Sponsor

Novartis

Generic Drug Name

N/A

Therapeutic Area of Trial

Respiratory

Approved Indication

"Investigational"

Study Number

CQAT370A2103

Title

A randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of an efficacious dose of QAT370 compared to open-label tiotropium bromide following once daily dosing for 7 days in COPD patients

Phase of Development

Phase I

Study Start/End Dates

27 Jul 2007 to 17 Jan 2008

Study Design/Methodology

The study was a multi-centre, randomized, double-blind, placebo-controlled, three-way crossover

study to assess the safety and tolerability of an efficacious dose of QAT370 or matched placebo compared to open-label tiotropium bromide in mild-to-moderate COPD patients.
The study consisted of a randomized 3 way crossover design with QAT370, QAT370 matched-placebo and tiotropium administered across three treatment periods within each of 6 treatment sequences. In each treatment period, the study medication was administered once daily for 7 days. There was a minimum of 7 days and maximum of 21 days washout period between the last dose of each treatment period and the first dose of the subsequent treatment period.
The dose of the investigational drug (QAT370) was 400 µg or matching placebo. The dose of tiotropium was 18 µg (the recommended single daily dose).

Centers

3 centers in Germany

Publication

None

Objectives

Primary objective(s)

- To assess the safety and tolerability of an efficacious dose of QAT370 following once daily dosing for 7 days in COPD patients.

Secondary objective(s)

- To assess the pharmacodynamics (maximal and trough FEV1) of an efficacious dose of QAT370 with respect to matched placebo and tiotropium following once daily dosing for 7 days in COPD patients.
- To assess the pharmacokinetics of an efficacious dose of QAT370 following once daily dosing for 7 days in COPD patients.

Exploratory objectives

- To assess the effect of an efficacious dose of QAT370 following once daily dosing for 7 days in COPD patients on exercise tolerance (exercise endurance time on sub-maximal constant-load cycle ergometry).
- To assess the effect of an efficacious dose of QAT370 following once daily dosing for 7 days in COPD patients on resting and exertional IC (dynamic hyperinflation).
- To assess the effect of an efficacious dose of QAT370 following once daily dosing for 7 days in COPD patients on resting and exertional dyspnoea (at isotime and peak) (Borg)

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

QAT370 400µg inhalation capsules (or matching placebo) administered once daily for 7 days in each treatment period.
The dose of QAT370 400µg was achieved by inhalation of a single 400µg capsule of QAT370.
The placebo treatment consisted of inhalation of the corresponding number of matching placebo capsules.
QAT370 and matched placebo was administered by oral inhalation using the Aerolizer™ device.

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

Tiotropium 18 µg (the recommended single daily dose).
Tiotropium was administered using the HandiHaler® device.

Criteria for Evaluation

Primary variables

Forced expiratory volume in 1 second (FEV1) on Days 1 and 7

Secondary variables

Forced expiratory volume in 1 second on Days 1 and 7 and corresponding parameters for inspiratory capacity.

Safety and tolerability

Frequency of adverse events, clinical laboratory evaluations, ECGs, vital signs, spirometry

Pharmacology

On Day 1, 3, 5 and 7, blood (plasma) samples were measured at the following timepoints;
- Day 1: predose, 0.167, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24hours (D2) post-dose.
- Days 3 and 5: Trough (predose) PK samples
- Day 7: predose, 0.167, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, (D8) 24, 36, (D9) 48, (D10) 72 and (D11) 96 hours post dose.

On Day 1 and 7, urine collections were made at the following timepoints;
- Day 1: predose (25ml urine spot sample), urine collections (25 mL urine per collection period) 0-4, 4-8, 8-24 hours post dose.
- Day 7: urine collections (25 mL urine per collection period) 0-4, 4-8, 8-24 hours post dose

Other

Whole body plethysmography, Cardio-pulmonary exercise testing, dynamic inspiratory capacity and evaluating the borg scale.

