D. Full Novartis CTRD Results Template

Sponsor Novartis
Generic Drug Name QAX028A
Therapeutic Area of Trial Respiratory, COPD
Approved Indication Investigational
Protocol Number CQAX028A2201
Title A randomized, double-blind, double-dummy, three period incomplete cross-over study to evaluate the safety and efficacy of multiple daily doses of QAX028 as compared to tiotropium bromide (positive control) and placebo in COPD patients
Phase of Development Phase 2
Study Start/End Dates First patient enrolled: 20-Jan-2010 Last patient completed: 09-Aug-2010
Study Design/Methodology Randomized, double-blind, double-dummy, three period incomplete cross-over study
Centres 4 centers in 1 countries: United States (4)

Publication

None

Outcome measures

Primary outcome measure

Measure: Compare the efficacy of QAX028 at a high dose, as measured by trough forced expiratory volume in 1 second (FEV1), to tiotropium [Time Frame: 7 days treatment]

Secondary outcome measure

Measure: Compare the efficacy of QAX028 at a low dose, as measured by trough FEV1, to tiotropium [Time Frame: 7 days treatment]

Measure: Compare the efficacy of QAX028 at two dose levels, as measured by trough FEV1, to placebo [Time Frame: 7 days treatment]

Measure: Evaluate the safety and tolerability of two dose levels of QAX028 in COPD patients [Time Frame: 7 days treatment]

Measure: Evaluate the pharmacokinetics of multiple inhaled does of QAX028 [Time Frame: 7 days treatment]

Measure: Assess bronchodilatory profile, as measured by FEV1, of multiple inhaled doses of QAX028 in COPD patients [Time Frame: 7 days treatment]

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

Test product: QAX028

Doses: 20 mcg, 60 mcg

Mode of Administration: Inhalation

Statistical Methods

FEV1 was analyzed using an analysis-of-covariance (ANCOVA) model including period and treatment as factors, the period baseline value as a covariate, and subject as a random effect. Least-squares mean differences were derived from this model and reported with 80% and 90% confidence intervals (CI). The efficacy objectives of the study were addressed by estimating the least square mean difference between FEV1 QAX028 at high dose vs. tiotropium (primary objective), between QAX028 low dose vs. tiotropium and between the two doses of QAX028 (secondary objectives). All comparisons were understood as placebo-corrected.

A repeated-measures ANCOVA analysis of FEV1 measurements following the last dose of treatment in each period was conducted. The model included period, treatment and time as factors, the period by time and treatment by time interaction terms, period baseline value as a covariate, and subject and subject by period as random effects. The default covariance structure included random subject and period by subject effects. Different covariance structures were investigated and the best fitting model (in terms of e.g. AIC and BIC) was used to estimate effects. Least-squares mean differences at each time points were estimated with 80% and 90% CI. The averaged effect over 24 hours (0–23h45 post-dosing) was also derived from this model.

The primary endpoint was also analyzed for internal decision-making using a Bayesian hierarchical model in order to quantify the probability that the primary endpoint and the a secondary endpoint of interest (i.e. the treatment difference between QAX028 high dose vs.

tiotropium and QAX028 low vs. tiotropium) in trough FEV1 on Day 7 was positive and was above 40 mL, which was assumed here to be a minimum significant improvement over tiotropium. The Bayesian modeling approach allowed derivation of the full distribution of the treatment effect (placebo-adjusted difference in trough FEV1) and therefore quantification of associated probabilities (e.g. chance that the treatment effect is above 40 mL).

The model included period and treatment as factors, the period pre-dose FEV1 as a covariate, and a subject-specific random effect. An informative prior on the treatment difference between tiotropium and placebo had been derived by using internal Novartis tiotropium data and meta-analysis methods.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Diagnosis of COPD according to GOLD guidelines
- Post-bronchodilator FEV1 that is 30%≤FEV1<80% of predicted normal and post-bronchodilator FEV1/FVC <0.7
- Smoking history of at least 10 pack years

Exclusion Criteria:

- Requiring oxygen therapy on a daily basis
- Exacerbation of airway disease in the 6 weeks prior to screening or between screening and dosing
- Lung reduction surgery
- Respiratory tract infection in the 6 weeks prior to screening
- Significant cardiac history
- History of asthma with onset of symptoms prior to age 40 years
- Active use of certain COPD medications, beta blockers

