	formation of metabolites QBP545	formation of metabolites QBV697
Number of Participants Analyzed [units: participants]	6	6	6	6	6	6
Cohorts 1 and 2: Pharmacokinetics (Cmax) of QBW276, QBP545, and QBV697 in plasma (units: ng/mL) Mean ± Standard Deviation						

Day 1	0.159 ± NA[1]	3.88 ± 1.38	1.21 ± 0.415	0.174 ± 0.0716	5.98 ± 3.72	1.63 ± 0.931
Day 7	0.145 ± 0.114	5.46 ± 1.26	1.45 ± 0.504			
Day 14				0.267 ± 0.109	7.80 ± 4.34	3.07 ± 1.72

[1] Not applicable

Cohorts 1 and 2: Pharmacokinetics (Tmax) of QBW276, QBP545, and QBV697 in plasma

(Time Frame: Day 1, 7 and 14)

	Cohort 1 QBW276	Cohort 1 QBP545	Cohort 1 QBV697	Cohort 2 QBW276	Cohort 2 QBP545	Cohort 2 QBV697
Arm/Group Description	QBW276 3mg bid	formation of metabolites QBP545	formation of metabolites QBV697	QBW276 6mg bid	formation of metabolites QBP545	formation of metabolites QBV697
Number of Participants Analyzed [units: participants]	6	6	6	6	6	6
Cohorts 1 and 2: Pharmacokinetics (Tmax) of QBW276, QBP545, and QBV697 in plasma (units: hr) Median (Full Range)						
Day 1	0.183 (0.167 to 0.200)	0.375 (0.233 to 0.933)	0.433 (0.233 to 0.500)	0.250 (0.167 to 0.250)	0.250 (0.167 to 2.03)	0.250 (0.167 to 1.03)
Day 7	0.183 (0.167 to 0.183)	0.500 (0.250 to 0.967)	0.375 (0.167 to 2.0)			
Day 14				0.258 (0.233 to 0.533)	0.500 (0.267 to 0.533)	0.500 (0.233 to 0.533)

Cohorts 1 and 2: Pharmacokinetics (AUCtau) of QBW276, QBP545, and QBV697 in plasma

(Time Frame: Day 1, 7 and 14)

	Cohort 1 QBW276	Cohort 1 QBP545	Cohort 1 QBV697	Cohort 2 QBW276	Cohort 2 QBP545	Cohort 2 QBV697

Arm/Group Description	QBW276 3mg bid	formation of metabolites QBP545	formation of metabolites QBV697	QBW276 6mg bid	formation of metabolites QBP545	formation of metabolites QBV697
Number of Participants Analyzed [units: participants]	6	6	6	6	6	6
Cohorts 1 and 2: Pharmacokinetics (AUCtau) of QBW276, QBP545, and QBV697 in plasma (units: hr*ng/mL) Mean ± Standard Deviation						
Day 1	0.0332 ± NA[1]	14.3 ± 4.09	1.35 ± 0.827	0.0634 ± 0.0473	13.9 ± 6.57	1.79 ± 1.54
Day 7	0.0278 ± 0.0362	18 ± 4.21	1.80 ± 0.797			
Day 14				0.0918 ± 0.0689	30.6 ± 6.59	2.94 ± 1.59

[1] NA- Not achievable

Cohorts 1 and 2: Pharmacokinetics accumulation ratio (Racc) of QBW276, QBP545, and QBV697 in plasma

(Time Frame: Cohort 1: 7 days; Cohort 2: 14 days)

	Cohort 1 QBW276	Cohort 1 QBP545	Cohort 1 QBV697	Cohort 2 QBW276	Cohort 2 QBP545	Cohort 2 QBV697
Arm/Group Description	QBW276 3mg bid	formation of metabolites QBP545	formation of metabolites QBV697	QBW276 6mg bid	formation of metabolites QBP545	formation of metabolites QBV697
Number of Participants Analyzed [units: participants]	6	6	6	6	6	6
Cohorts 1 and 2: Pharmacokinetics accumulation ratio (Racc) of QBW276, QBP545, and QBV697 in plasma (units: Ratio) Mean ± Standard Error						