Statistical Methods

All randomized subjects were included in the pharmacodynamic and safety data analyses. Patients 5111 and 5119 did not contribute any data to the pharmacokinetic analysis, effectively leaving 20 subjects in the pharmacokinetic analysis set.
Pharmacodynamic endpoints analyzed included Day 1 and Day 7 values of FEV1 AUC0-24h/24, FEV1 AUC23-24h (i.e. average of 23h and 24h measurements), FEV1 Emax, and the corresponding parameters for inspiratory capacity.
The primary endpoint was the natural logarithm transformed FEV1 AUC0-24h/24 on Day 7. An analysis of covariance (ANCOVA) was carried out on this endpoint. The ANCOVA model included fixed factors for sequence, period and treatment, the log pre-dose FEV1 value as a covari-

ate, and patient as a random effect. Mean differences for QAT370 vs. placebo, tiotropium vs. placebo and QAT370 vs. tiotropium were derived with 90% confidence intervals (CI). These were back transformed to provide estimates of fold differences with corresponding 90% CI. Other derived PD endpoints were analyzed similarly.
A repeated-measures ANCOVA model was also fitted to individual FEV1 and IC measurements on Day 7. Heart rate measurements were analyzed similarly.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria;

1. Male or female (post menopausal or surgically sterilized) patients with COPD, aged 40-80 years, with a smoking history of at least 10 pack years (i.e. smokers or ex-smokers).
2. Diagnosis of COPD according to the GOLD guidelines, with post-bronchodilator FEV1 at screening ≥ 40% of the predicted normal value.
3. Prior to administration of any study procedures, eligible subjects must understand and provide written informed consent. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
4. Body mass index (BMI) must be within the range of 18 to 32 kg/m2. Patients must weigh at least 50 kg to participate in this study.
5. Bronchodilatory response to tiotropium at screening. Reversibility to 18 µg tiotropium (i.e. post-bronchodilation FEV1 at 2 h post-dose) must be greater than 5%. This criterion for reversibility must be demonstrated after the patients have adhered to the following washout periods:
    - 6 h for short-acting bronchodilators
    - 48 h for long-acting β2-agonists / anticholinergics including tiotropium
6. Post-bronchodilator FEV1/FVC < 70%
7. No COPD exacerbations within the 6 weeks prior to dosing.
8. No history of concomitant lung disease such as carcinoma, active TB or prior thoracic surgery. No requirement for long term oxygen treatment or history of lung reduction surgery.
9. Male patients must be using a double-barrier local contraception, i.e., spermicidal gel plus condom, for the entire duration of the study, up to Study Completion visit, and refrain from fathering a child in the three (3) months following last study drug administration.
10. Female patients must have been surgically sterilized at least 6 months prior to screening. Surgical sterilization procedures must be supported with clinical documentation made available to sponsor and noted in the Relevant Medical History / Current Medical Conditions section of the CRF. For female patients who have undergone hysterectomy, the hysterectomy must have occurred more than six (6) months prior to first dosing.
    Or:
    Postmenopausal women must have no regular menstrual bleeding for at least 1 year prior to inclusion. Menopause will be confirmed by a plasma FSH level of >40 IU/L.

Exclusion criteria;

1. Patients currently on or have a clinical need for non permitted concomitant medications. Non permitted medications include:
    - Any additional treatments for Chronic Obstructive Lung Disease with the exception of short –acting β2 agonists and current treatment with a stable dose of in-

haled corticosteroid within a minimum of 8 weeks prior to inclusion and during the treatment periods. Examples of COPD treatments not permitted in the study include; theophylline, oral corticosteroids (within 8 weeks prior to inclusion and during the study), anticholinergics (48 h before assessment of bronchodilatory response to tiotropium and then throughout the study) and long acting β2 agonists (48 h before the assessment of bronchodilatory response and then throughout the study).

- Drugs that are known to have a drug interaction potential (e. g. CYP-enzyme inducers or inhibitors, or inhibitors of drug transporters like p-glycoprotein).
- Drugs that may aggravate known side effects of anticholinergic drugs, e. g. drugs that show anticholinesterase activity, that could produce tachycardia, that could lead to increased intraocular pressure or that could aggravate bladder obstruction.