Participant Flow

	Total N=62
Subjects	
Completed	59 (95.2%)
Discontinued	3 (4.8%)
Main cause of discontinuation	
Adverse event	1 (1.6%)
Protocol deviations	2 (3.2%)

Baseline Characteristics

		Total N=62
Age (years)	Mean (SD)	59.4 (7.64)
	Median	59.0
	Range	(40, 73)
Gender – n (%)	Male	26 (41.9 %)
	Female	36 (58.1 %)
Race – n (%)	Caucasian	55 (88.7 %)
	Black	4 (6.5 %)
	Native American	3 (4.8 %)
Ethnicity – n (%)	Mixed ethnicity	1 (1.6 %)
	Other	61 (98.4 %)
Weight (kg)	Mean (SD)	82.230 (24.2049)
	Median	77.400
	Range	(44.90, 149.70)
Height (cm)	Mean (SD)	167.87 (10.051)
	Median	167.25
	Range	(147.0, 193.0)
BMI (kg/m^2)	Mean (SD)	28.926 (7.0639)
	Median	27.276
	Range	(18.88, 50.02)
Pack years	Mean (SD)	52.5 (24.60)
	Median	44.5
	Range	(16, 120)
Baseline FEV_1 (L)	Mean (SD)	1.346 (0.5066)
	Median	1.284
	Range	(0.50, 2.58)

Outcome measures

Primary Outcome Result

Measure: Compare the efficacy of QAX028 at a high dose, as measured by trough FEV1, to tiotropium [Time Frame: 7 days treatment]

Treatment		FEV_1 (L)
QAX028 60 mcg	Mean (SD)	1.476 (0.5183)

	Median	1.478
	Range	(0.58, 2.99)
Tiotropium	Mean (SD)	1.475 (0.5269)
	Median	1.495
	Range	(0.69, 3.10)

Secondary Outcome Result(s)

Measure: Compare the efficacy of QAX028 at a low dose, as measured by trough FEV1, to tiotropium [Time Frame: 7 days treatment]

Treatment		**FEV_1 (L)**
QAX028 20 mcg	Mean (SD)	1.394 (0.4940)
	Median	1.375
	Range	(0.50, 2.48)
Tiotropium	Mean (SD)	1.475 (0.5269)
	Median	1.495
	Range	(0.69, 3.10)

Measure: Compare the efficacy of QAX028 at two dose levels, as measured by trough FEV1, to placebo [Time Frame: 7 days treatment]

Treatment		**FEV_1 (L)**
QAX028 60 mcg	Mean (SD)	1.476 (0.5183)
	Median	1.478
	Range	(0.58, 2.99)
QAX028 20 mcg	Mean (SD)	1.394 (0.4940)
	Median	1.375
	Range	(0.50, 2.48)
Placebo	Mean (SD)	1.377 (0.4826)
	Median	1.360
	Range	(0.59, 2.42)

Measure: Evaluate the pharmacokinetics of multiple inhaled does of QAX028 [Time Frame: 7 days treatment]

		AUC0-24h (hr*pg/mL)	**Cmax (pg/mL)**	**Tmax (hr)**
QAX028 20 mcg	n	12	12	12
	Mean (SD)	71.5 (69.5)	21.0 (7.90)	-
	Geo-mean (CV%)	43.0 (155)	19.7 (39.2)	-
	Median	30.0	19.6	0.40
	Range	[8.08; 215]	[10.6; 37.0]	[0.15; 1.52]
QAX028 60 mcg	n	16	17	17
	Mean (SD)	170 (127)	58.3 (19.7)	-
	Geo-mean (CV%)	135 (80.1)	55.2 (35.2)	-
	Median	131	58.5	0.27
	Range	[43.8; 504]	[31.0; 103]	[0.17; 1.00]

Measure: Assess bronchodilatory profile, as measured by FEV1, of multiple inhaled doses of QAX028 in COPD patients [Time Frame: 7 days treatment]

Treatment		AUC FEV_1 (L)
QAX028 20 mcg	Mean	1.477
QAX028 60 mcg	Mean	1.441

Measure: Evaluate the safety and tolerability of two dose levels of QAX028 in COPD patients [Time Frame: 7 days treatment]

