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COMPOUND NUMBER: UK-500,001

PROTOCOL NO.: A5641009

PROTOCOL TITLE: A Phase II, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of UK-500,001 Dry Powder for Inhalation (DPI) in Adults With Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Study Centers: Twenty five (25) centers took part in the study and randomized subjects: 5 in Argentina, 4 in Australia, 4 in Canada, 2 in Chile, 1 in Croatia, 3 in Czech Republic, 3 in Hungary, 2 in Spain and 1 in the United Kingdom.

Study Initiation and Final Completion Dates: 22 November 2005 and 01 September 2006.

The study was terminated prematurely due to futility following the interim analysis.

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To evaluate the efficacy and safety/tolerability of UK-500,001 Dry Powder for Inhalation (DPI) in adults with moderate to severe Chronic Obstructive Pulmonary Disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease Stage II/III).

Secondary Objectives:

- To explore the efficacious dose range for UK-500,001 DPI in COPD and provide information for a Phase IIb dose ranging;
- To evaluate the time course of response to UK-500,001 DPI;
- To evaluate the persistence of UK-500,001 DPI effects on lung function and symptoms for 2 weeks after stopping the drug;
- To evaluate the pharmacokinetic-pharmacodynamic relationship between dose and/or systemic UK-500,001 exposure versus efficacy and/or safety/tolerability in COPD subjects.

METHODS

Study Design:

This was a 6 week, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety and tolerability of UK-500,001 DPI in adult subjects with moderate to severe COPD. The study consisted of 8 clinic visits; a screening visit, 2 visits during the run-in phase (Weeks -2 and -1), a Baseline/Randomization Visit (Week 0) at the start of the double-blind treatment phase, 3 visits during the double-blind treatment phase (Weeks 2, 4 and 6) and a Follow-up Visit (Week 8) following a 2-week washout (run out) phase. Subjects were randomized to the treatment groups 0.1 mg twice a day (BID): 0.4 mg BID: 1 mg BID: placebo in the ratio 1:1:1:1. An interim analysis was performed once 66 subjects completed double-blind treatment in the 1 mg and placebo treated groups, and the study was terminated at that stage according to a pre-defined stopping rule based on futility. Subjects who discontinued during the period from randomization (Week 0) to follow-up (Week 8) were not replaced.

Table 1 summarizes the schedule of activities.

Table 1. Schedule of Activities

	Screening	Run-In		Double-Blind Treatment Phase				Follow-Up
Study Week	**-4 to -3**	**-2**	**-1**	**0 Baseline**	**2**	**4**	**6 End of Study**	**8 Follow-Up ET[a]**
Informed consent	X							
Impala registration/contact	X			X	X	X		X
Medical history/demographics	X							
Concomitant medication review	X	X	X	X	X	X	X	X
Physical examination	X			X[b]		X[b]	X[b]	X
Blood pressure/pulse rate[c]	X			X	X	X	X	X
Review inclusion/exclusion criteria (and FEV_1 randomization criteria Week 0)	X	X	X	X				
Dispense short acting bronchodilators	X			X		X		
Inhaler device training	X			X				
Review of adverse events		X	X	X	X	X	X	X
Chest x-ray (if none within 12 months)	X							
12-lead resting ECG[d]	X			X	X	X	X	X
Laboratory safety tests (hematology, chemistry), FSH for amenorrheic women aged 45-60	X			X	X		X	X[e]
Whole blood for genotyping[f]				X				
Routine urinalysis	X			X	X		X	X[e]
Urine pregnancy test (WOCBP only)	X			X		X		X
Blood sample for biomarker/RNA analysis[f]				X			X	
Baseline/transition dyspnea index				XBase	XTran	XTran	XTran	
Spirometry, trough	X	X	X	X	X	X	X[g]	X
Randomization				X				
Study drug administered during clinic visit				X	X	X	X	
Spirometry, post-study drug[h]				X	X	X	X	
Salbutamol administered at clinic visit[i]	X	X	X	X			X	
Spirometry, post-salbutamol[j]	X	X	X	X			X	
PK, trough[k]				X	X	X	X	
PK, post-dosing with study drug[l]					X	X[m]	X	
Study drug dispensed				X	X	X		
Study drug return and accountability					X	X	X	
Provide paper diary, bronchodilators[n] and AM2[o]	X	X	X	X	X	X	X	
Daily diary collection and review (PEFR, symptom and		X	X	X	X	X	X	X

Table 1. Schedule of Activities

	Screening	Run-In		Double-Blind Treatment Phase				Follow-Up
Study Week	**-4 to -3**	**-2**	**-1**	**0 Baseline**	**2**	**4**	**6 End of Study**	**8 Follow-Up ET[a]**
bronchodilator use)								
Global impression of change (clinician and subject) and global rating of change (subject)							X	

AM = asthma monitor, Base = baseline; ECG = electrocardiogram, ET = early termination, FEV_1 = forced expiratory volume in 1 second, FSH = follicle stimulating hormone, PEFR = peak expiratory flow rate, PK = pharmacokinetic, RNA = ribonucleic acid, Tran = transition; WOCBP = women of child-bearing potential.