2. Any significant medical condition that in the opinion of the Investigator may compromise patient safety, patient compliance, interfere with evaluations, or preclude completion of the trial. For example, COPD exacerbations within the 6 weeks prior to dosing. Exacerbations are defined as 1) an increase in inhaled steroids or oral steroids per se 2) use of antibiotics for a chest infection 3) hospitalization for a chest infection. Patients with severe COPD will be excluded.
3. Any medical condition that may make spirometry unsafe e.g. recurrent or recent pneumothorax.
4. Any history of a clinical condition that may make the exercise procedure unsafe, particular attention should be paid to a history of iscahemic heart disease, patients with unstable or effort related angina should be excluded, as should subjects with a history of ventricular arrthymia.
5. Any medical condition that may interfere with exercise testing e.g. arthritis.
6. Patients with narrow-angle glaucoma.
7. Patients with prostate hypertrophy.
8. Patients with a history of bladder abnormalities, e.g. constriction of the neck of the bladder.
9. Patients with a creatinine clearance <50 ml/min (evaluation according to DRD/Cockcroft Gault).
10. Patients with a history of asthma as suggested by intermittent, non-smoking, allergy related symptoms.
11. Patients with concurrent allergic rhinitis.
12. Patients with clinically significant cardiac conditions e.g. clinically relevant cardiac arrhythmia and paroxysmal tachycardia (>100 bpm).
13. Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulations, and for any other limitation of participation based on local regulations. Previous participation in a study with either the investigational or comparator drugs does not exclude a patient from participation in this study.
14. Donation or loss of 400 ml or more of blood within 8 weeks prior to first dosing, or longer if required by local regulation.
15. Significant illness (other than respiratory illness) within the two weeks prior to dosing.
16. A past medical history of clinically significant ECG abnormalities or a family history grandparents, parents and siblings of a prolonged QT-interval syndrome, defined as a corrected QT interval, by Bazett's formula of >450 msec for males and >470 msec for females.

17. History of clinically significant drug allergy. A known hypersensitivity to the study drug or drugs similar to the study drug.
18. History of immunocompromise, including a positive HIV (ELISA and Western blot) test result.
19. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.
20. History of drug or alcohol abuse within the 12 months prior to dosing as evidenced from the history.

Number of Subjects

	Novartis product	Comparator (N/A)
Planned N	24	N/A
Randomised n	22	N/A
Intent-to-treat population (ITT) n (%)	22	N/A
Completed n (%)	20	N/A
Withdrawn n (%)	2	N/A
Withdrawn due to adverse events n (%)	2	N/A
Withdrawn due to lack of efficacy n (%)	0	N/A
Withdrawn for other reasons n (%)	0	N/A

Demographic and Background Characteristics

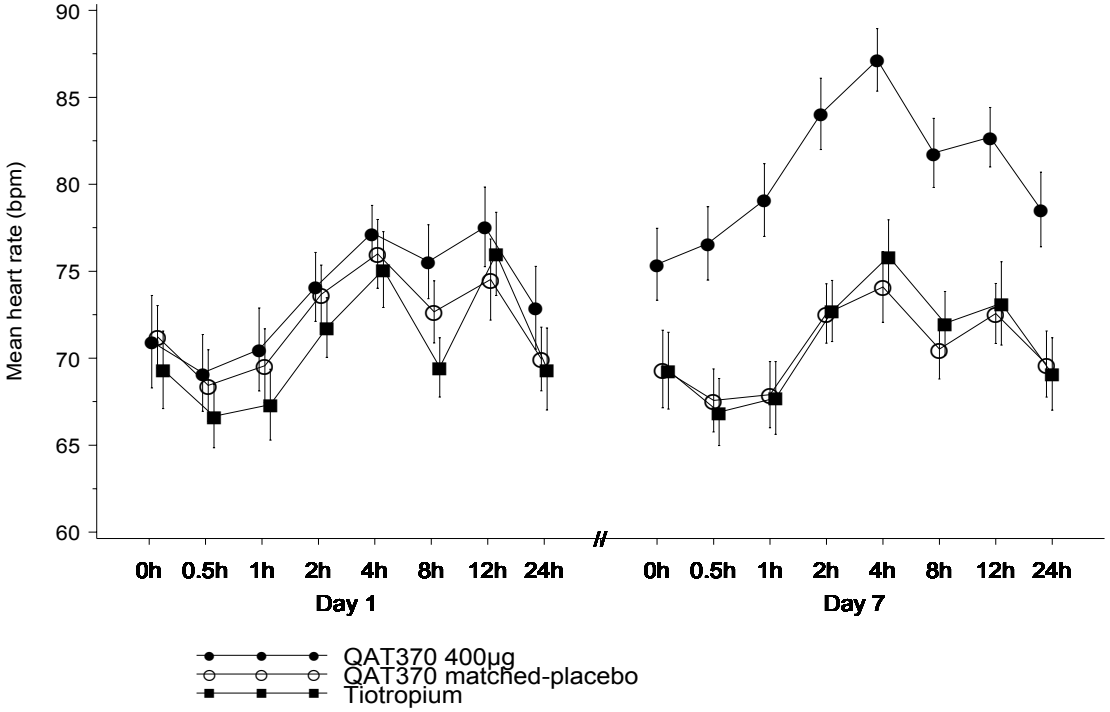
	All subjects (N=22)
Age (years) Mean (SD)	59.9 (8.26)
Sex: Male (%)	15 (68.2 %)
Female (%)	7 (31.8 %)
Predominant Race: Caucasian (%)	21 (95.5 %)
Other (%)	1 (4.5 %)
Ethnicity: Other (%)	22 (100.0 %)
Height (cm) Mean (SD)	171.1 (8.01)
Weight (Kg) Mean (SD)	74.63 (14.618)
BMI (kg/m2) Mean (SD)	25.30 (3.205)
Screening spirometry:	
Reversibility (%) Mean (SD)	40.2 (39.99)
% of predicted FEV1 (%) Mean (SD)	60.4 (16.80)