Safety Results

Adverse Events by System Organ Class

	QAX028 20 mcg N=42 n (%)	QAX028 60 mcg N=60 n (%)	Placebo N=40 n (%)	Tiotropium N=42 n (%)	Total N=62 n (%)
Subjects with AEs	7 (16.7)	17 (28.3)	9 (22.5)	5 (11.9)	31 (50.0)
System organ class					
Respiratory, thoracic and mediastinal disorders	3 (7.1)	7 (11.7)	3 (7.5)	2 (4.8)	14 (22.6)
Infections and infestations	3 (7.1)	8 (13.3)	1 (2.5)	1 (2.4)	13 (21.0)
Gastrointestinal disorders	3 (7.1)	1 (1.7)	3 (7.5)	0 (0.0)	6 (9.7)
Injury, poisoning and procedural complications	0 (0.0)	1 (1.7)	1 (2.5)	1 (2.4)	3 (4.8)
Investigations	0 (0.0)	2 (3.3)	1 (2.5)	0 (0.0)	3 (4.8)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (1.7)	1 (2.5)	0 (0.0)	2 (3.2)
Nervous system disorders	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	2 (3.2)
Vascular disorders	0 (0.0)	1 (1.7)	0 (0.0)	1 (2.4)	2 (3.2)
Eye disorders	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
General disorders and administration site conditions	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (1.6)
Renal and urinary disorders	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.6)

Reported AEs Overall by Preferred Term n (%)

	QAX028 20 mcg N=42 n (%)	QAX028 60 mcg N=60 n (%)	Placebo N=40 n (%)	Tiotropium N=42 n (%)	Total N=62 n (%)
Subjects with AE(s)	7 (16.7)	17 (28.3)	9 (22.5)	5 (11.9)	31 (50.0)
Preferred term					
Acute sinusitis	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Ankle fracture	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (1.6)
Arthropod bite	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Aspartate aminotransferase increased	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Blood glucose increased	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Bronchitis	2 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.2)
Chest discomfort	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Chronic obstructive pulmonary disease	0 (0.0)	1 (1.7)	0 (0.0)	1 (2.4)	2 (3.2)
Cough	0 (0.0)	1 (1.7)	1 (2.5)	0 (0.0)	2 (3.2)
Diarrhea	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Dyspnea	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Excoriation	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (1.6)
Gastroenteritis	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	2 (3.2)
Hematuria	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Headache	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	2 (3.2)
Hypercalcemia	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (1.6)
Hyperkeratosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.6)
Hypertension	0 (0.0)	1 (1.7)	0 (0.0)	1 (2.4)	2 (3.2)
Lipase increased	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (1.6)
Muscle strain	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.6)
Musculoskeletal pain	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (1.6)
Myalgia	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Nasal congestion	1 (2.4)	1 (1.7)	0 (0.0)	0 (0.0)	2 (3.2)
Nausea	2 (4.8)	0 (0.0)	1 (2.5)	0 (0.0)	2 (3.2)
Esophagitis	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (1.6)
Oropharyngeal pain	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	2 (3.2)
Paranasal sinus hypersecretion	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Periodontitis	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Photophobia	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Pleuritic pain	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (1.6)
Postnasal drip	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Productive cough	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Rhinitis	0 (0.0)	3 (5.0)	1 (2.5)	0 (0.0)	4 (6.5)
Sinus congestion	0 (0.0)	0 (0.0)	1 (2.5)	2 (4.8)	2 (3.2)
Sinusitis	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	2 (3.2)
Skin laceration	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (1.6)
Upper respiratory tract infection	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.6)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (1.6)
Vasomotor rhinitis	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Vomiting	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (1.6)

Wound infection	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

Serious Adverse Events and Deaths

	Total N=62
Subjects	
Completed	59 (95.2%)
Discontinued	3 (4.8%)
Number (%) of subjects with serious or other significant events	
Discontinued due to SAE(s)	0 (0.0%)
SAE's	0 (0.0%)
Death	0 (0.0%)

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

Report date(s): 15-Sep-2011 (content final)

Date Inclusion on Novartis Clinical Trial Results Database

30 March 2012

Date of Latest Update

30 March 2012