a. ET Visit for subjects who discontinued the study prior to Week 8.
b. Only a brief physical exam was required. Full physical exams were required at screening and Week 8 or End of Study Visit if earlier than Week 8.
c. Vital signs (blood pressure and pulse) were measured prior to any other post-dose visit procedures (eg, blood sampling, spirometry) and as follows: At Weeks 0 and 6 obtained 10-15 minutes before and 5-15 minutes after study drug dosing; at Weeks 2 and 4 obtained 5-15 minutes after study drug dosing; at screening and Week 8 at the beginning of the visit, prior to blood sample or spirometry.
d. Obtained ECGs as follows: At Weeks 0 and 6 obtained 10-15 minutes before and 30-60 minutes after study drug dosing; at Weeks 2 and 4 obtained 30-60 minutes after study drug dosing (prior to administration of salbutamol); at screening and Week 8 obtained with vital signs at the beginning of the visit, prior to blood sample or spirometry.
e. Collected and analyzed blood and urine if ET. If follow-up, only collected samples if abnormalities were detected in results obtained at Week 6.
f. Performed on a voluntary basis only.
g. At the Week 6 Visit only, collected replicate trough spirometry measurements 30-60 minutes after initial spirometry assessment, and before administration of study drug.
h. Performed post-study drug spirometry 15-30 minutes after dosing with study drug.
i. Salbutamol (albuterol) was administered after all spirometry related to study drug and after any scheduled ECG (pre or post-dose) was completed.
j. Performed post-salbutamol spirometry 15-30 minutes after salbutamol (albuterol) dosing.
k. Trough PK samples were collected before the dose of study drug.
l. At Weeks 2, 4 and 6, collected post-dose PK samples 30-60 minutes and >90 minutes after study drug dosing.
m. At Week 4 only, collected an additional PK sample 2-7 hours after study drug dosing.
n. Short acting bronchodilators provided at screening, Week –2, Week 0, Week 2, Week 4 and Week 6.
o. Asthma Monitor AM2 device provided at screening only for use throughout the study.

Number of Subjects (Planned and Analyzed):

Approximately 324 subjects were to be randomized at approximately 40 sites across 12 countries. A total of 401 subjects were screened at 30 sites across 10 countries. A total of 209 were randomized to and received study treatment and were analyzed for safety; 191 were analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion:

Male or female subjects aged between 40 to 80 years, weighing >40 kg with body mass index <35 kg/m^2 and females using acceptable methods of contraception; current smokers or ex-smokers having a history of at least 10 pack-years; subjects who had a stable disease for at least 1 month and able to manage disease symptoms adequately; subjects willing to give informed consent and able to comply with all study procedures were included in the study.

Main Exclusion Criteria:

Subjects presenting with >2 exacerbations of COPD requiring treatment with oral steroids in the preceding year or hospitalization for the treatment of COPD within 3 months of screening or more than twice during the preceding year; history of a lower respiratory tract infection or significant disease instability during the month preceding screening or during the time between screening and randomization; history or presence of respiratory failure, cor pulmonale or right ventricular failure; subjects with home oxygen therapy (either puffs as required or long term oxygen therapy); any clearly documented history of adult asthma or other chronic respiratory disorders (eg, bronchiectasis, pulmonary fibrosis, pneumoconiosis); history of cancer (other than cutaneous basal cell) in the previous 5 years; history within the previous year of myocardial infarction, cardiac arrhythmia (eg, atrial fibrillation, paroxysmal atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular tachycardia), left ventricular failure, unstable angina, coronary angioplasty, coronary artery bypass grafting or cerebrovascular accident (including transient ischemic attacks); active tuberculosis within the previous 2 years; and history within the previous 6 months of an epileptic seizure, poorly controlled Type 1 or Type 2 diabetes, acute hepatitis of any etiology, atrioventricular block >first degree were excluded from the study.

Study Treatment:

UK-500,001/Placebo: UK-500,001 was supplied as capsules containing 0.1 mg, 0.4 mg, or 1.0 mg of UK-500,001 DPI and matching placebo. Study medication was packaged as 7-day blister cards containing sufficient medication for 7 days plus 2 days overage to allow for missed or re-scheduled visits. All study drugs were administered by inhalation BID via the single pin monodose capsule inhaler device: 1 capsule in the morning and 1 capsule in the evening, at approximately 12-hour intervals. The study drug could be taken without observing specific relation to food or meals. Missed doses were not to be 'caught up'. After a 2 week run-in period, the actual randomized treatment started at Week 0 and continued for 6 weeks. The dose scheduled for the day of the clinic visit was administered in the clinic using the first capsule from the following weeks' supplies. The dose administered at the Week 6 clinic Visit was taken from the overage supplied at the Week 4 Visit.

Short-Acting Bronchodilators (Ipratropium Bromide and Salbutamol Sulphate/Albuterol Sulfate): Ipratropium bromide was supplied as metered dose inhaler (MDI) (20 μg/actuation); 200 actuations/MDI. Salbutamol was supplied as MDI (100 μg/actuation); 200 actuations/MDI. Suitable spacer devices were provided by the Sponsor. Subjects used ipratropium bromide MDI (20 μg/actuation) 2 actuations 4 times daily as maintenance therapy throughout the study (ie, screening through to Week 8). All maintenance therapy used was recorded daily in the paper diary by the subject.

Efficacy and Safety Endpoints:

Primary Efficacy Endpoints:

- Mean change from Baseline in trough (prior to administration of study drug) forced expiratory volume in 1 second (FEV_1) at Week 6.