1.20 ± 0.047	1.28 ± 0.122	1.84 ± 0.384	1.59 ± 0.126	1.01 ± 0.714	1.74 ± 0.765

Secondary Outcome Result(s)

Cohorts 1 and 2: Change from baseline in percent predicted forced expiratory volume in the first second by spirometry (% predicted FEV1)

(Time Frame: Baseline to End of study (EOS))

	Cohort 1 QBW276	Cohort 2 QBW276	Placebo
Arm/Group Description	QBW276 3mg bid	QBW276 6mg bid	Placebo to QBW276 dose 3mg bid Cohort 1, and Placebo to QBW276 dose 6mg bid Cohort 2.
Number of Participants Analyzed [units: participants]	6	6	4
Cohorts 1 and 2: Change from baseline in percent predicted forced expiratory volume in the first second by spirometry (% predicted FEV1) (units: Percent predicted FEV1) Mean ± Standard Deviation			
	-0.1 ± 2.30	-0.1 ± 1.32	-2.7 ± 3.71

Cohorts 1, 2: Change from baseline in Lung Clearance Index (LCI) from baseline to Day 7 for Cohort 1, Day 14 for Cohort 2.

(Time Frame: Baseline to EOS)

	Cohort 1 QBW276	Cohort 2 QBW276	Placebo
Arm/Group Description	QBW276 3mg bid	QBW276 6mg bid	Placebo to QBW276 dose 3mg bid Cohort 1, and Placebo to QBW276 dose 6mg bid Cohort 2.
Number of Participants Analyzed [units: participants]	6	6	4
Cohorts 1, 2: Change from baseline in Lung Clearance Index (LCI) from baseline to Day 7 for Cohort 1, Day 14 for Cohort 2. (units: Ratio) Mean ± Standard Deviation			
	1.530 ± 2.0167	2.478 ± 3.1397	0.470 ± 0.4101

Summary of Safety

Safety Results

All-Cause Mortality

	Cohort 1 QBW276 N = 6	Cohort 2 QBW276 N = 6	Placebo N = 4
Arm/Group Description	QBW276 3 mg bid	QBW276 6 mg bid	Placebo to QBW276 dose 3mg bid Cohort 1, and Placebo to QBW276 dose 6mg bid Cohort 2.
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Other Adverse Events by System Organ Class

Time Frame	Up to 18 days
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 2%

	Cohort 1 QBW276 N = 6	Cohort 2 QBW276 N = 6	Placebo N = 4
Arm/Group Description	QBW276 3 mg bid	QBW276 6 mg bid	Placebo to QBW276 dose 3mg bid Cohort 1, and Placebo to QBW276 dose 6mg bid Cohort 2.
Total participants affected	2 (33.33%)	6 (100.00%)	0 (0.00%)
Ear and labyrinth disorders			
Vertigo	0 (0.00%)	1 (16.67%)	0 (0.00%)
Gastrointestinal disorders			
Abdominal distension	0 (0.00%)	1 (16.67%)	0 (0.00%)
Abdominal pain upper	0 (0.00%)	1 (16.67%)	0 (0.00%)
General disorders and administration site conditions			
Feeling cold	0 (0.00%)	1 (16.67%)	0 (0.00%)
Mucosal dryness	0 (0.00%)	1 (16.67%)	0 (0.00%)
Pyrexia	0 (0.00%)	1 (16.67%)	0 (0.00%)
Immune system disorders			
Seasonal allergy	0 (0.00%)	1 (16.67%)	0 (0.00%)