Primary Objective Result(s)

There were 13 patients with AEs under QAT370, 9 patients with AEs under Placebo and 7 patients with AEs under tiotropium. There were no SAEs. Two patients were withdrawn due to AEs. There was a clear increase in heart rate on Day 7 (at all time points) for QAT370 which was not seen on Day 1. There was a statistically significant increase following 7-day treatment with QAT370 compared with placebo. The mean heart rate increase ranged between 6 bpm (pre-dose)

and 13 bpm (4 hours post-dose).

Figure 1 - Mean heart rate (± SE) on Day 1 and Day 7

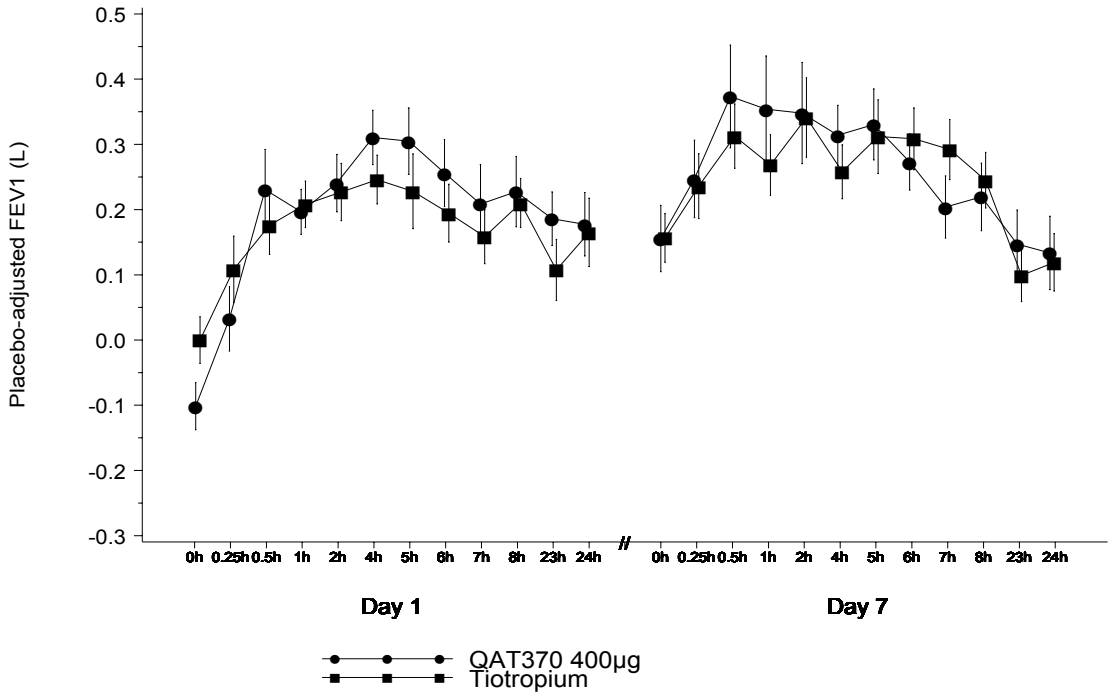


There were no clinically relevant changes to blood pressure.
There were no relevant changes to ECG-intervals (outside the effect on RR-interval, which is a value inversely proportional to heart rate). There was a slightly higher proportion of patients having QTc-values above normal range with QAT370, but applying the Fredericia correction (which is the more appropriate correction in case of observed heart rate increases) there was no value above 480 ms in any of the treatments.
There were no trends in clinical laboratory variables.