Secondary Efficacy Endpoints:

- Mean change from Baseline in trough forced expiratory volume in 6 seconds (FEV_6) (prior to administration of study drug) at Week 6;
- Change from Baseline in trough FEV_1, FEV_6, forced vital capacity (FVC) and Inspiratory Capacity (IC) at 2 and 4 weeks of therapy and at 2 weeks after the completion of therapy;
- Change from Baseline in trough FEV_6, FVC and IC at 6 weeks;
- Change from Baseline in post-study drug FEV_1, FEV_6, FVC, and IC at 2, 4 and 6 weeks of therapy;
- Change from Baseline in post-bronchodilator FEV_1, FEV_6, FVC, and IC at 6 weeks of therapy;
- Change from Baseline in dyspnea (Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI]) at Weeks 2, 4 and 6;

- Change from Baseline of COPD symptoms, rescue bronchodilator use (per daily diary) and peak expiratory flow rate (PEFR);

- Global impression of change (clinician and subject) at End of Study.

Safety Endpoints:

- Adverse events (AEs);

- Laboratory safety data;

- Change in vital signs (pulse and blood pressure [BP]) and 12-lead electrocardiogram (ECG) post-study drug;

- Acute change in FEV_1 post-study drug compared to pre-study drug (Week 0 only).

Safety Evaluations: AEs were monitored throughout the study. BP and pulse rate (supine) and ECGs were measured (screening, randomization, Weeks 2, 4 and 6 and at follow-up Week 8), blood and urine samples were taken for laboratory tests and a physical examination was conducted during screening. Spirometry function was performed at all clinic visits and PEFR was performed twice daily.

Statistical Methods:

Sample Size: The sample size calculation was based on the primary efficacy endpoint, mean change from Baseline in trough FEV_1 at Week 6. The study size was chosen to give both a reasonable chance of stopping for futility at the interim analysis if the true treatment difference between the top dose and placebo was small, and also to test for efficacy at the End of the Study (futility triggered or not). A maximum sample size of 72 completed subjects per group had approximately 80% power to detect a difference in mean change from Baseline in trough FEV_1 at Week 6 of 75 mL, based on a 1-sided 5% significance level. This power calculation accounted for an adjustment needed for the effect of the interim futility analysis.

Analysis Sets:

The Full Analysis Set/Intent-to-Treat (ITT) group was considered the primary analysis data set and consisted of all randomized subjects who took at least 1 dose of study medication. The Per Protocol (PP) Analysis Set consisted of an Evaluable subject group defined as all randomized subjects who had no major protocol violations, completed at least 2 weeks of dosing and had at least 1 valid trough FEV_1 measurement during the active double-blind phase of the study, and a Completer subject group defined as all subjects who had no major protocol violations, received 6 weeks of double-blind therapy and produced valid trough FEV_1 readings at both Baseline and the Week 6 Visit.

Primary Efficacy Analysis: The primary analysis was based on the ITT dataset and the primary endpoint was change from Baseline in trough FEV_1 at Week 6. Trough FEV_1

measured at Baseline (average of Week -1 and Week 0) and values recorded at Weeks 2, 4, 6, and 8 were included in the statistical model.

Secondary Efficacy Analyses: Baseline and changes from Baseline were analyzed for: Trough FEV_1 at Weeks 2, 4 and 8; trough FEV_6, FVC, and IC at Weeks 2, 4, 6 and 8; post-study drug FEV_1, FEV_6, FVC, and IC at Weeks 2, 4 and 6; post-bronchodilator FEV_1, FVC, FEV_6, and IC at Week 6. The TDI total focal score at Week 6 was used as the key measure of the impact of COPD on a subject's dyspnea. TDI total focal scores at Weeks 2, 4 and 6 were included with BDI at Week 0 as a covariate. For the Subject Daily Symptom Diary (cough, breathlessness, sputum), a subject's daily score and for rescue bronchodilator use, a subject's daily use (puffs/day) was averaged over each Week 0, 1, 2, 3, 4, 5, 6, 7, and 8. For daily PEFR (morning and evening separately), a subject's daily values were averaged over each Week 0, 1, 2, 3, 4, 5, 6, 7, and 8. The physician and subject global impression of change score was summarized as percent of response by treatment group. The data were analyzed using proportional odds logistic regression with treatment and center (or center grouping) as factors.

Safety Analysis: AEs and laboratory data were listed and summarized according to Sponsor data standards. Vital signs and ECG were evaluated descriptively.

RESULTS

Due to lack of efficacy determined at the interim analysis, the study was terminated early for futility on 31 August 2006.

Subject Disposition and Demography:

Of the 401 subjects screened, 209 subjects were randomized for the study. The data sets analyzed are summarized in Table 2. A total of 33 subjects discontinued from all treatment groups. Subject discontinuations are summarized in Table 3.

Table 2. Data Sets Analyzed

Number of Subjects (%)	UK-500,001			Double-Blind Placebo BID
	0.1 mg BID	0.4 mg BID	1.0 mg BID	
Assigned to study treatment: 209				
Treated	53	55	48	53
Completed	47 (88.7)	43 (78.2)	39 (81.3)	47 (88.7)
Analyzed for efficacy				
ITT	52 (98.1)	52 (94.5)	47 (97.9)	52 (98.1)
Completer	46 (86.8)	40 (72.7)	37 (77.1)	44 (83.0)
Evaluable	49 (92.5)	48 (87.3)	42 (87.5)	52 (98.1)
Analyzed for safety				
Adverse events	53 (100.0)	55 (100.0)	48 (100.0)	53 (100.0)
Laboratory data	53 (100.0)	52 (94.5)	46 (95.8)	53 (100.0)

BID = twice a day, ITT = intent-to-treat.