Investigations			
Alanine aminotransferase increased	0 (0.00%)	1 (16.67%)	0 (0.00%)
Aspartate aminotransferase increased	0 (0.00%)	1 (16.67%)	0 (0.00%)
Blood creatine phosphokinase increased	0 (0.00%)	1 (16.67%)	0 (0.00%)
Blood uric acid increased	0 (0.00%)	1 (16.67%)	0 (0.00%)
Metabolism and nutrition disorders			
Hypoglycaemia	0 (0.00%)	1 (16.67%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			
Joint swelling	0 (0.00%)	1 (16.67%)	0 (0.00%)
Musculoskeletal chest pain	0 (0.00%)	1 (16.67%)	0 (0.00%)
Nervous system disorders			
Headache	0 (0.00%)	3 (50.00%)	0 (0.00%)
Renal and urinary disorders			
Haematuria	1 (16.67%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Cough	0 (0.00%)	4 (66.67%)	0 (0.00%)

Dyspnoea	1 (16.67%)	2 (33.33%)	0 (0.00%)
Haemoptysis	0 (0.00%)	1 (16.67%)	0 (0.00%)
Oropharyngeal pain	0 (0.00%)	1 (16.67%)	0 (0.00%)
Pulmonary congestion	0 (0.00%)	1 (16.67%)	0 (0.00%)
Sinus congestion	0 (0.00%)	1 (16.67%)	0 (0.00%)
Sputum increased	0 (0.00%)	1 (16.67%)	0 (0.00%)
Wheezing	0 (0.00%)	1 (16.67%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Hyperhidrosis	0 (0.00%)	1 (16.67%)	0 (0.00%)
Rash papular	0 (0.00%)	1 (16.67%)	0 (0.00%)

Other Relevant Findings

Conclusion:

Low QBW276 concentrations were measured in plasma samples with most samples showing BLOQ values. As expected, QBW276 showed rapid elimination from systemic circulation and its half-life could not be estimated. Half-lives of metabolites QBP545 and QBV697 ranged from 1.1 to 2.4 h. Median Tmax of QBW276 ranged from 0.18-0.26 h, indicating rapid absorption into systemic circulation after inhalation dosing. Due to short half-lives observed for QBW276 and its metabolites, their Cmax and AUCtau exposures likely reached steady state by Day 7 after 3 mg or 6 mg twice daily oral inhalation dosing. The Cmax and AUClast values of QBW276 and metabolites after 6 mg BID oral inhalation dose on Day 14 were ~1.4 to 3.7-fold higher than resulting from 3 mg BID dose on Day 7. Based on Day 14 AUC and Cmax values, exposure of QBW276 and its metabolites after 6 mg BID oral inhalation dose in CF patients appear approximately 0.3 to 0.6-fold of steady state exposures in healthy volunteers (study CQBW276X2101).

Change in lung function (% predicted FEV_1 (assessed by spirometry) $LCI_{2.5}$ (assessed by MBNW) if FEV_1 at screening is > 80% of predicted) in the patients treated with multiple doses of inhaled QBW276 in Cohort 1 and Cohort 2 did not reveal any specific trends with respect to changes in mean levels from baseline to the end of study. However, as Cohorts 1 and 2 were safety/PK cohorts primarily, and therefore any observations pertaining to PD parameters in these cohorts are limited and potentially uninformative.

The overall incidence of AEs was higher in QBW276 6 mg bid dose group (100%) than in QBW276 3 mg bid dose group (33.3%), however the majority of AEs were mild and no AE led to discontinuation of study drug treatment. The only moderate AEs were abnormalities in liver function tests reported in one patient from QBW276 6 mg bid dose group on Study Day 15, with an increase in ALT (~1.5 fold ULN), AST (~1.5 fold ULN) and CPK (~15 fold ULN). The ALT and AST abnormalities resolved by Day 20 and the blood creatine phospokinase increased was ongoing at EOS/Day20, however went back to normal range (92 U/L) at unscheduled visit (Day30).

The individual patient profiles revealed a reversible and clinically insignificant increase in plasma aldosterone in patients dosed with 3 mg bid multiple dose and 6 mg bid multiple dose, when compared with those who received placebo. The elevation was however not associated with a decrease in potassium, and was not considered clinically significant by the investigator and was not reported as an AE.

No specific trend was observed in the levels of urine sodium/potassium ratio in patients dosed with QBW276 3 mg bid and QBW276 6 mg bid versus patients who received placebo during the study

Date of Clinical Trial Report

25-Feb-2019