Secondary Objective Result(s)

Figure 2 below shows the time course of the placebo adjusted treatment response for FEV_1 over 24 h on Day 1 and Day 7. A clear treatment effect can be seen for all post dose timepoints after 0.25h on Day 1 for QAT370.

Figure 2 Mean placebo-corrected FEV_1 (± SE) on Day 1 and Day 7



As shown in Table 1 below, QAT370 400 µg significantly increased the standardized FEV1 AUC0-24h on Day 7 by 24% relative to placebo, and the increase by Tiotropium was 16% when compared to placebo. The effect on FEV1 at trough, i.e. FEV1 AUC23-24h, was also statistically significant but slightly lower in magnitude.

Table 1 - Results of ANCOVA analysis on FEV1 spirometry parameters (FEV_1 $AUC_{0-24\,h}$/24 and FEV_1 AUC_{23-24h} on day 7)

		Geometric mean		vs. QAT370 matched-placebo		
Parameter	Treatment	QAT370 or Tiotropium	QAT370 matched-placebo	Ratio	90% CI	p-value
FEV_1 AUC_{0-24h}/24 (L)	QAT370 400µg	1.58	1.27	1.24	(1.18, 1.31)	<0.001
FEV_1 AUC_{0-24h}/24 (L)	Tiotropium	1.48	1.27	1.16	(1.10, 1.23)	<0.001
FEV_1 AUC_{23-24h} (L)	QAT370 400µg	1.50	1.27	1.18	(1.11, 1.27)	<0.001
FEV_1 AUC_{23-24h} (L)	Tiotropium	1.40	1.27	1.10	(1.03, 1.17)	0.021

CI = Confidence Interval

Table 2 below provides the results for further secondary PD endpoints derived from spirometry.

The results show that the effect on the secondary readouts was consistent and statistically significant for the IC derived variables for QAT370 while this was not the case for tiotropium.
Day 1 results were generally consistent with Day 7 results for FEV1. When looking at individual time points, the mean FEV1 improvement over placebo ranged between 10% and 24% on Day 7 and was statistically significant at all times. The overall comparison of QAT370 to placebo (averaging over all time points) was significant for FEV1 but did not reach statistical significance for Inspiratory Capacity, although it showed a positive trend at all time points examined which is consistent with AUC0-24h results presented in Table 2 below.

Table 2 - Results of ANCOVA analysis on secondary spirometry parameters (FEV_1 E_{max} , IC $AUC_{0\text{-}24\,h}$/24, IC $AUC_{23\text{-}24h}$, IC E_{max}) on day 7

		Geometric mean		vs. QAT370 matched-placebo		
Parameter	**Treatment**	**QAT370 or Tiotropium**	**QAT370 matched-placebo**	**Ratio**	**90% CI**	**p-value**
FEV_1 E_{max} (L)	QAT370 400µg	1.85	1.44	1.29	(1.21, 1.36)	<0.001
FEV_1 E_{max} (L)	Tiotropium	1.74	1.44	1.21	(1.14, 1.28)	<0.001
IC $AUC_{0\text{-}24h}$/24 (L)	QAT370 400µg	2.18	2.02	1.08	(1.01, 1.15)	0.056
IC $AUC_{0\text{-}24h}$/24 (L)	Tiotropium	2.14	2.02	1.06	(1.00, 1.13)	0.119
IC $AUC_{23\text{-}24h}$ (L)	QAT370 400µg	2.11	1.98	1.07	(1.02, 1.12)	0.021
IC $AUC_{23\text{-}24h}$ (L)	Tiotropium	2.08	1.98	1.05	(1.00, 1.10)	0.076
IC E_{max} (L)	QAT370 400µg	2.61	2.37	1.10	(1.02, 1.19)	0.031
IC E_{max} (L)	Tiotropium	2.51	2.37	1.06	(0.99, 1.14)	0.178

CI=confidence interval, Emax= peak effect, AUC= area under the curve, IC=inspiratory Capacity

QAT370 appeared to increase exercise endurance and reduce dynamic hyperinflation and exertional dyspnoea.