Table 3. Discontinuations From the Study

Reasons for Discontinuations, n (%)	UK-500,001			Double-Blind Placebo
	0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Related to study drug	4 (7.5)	6 (10.9)	6 (12.5)	5 (9.4)
Adverse event	0 (0)	2 (3.6)	1 (2.1)	0 (0)
Other	4 (7.5)	4 (7.3)	5 (10.4)	5 (9.4)
Not related to study drug	2 (3.8)	6 (10.9)	3 (6.3)	1 (9.1)
Adverse event	2 (3.8)	4 (7.3)	2 (4.2)	0 (0)
Other	0 (0)	2 (3.6)	0 (0)	1 (1.9)
Subject default	0 (0)	0 (0)	1 (2.1)	0 (0)
Total number of discontinuations	6 (11.3)	12 (21.8)	9 (18.8)	6 (11.3)

BID = twice a day, n = number of subjects.

The demographic characteristics were similar across treatment groups (Table 4). Lung function characteristics at Baseline and smoking status of subjects are shown in Table 5. Baseline smoking status included both current and ex-smokers. The proportion of current and ex-smokers was similar across treatment groups, with more ex-smokers than current smokers.

Table 4. Summary of Demographic Characteristics

Demographic Characteristic	UK-500,001			Double-Blind Placebo
	0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Gender				
Male	37	44	33	38
Female	16	11	15	15
Age, years				
Mean (SD)	65.0 (7.4)	62.9 (8.9)	61.9 (7.2)	64.8 (8.3)
Range	45-80	43-78	46-79	45-78
Height, cm				
Mean (SD)	167.1 (8.5)	170.1 (8.5)	169.0 (8.0)	168.4 (9.1)
Range	150.0-185.0	151.0-187.0	153.0-186.0	150.0-193.0
Weight, kg				
Mean (SD)	68.5 (13.5)	74.8 (14.6)	76.6 (15.2)	72.9 (14.3)
Range	43.6-95.0	46.0-107.0	48.0-110.0	48.0-107.8

BID = twice a day, SD = standard deviation.

Table 5. Spirometry (Lung Function Characteristics) and Smoking History at Baseline

Spirometry Parameters	UK-500,001			Double-Blind Placebo
	0.1 mg BID N=53	0.4 mg BID N=55	1.0 mg BID N=48	BID N=53
% predicted FEV_1				
Mean (SD)	50.98 (14.59)	49.25 (12.31)	53.88 (14.21)	52.17 (14.21)
FEV_1 (L)				
Mean (SD)	1.37 (0.46)	1.45 (0.47)	1.53 (0.48)	1.43 (0.49)
% FEV_1 reversibility				
Mean (SD)	16.19 (14.95)	14.09 (14.84)	14.01 (14.10)	13.69 (16.36)
Smoking history				
Smoker, n (MPY)	25 (52.72)	14 (42.93)	16 (52.38)	24 (56.17)
Ex-smoker, n (MPY)	28 (50.14)	41 (43.63)	32 (44.50)	29 (49.97)

BID = twice a day, FEV_1 = forced expiratory volume in 1 second, MPY = mean pack years, N = total number of subjects, n = number of subjects with specified criteria, SD = standard deviation.

Efficacy Results:

Primary Efficacy Results:

The mean changes from Baseline to Week 6 in trough FEV_1 (ITT population) were small in magnitude (Table 6). There were no statistically significant differences for trough FEV_1 at Week 6 between the placebo and UK-500,001 groups. The p-value and confidence interval (CI) were 0.506 (-0.054, 0.053)for the 0.1 mg group; 0.708 (-0.073, 0.037)for the 0.4 mg group; and 0.141 (-0.020, 0.093) for the 1.0 mg group.

Secondary Efficacy Results:

Mean change from Baseline in trough FEV_1, FEV_6, and FVC at Weeks 2, 4, 6 and 8 are summarized in Table 6, Table 7 and Table 8 respectively. Analysis of the mean changes from Baseline showed that there were no statistically significant differences between 0.1 mg BID and placebo or 0.4 mg BID and placebo at any time points. Comparison between 1 mg and placebo showed a statistically significant treatment effect at Week 2 (p-value and CI were 0.0036 [0.0536, 0.2197] for FEV_6). The magnitude of this effect declined over time and was not statistically significant at Weeks 4 or 6. This pattern of response was consistently observed in the ITT, evaluable and completer populations for FEV_1, and for the ITT and completer populations for FEV_6 and FVC.

Table 6. Mean Change From Baseline in Trough FEV_1 at Weeks 2, 4, 6 and 8 (ITT Population)

Time Point		UK-500,001			Double-Blind Placebo
		0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Baseline		n=52	n=52	n=47	n=52
	Mean (SD)	1.24 (0.38)	1.33 (0.45)	1.43 (0.44)	1.34 (0.49)
	Range	(0.49, 2.36)	(0.63, 2.31)	(0.76, 2.38)	(0.67, 2.69)
Week 2		n=47	n=48	n=43	n=50
	Mean (SD)	-0.03 (0.11)	0.00 (0.16)	0.08 (0.19)	-0.03 (0.15)
	Range	(-0.21, 0.26)	(-0.30, 0.39)	(-0.32, 0.59)	(-0.50, 0.28)
Week 4		n=46	n=42	n=39	n=46
	Mean (SD)	-0.01 (0.13)	0.01 (0.20)	0.03 (0.17)	-0.02 (0.16)
	Range	(-0.27, 0.27)	(-0.27, 0.77)	(-0.36, 0.42)	(-0.53, 0.32)
Week 6		n=46	n=42	n=38	n=46
	Mean (SD)	-0.01 (0.12)	-0.03 (0.18)	0.01 (0.11)	-0.01 (0.20)
	Range	(-0.25, 0.30)	(-0.61, 0.38)	(-0.23, 0.32)	(-0.45, 0.60)
Week 8		n=43	n=41	n=37	n=46
	Mean (SD)	-0.03 (0.15)	-0.04 (0.18)	-0.01 (0.16)	0.02 (0.24)
	Range	(-0.41, 0.19)	(-0.71, 0.41)	(-0.43, 0.27)	(-0.65, 0.50)

BID = twice a day, FEV_1 = forced expiratory volume in 1 second, ITT = intent-to-treat, n = number of subjects, SD = standard deviation.

Table 7. Mean Change From Baseline in Trough FEV_6 at Weeks 2, 4, 6 and 8 (ITT Population)

Time Point		UK-500,001			Double-Blind Placebo
		0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Baseline		n=52	n=52	n=47	n=52
	Mean (SD)	2.48 (0.61)	2.73 (0.62)	2.71 (0.64)	2.67 (0.84)
	Range	(1.14, 3.76)	(1.55, 4.31)	(1.52, 4.67)	(1.36, 5.71)
Week 2		n=47	n=48	n=43	n=50
	Mean (SD)	-0.04 (0.22)	0.01 (0.27)	0.08 (0.26)	-0.06 (0.22)
	Range	(-0.46, 0.52)	(-0.55, 0.78)	(-0.60, 0.71)	-0.56 (0.69)
Week 4		n=46	n=42	n=39	n=46
	Mean (SD)	-0.04 (0.24)	0.05 (0.32)	0.03 (0.25)	-0.02 (0.27)
	Range	(-0.78, 0.45)	(-0.44, 1.21)	(-0.55, 0.57)	(-0.68, 0.71)
Week 6		n=46	n=42	n=38	n=46
	Mean (SD)	-0.04 (0.18)	-0.05 (0.29)	-0.02 (0.17)	-0.01 (0.30)
	Range	(-0.44, 0.42)	(-0.92, 0.64)	(-0.47, 0.35)	(-0.75, 0.89)
Week 8		n=43	n=41	n=37	n=46
	Mean (SD)	-0.05 (0.24)	-0.07 (0.27)	-0.03 (0.25)	0.03 (0.34)
	Range	(-0.61, 0.48)	(-0.87, 0.57)	(-0.78, 0.44)	(-0.80, 0.80)

BID = twice a day, FEV_6 = forced expiratory volume in 6 seconds, ITT = intent-to-treat, n = number of subjects, SD = standard deviation.

Table 8. Mean Changes From Baseline for FVC (ITT Population)

Time Point		UK-500,001			Double-Blind Placebo
		0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Week 2		n=47	n=48	n=43	n=50
	Mean (SD)	-0.02 (0.31)	-0.03 (0.35)	0.09 (0.35)	-0.05 (0.32)
	Range	(-0.91, 0.53)	(-1.01, 1.26)	(-0.81, 0.79)	(-0.73, 0.84)
Week 4		n=46	n=42	n=39	n=46
	Mean (SD)	-0.05 (0.32)	0.03 (0.37)	0.04 (0.32)	-0.03 (0.39)
	Range	(-0.91, 0.75)	(-0.46, 1.12)	(-0.67, 0.65)	(-0.79, 0.85)
Week 6		n=46	n=42	n=38	n=46
	Mean (SD)	-0.08 (0.25)	-0.09 (0.39)	-0.03 (0.27)	-0.01 (0.38)
	Range	(-0.78, 0.50)	(-1.20, 0.72)	(-0.58, 0.80)	(-0.76, 0.92)
Week 8		n=43	n=41	n=37	n=46
	Mean (SD)	-0.06 (0.39)	-0.11 (0.33)	-0.03 (0.41)	0.04 (0.46)
	Range	(-1.01, 0.87)	(-0.99, 0.80)	(-1.12, 0.74)	(-0.78, 1.31)

BID = twice a day, FVC = forced vital capacity, ITT = intent-to-treat, n = number of subjects, SD = standard deviation.

Mean changes from Baseline for trough IC (ITT analysis) are summarized in Table 9. Analysis of the mean change from Baseline in trough IC at Weeks 2, 4, 6 and 8 showed that there were no statistically significant differences between 0.1 mg BID, 0.4 mg BID or 1.0 mg BID and placebo at any time points in the ITT population.

Table 9. Mean Changes From Baseline for IC (ITT Population)

Time Point		UK-500,001			Double-Blind Placebo
		0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Week 2		n=47	n=48	n=43	n=50
	Mean (SD)	0.03 (0.32)	0.06 (0.29)	0.04 (0.25)	-0.03 (0.29)
	Range	(-0.58, 1.28)	(-0.72, 0.58)	(-0.51, 0.57)	(-0.64, 0.70)
Week 4		n=46	n=42	n=39	n=47
	Mean (SD)	-0.02 (0.36)	-0.09 (0.36)	-0.10 (0.30)	-0.18 (0.48)
	Range	(-1.40, 0.90)	(-1.32, 0.61)	(-0.79, 0.43)	(-2.21, 0.89)
Week 6		n=46	n=42	n=38	n=46
	Mean (SD)	0.09 (0.29)	0.00 (0.37)	-0.04 (0.23)	0.02 (0.34)
	Range	(-0.77, 0.71)	(-1.13, 0.86)	(-0.56, 0.44)	(-0.87, 0.82)
Week 8		n=43	n=41	n=37	n=46
	Mean (SD)	0.04 (0.31)	0.03 (0.30)	-0.01 (0.26)	0.02 (0.35)
	Range	(-0.56, 0.73)	(-0.79, 0.80)	(-0.68, 0.36)	(-0.97, 0.80)

BID = twice a day, IC = inspiratory capacity, ITT = intent-to-treat, n = number of subjects, SD = standard deviation.