Day 1 pre-dose concentrations for subjects 5105 and 5106 were greater than 5 % of Cmax resulting in the exclusion of these subjects from non-compartment PK analysis. However, these subjects were included in the Day 7 non-compartmental PK analysis but not the assessment of QAT370 accumulation.

QAT370 was quantifiable in all 10 minute to 4 h post-dose samples, 71 % of 12 h samples and 50 % of 24 h plasma samples on Day 1. Day 3 and Day 5 trough samples were generally above LLOQ (68 % and 90 %, respectively) as were Day 7 pre-dose samples (85 %). QAT370 was quantifiable in all 10 minute to 6 h post-dose samples, 80 % of 24 hours samples and 55 % of 96 h post-dose plasma samples on Day 7 (Table 16.2.5-1.3). Mean predose Day 5 and Day 7 plasma concentrations were similar (85.6 pg/mL vs. 85.9 pg/mL) indicating steady-state had been achieved by Day 5.

QAT370 was absorbed rapidly following inhalation. The maximum plasma concentration was

reached between 10 and 30 minutes post-dose; median tmax was 10 minutes on Day 1 and Day 7. The apparent accumulation of QAT370 in plasma of each subject during multiple dosing, i.e. between Day 1 and 7, was characterized by the accumulation ratios (=RA) of Cmax and AUC0-24 (Table below); Cmax increased 1.18-fold and AUC0-24 1.82-fold. The mean terminal elimination half-life (t1/2) was 65.4 h (determined in 9 of the 20 enrolled subjects)

Plasma pharmacokinetic parameters of QAT370

Day	Statistic	[1]t_{max} (h)	C_{max} (pg/mL)	AUC_{0-24} (pg.h/mL)	CL_{ss}/F (L/h)	$t_{1/2}$ (h)	V_z/F (L)	R_A (C_{max})	R_A (AUC_{0-24})
1	N	18	18	18	-	-	-	-	-
	Mean/median	0.17	824	1635	-	-	-	-	-
	SD/range	0.17-0.25	493	978	-	-	-	-	-
7	N	20	20	20	20	9	9	18	18
	Mean/median	0.17	854	2518	234	65.4	14581	1.18	1.82
	SD/range	0.17-0.50	451	1130	223	34.8	12788	0.63	1.08

[1]t_{max} – median and range

Safety Results

All treatments were safe and well tolerated.

Adverse Events by System Organ Class

There were 13 patients with AEs under QAT370, 9 patients with AEs under Placebo and 7 patients with AEs under tiotropium.

	QAT370 400ug	Matched Placebo	Tiotrpium
Patients studied	**N = 20**	**N = 21**	**N = 21**
Randomized patients	22		
Patients with drug-related AE	0 (0)		
	n (%)	**n (%)**	**n (%)**
Any body system (TOTAL)	**13 (65.0)**	**9 (42.9)**	**7 (33.3)**
Drug-related AEs by primary system organ class			
Respiratory, thoracic and mediastinal disorders	6 (30)	8 (38.1)	3 (14.3)
Nervous system disorders	4 (20)	5 (23.8)	4 (19)
Gastrointestinal disorders	5 (25)	1 (4.8)	1 (4.8)
General disorders	1 (5)	1 (4.8)	0 (0)
Cardiac disorders	2 (10)	1 (4.8)	1 (4.8)
Musculoskeletal and connective tissue	1 (5)	0 (0)	2 (9.5)
Skin and subcutaneous tissue disorders	0 (0)	0 (0)	1 (4.8)
Infections and infestations	0 (0)	1 (4.8)	1 (4.8)
Psychiatric disorders	0 (0)	1 (4.8)	2 (9.5)

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

	QAT370 400ug	Matched Placebo	Tiotrpium
Nasopharyngitis	0 (0)	1 (4.8)	1 (4.8)
Headache	4 ((20.0)	4 (19.0)	4 (19.0)
Diarrhea	0 (0)	1 (4.8)	0 (0)
Palpitations	0 (0)	1 (4.8)	0 (0)
Vertigo			

Serious Adverse Events and Deaths

None

Other Relevant Findings

None

Date of Clinical Trial Report

16-Mar-09

Date Inclusion on Novartis Clinical Trial Results Database

23 March 2009

Date of Latest Update

23 March 2009