Post-study drug mean FEV_1, FEV_6 and FVC at Weeks 2, 4, and 6 are summarized in Table 10, Table 11 and Table 12 respectively. Analysis of the mean changes from Baseline showed that there were no statistically significant differences between 0.1 mg BID and placebo or 0.4 mg BID and placebo at any time points. Comparison between 1 mg and

placebo showed a statistically significant treatment effect at Week 2. The magnitude of this effect declined over time and was not statistically significant at Weeks 4 or 6. This pattern of response was consistently observed in the ITT and completer populations.

Table 10. Post-Study Drug FEV_1 at Weeks 2, 4 and 6 (ITT Population)

Time Point		UK-500,001			Double-Blind Placebo
		0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Week 2		n=47	n=47	n=42	n=49
	Mean (SD)	-0.02 (0.12)	-0.00 (0.16)	0.08 (0.19)	-0.03 (0.16)
	Range	(-0.29, 0.26)	(-0.32, 0.39)	(-0.29, 0.70)	(-0.47, 0.40)
Week 4		n=46	n=42	n=39	n=46
	Mean (SD)	-0.01 (0.12)	0.02 (0.20)	0.05 (0.18)	0.01 (0.15)
	Range	(-0.26, 0.23)	(-0.32, 0.75)	(-0.27, 0.45)	(-0.44, 0.43)
Week 6		n=46	n=39	n=37	n=44
	Mean (SD)	0.00 (0.13)	-0.05 (0.18)	0.01 (0.14)	-0.01 (0.19)
	Range	(-0.25, 0.30)	(-0.82, 0.29)	(-0.27, 0.41)	(-0.48, 0.53)

BID = twice a day, FEV_1 = forced expiratory volume in 1 second, ITT = intent-to-treat, n = number of subjects, SD = standard deviation.

Table 11. Post-Study Drug FEV_6 at Weeks 2, 4 and 6 (ITT Population)

Time Point		UK-500,001			Double-Blind Placebo
		0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Week 2		n=47	n=47	n=42	n=49
	Mean (SD)	-0.05 (0.20)	-0.02 (0.26)	0.06 (0.27)	-0.07 (0.23)
	Range	(-0.63, 0.39)	(-0.51, 0.78)	(-0.70, 0.96)	(-0.53, 0.54)
Week 4		n=46	n=42	n=39	n=46
	Mean (SD)	-0.04 (0.23)	0.04 (0.30)	0.02 (0.24)	0.02 (0.28)
	Range	(-0.76, 0.35)	(-0.44, 1.00)	(-0.57, 0.65)	(-0.70, 1.04)
Week 6		n=46	n=39	n=37	n=44
	Mean (SD)	-0.05 (0.23)	-0.08 (0.25)	-0.02 (0.21)	-0.04 (0.31)
	Range	(-0.53, 0.53)	(-0.96, 0.51)	(-0.81, 0.40)	(-0.87, 0.80)

BID = twice a day, FEV_6 = forced expiratory volume in 6 seconds, ITT = intent-to-treat, n = number of subjects, SD = standard deviation.

Table 12. Post-Study Drug FVC at Weeks 2, 4 and 6 (ITT Population)

Time Point		UK-500,001			Double-Blind Placebo
		0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Week 2		n=47	n=47	n=42	n=49
	Mean (SD)	-0.05 (0.30)	-0.07 (0.38)	0.01 (0.34)	-0.10 (0.29)
	Range	(-1.12, 0.48)	(-1.11, 1.10)	(-0.98, 0.96)	(-0.66, 0.70)
Week 4		n=46	n=42	n=39	n=46
	Mean (SD)	-0.05 (0.33)	0.02 (0.33)	0.02 (0.31)	-0.00 (0.40)
	Range	(-1.01, 0.49)	(-0.69, 0.87)	(-0.61, 0.62)	(-0.88, 1.21)
Week 6		n=46	n=39	n=37	n=44
	Mean (SD)	-0.10 (0.26)	-0.14 (0.39)	-0.04 (0.35)	-0.06 (0.42)
	Range	(-0.66, 0.50)	(-1.34, 0.52)	(-1.10, 0.56)	(-1.01, 1.10)

BID = twice a day, FVC = forced vital capacity, ITT = intent-to-treat, n = number of subjects, SD = standard deviation.

Mean change from Baseline in post-study drug IC at Weeks 2, 4 and 6 are summarized in Table 13. Analysis of the mean changes from Baseline showed that there was a statistically significant difference (p=0.0146) between 0.4 mg BID and placebo at Week 2 for the ITT analysis. No other comparisons were statistically significant for the ITT analysis. There were no statistically significant differences between 0.1 mg BID, 0.4 mg BID or 1.0 mg BID and placebo at any time points in the completer population analysis.

Table 13. Post-Study Drug IC at Weeks 2, 4 and 6 (ITT Population)

Time Point		UK-500,001			Double-Blind Placebo
		0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Week 2		n=47	n=47	n=42	n=49
	Mean (SD)	-0.00 (0.26)	0.11 (0.30)	0.05 (0.25)	-0.01 (0.32)
	Range	(-1.01, 0.48)	(-0.73, 0.67)	(-0.87, 0.49)	(-0.64, 0.84)
Week 4		n=46	n=42	n=39	n=46
	Mean (SD)	-0.01 (0.31)	-0.03 (0.42)	-0.08 (0.33)	-0.07 (0.42)
	Range	(-1.01, 0.70)	(-1.19, 0.74)	(-0.83, 0.77)	(-1.13, 0.79)
Week 6		n=46	n=39	n=37	n=44
	Mean (SD)	0.09 (0.31)	-0.01 (0.39)	0.00 (0.27)	0.08 (0.30)
	Range	(-0.58, 0.68)	(-0.81, 0.89)	(-0.60, 0.87)	(-0.84, 0.63)

BID = twice a day, IC = inspiratory capacity, ITT = intent-to-treat, n = number of subjects, SD = standard deviation.

Mean change from Baseline in post-bronchodilator FEV_1, FEV_6, FVC and IC at Week 6 are summarized in Table 14. Analysis of the mean changes from Baseline showed that there were no statistically significant differences between 0.1 mg BID, 0.4 mg BID or 1.0 mg BID and placebo at any time points in the ITT and completer populations.

Table 14. Post-Bronchodilator FEV_1, FVC, FEV_6 and IC at Week 6 (ITT Population)

Time Point		UK-500,001			Double-Blind Placebo
		0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
FEV_1					
	n	46	39	37	43
	Mean (SD)	-0.01 (0.13)	-0.01 (0.14)	0.02 (0.14)	0.01 (0.16)
	Range	(-0.25, 0.32)	(-0.44, 0.28)	(-0.26, 0.34)	(-0.31, 0.37)
FVC					
	n	46	39	37	43
	Mean (SD)	-0.15 (0.34)	-0.06 (0.44)	0.01 (0.27)	-0.08 (0.30)
	Range	(-1.71, 0.34)	(-1.24, 0.66)	(-0.48, 0.59)	(-0.68, 0.50)
FEV_6					
	n	46	39	37	43
	Mean (SD)	-0.06 (0.27)	-0.01 (0.27)	0.02 (0.20)	-0.05 (0.22)
	Range	(-1.19, 0.42)	(-0.79, 0.44)	(-0.37, 0.39)	(-0.56, 0.35)
IC					
	n	46	39	37	44
	Mean (SD)	0.03 (0.32)	0.06 (0.32)	-0.06 (0.29)	0.03 (0.24)
	Range	(-0.59, 0.85)	(-0.60, 0.91)	(-0.73, 0.61)	(-0.44, 0.59)

BID = twice a day, FEV_1 = forced expiratory volume in 1 second, FEV_6 = forced expiratory volume in 6 seconds, FVC = forced vital capacity, IC = inspiratory capacity, ITT = intent-to-treat, n = number of subjects, SD = standard deviation.

The TDI total focal score at Weeks 2, 4 and 6 is summarized in Table 15. Analysis of the adjusted (for BDI score) mean TDI total focal score at Weeks 2, 4 and 6 showed that there were no statistically significant differences between 0.1 mg BID, 0.4 mg BID or 1.0 mg BID and placebo at any time points in the ITT populations.

Table 15. TDI Total Focal Score (ITT Population)

Time Point	UK-500,001			Double-Blind Placebo BID
	0.1 mg BID	0.4 mg BID	1.0 mg BID	
Baseline				
n	51	50	46	50
Mean (SD)	6.84 (2.06)	6.90 (2.10)	8.04 (1.96)	7.08 (2.10)
Range	(2.00, 11.00)	(3.00, 12.00)	(4.00, 12.00)	(2.00, 12.00)
Week 2				
n	49	48	40	50
Mean (SD)	0.51 (2.15)	0.50 (2.84)	1.48 (1.78)	0.45 (2.01)
Range	(-6.00, 5.00)	(-7.00, 7.00)	(-3.00, 6.00)	(-5.00, 4.50)
Week 4				
n	46	44	39	46
Mean (SD)	1.35 (2.02)	1.34 (2.34)	1.49 (2.74)	0.59 (2.44)
Range	(-5.00, 6.00)	(-3.00, 7.00)	(-5.00, 6.00)	(-6.00, 6.00)
Week 6				
n	46	41	37	46
Mean (SD)	1.11 (2.73)	1.00 (2.38)	1.81 (2.56)	0.80 (3.23)
Range	(-8.00, 6.00)	(-3.00, 6.00)	(-3.00, 6.00)	(-5.00, 12.00)

BID = twice a day, ITT = intent-to-treat, n = number of subjects, SD = standard deviation, TDI = transition dyspnea index.

Changes from Baseline at Weeks 1, 2, 3, 4, 5, 6, 7 and 8 in weekly mean breathlessness score are summarized in Table 16. Analysis of the mean changes from Baseline showed that there were no statistically significant differences between 0.1 mg BID and placebo or 0.4 mg BID and placebo at any time points. Comparison between 1 mg and placebo suggested a trend towards a treatment effect at Week 2 that was not statistically significant.

Table 16. Changes From Baseline in Mean Weekly Breathlessness Score (ITT Population)

Time Point	UK-500,001			Double-Blind Placebo
	0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Baseline (Week 0)				
n	52	52	47	52
Mean (SD)	1.25 (0.67)	1.03 (0.74)	1.13 (0.70)	1.28 (0.75)
Range	(0.00, 2.57)	(0.00, 3.00)	(0.00, 3.00)	(0.00, 3.00)
Week 1				
n	52	52	45	52
Mean (SD)	1.25 (0.67)	1.10 (0.70)	0.94 (0.65)	1.26 (0.72)
Range	(0.00, 2.71)	(0.00, 3.00)	(0.00, 2.29)	(0.00, 2.57)
Week 2				
n	52	52	44	52
Mean (SD)	1.27 (0.68)	1.13 (0.78)	0.98 (0.71)	1.39 (0.77)
Range	(0.00, 3.00)	(0.00, 3.00)	(0.00, 2.83)	(0.00, 3.00)
Week 3				
n	48	47	41	51
Mean (SD)	1.28 (0.74)	1.02 (0.764)	1.02 (0.72)	1.25 (0.73)
Range	(0.00, 3.00)	(0.00, 2.86)	(0.00, 2.43)	(0.00, 3.00)
Week 4 n	46	47	42	51
Mean (SD)	1.25 (0.75)	0.96 (0.70)	1.08 (0.76)	1.28 (0.76)
Range	(0.00, 3.00)	(0.00, 3.00)	(0.00, 2.71)	(0.00, 3.00)
Week 5				
n	46	43	39	46
Mean (SD)	1.22 (0.74)	1.02 (0.66)	0.96 (0.69)	1.24 (0.74)
Range	(0.00, 3.00)	(0.00, 2.86)	(0.00, 2.43)	(0.00, 2.43)
Week 6				
n	46	42	39	46
Mean (SD)	1.26 (0.75)	1.08 (0.76)	1.00 (0.73)	1.28 (0.73)
Range	(0.00, 3.00)	(0.00, 2.86)	(0.00, 2.57)	(0.00, 2.29)
Week 7				
n	46	42	38	46
Mean (SD)	1.28 (0.76)	1.04 (0.68)	1.03 (0.65)	1.31 (0.73)
Range	(0.00, 3.00)	(0.00, 2.71)	(0.00, 2.57)	(0.00, 2.43)
Week 8				
n	45	42	38	46
Mean (SD)	1.28 (0.75)	1.07 (0.71)	1.01 (0.66)	1.30 (0.75)
Range	(0.00, 2.71)	(0.00, 3.00)	(0.00, 2.00)	(0.00, 2.43)

BID = twice a day, ITT = intent-to-treat, n = number of subjects, SD = standard deviation.

Mean change from Baseline at Weeks 1, 2, 3, 4, 5, 6, 7 and 8 in (weekly mean) cough score sputum score, morning PEFR, evening PEFR and rescue bronchodilator usage are summarized in Table 17, Table 18, Table 19, Table 20 and Table 21 respectively. Analysis of the mean changes from Baseline showed that there were no statistically significant

differences between 0.1 mg BID, 0.4 mg BID or 1.0 mg BID and placebo at any time points in the ITT populations.

Table 17. Daily Symptoms Diary: Adjusted Mean Change From Baseline in Weekly Cough Score by Treatment and Week (ITT Population)

Visit	Adjusted Means			
	UK-500,001			Double-Blind Placebo BID
	0.1 mg BID	0.4 mg BID	1.0 mg BID	
Week 1	-0.017	-0.022	-0.055	0.034
Week 2	-0.064	-0.006	-0.056	0.038
Week 3	-0.059	-0.076	-0.108	-0.012
Week 4	-0.096	-0.162	-0.053	0.020
Week 5	-0.092	-0.109	-0.104	-0.006
Week 6	-0.100	-0.077	-0.120	0.080
Week 7	-0.054	-0.140	-0.072	0.138
Week 8	0.004	-0.206	-0.074	0.164

BID = twice a day, ITT = intent-to-treat.

Table 18. Daily Symptoms Diary: Adjusted Mean Change From Baseline in Weekly Sputum Score by Treatment and Week (ITT Population)

Visit	Adjusted Means			
	UK-500,001			Double-Blind Placebo BID
	0.1 mg BID	0.4 mg BID	1.0 mg BID	
Week 1	0.054	0.025	-0.018	0.026
Week 2	0.104	0.112	-0.025	0.005
Week 3	0.123	0.038	-0.050	-0.046
Week 4	0.104	0.012	0.041	-0.063
Week 5	0.033	0.051	-0.035	-0.110
Week 6	0.023	0.126	0.038	-0.006
Week 7	0.044	0.058	-0.001	0.042
Week 8	0.045	-0.018	0.018	0.043

BID = twice a day, ITT = intent-to-treat.

Table 19. Daily Symptoms Diary: Adjusted Mean Change From Baseline in Weekly Morning PEFR (L/min) by Treatment and Week (ITT Population)

Visit	Adjusted Means			
	UK-500,001			Double-Blind Placebo BID
	0.1 mg BID	0.4 mg BID	1.0 mg BID	
Week 1	0.280	-1.006	-1.743	1.937
Week 2	-2.260	-0.674	0.012	0.503
Week 3	-2.565	-0.316	1.823	0.250
Week 4	1.800	-0.441	1.461	-1.877
Week 5	2.681	-3.298	3.752	-0.178
Week 6	1.458	-7.757	-3.015	-1.505
Week 7	-0.751	-4.459	-0.239	-4.884
Week 8	-3.527	-0.401	-4.578	-2.768

BID = twice a day, ITT = intent-to-treat, PEFR = peak exploratory flow rate.

Table 20. Daily Symptoms Diary: Adjusted Mean Change From Baseline in Weekly Evening PEFR (L/min) by Treatment and Week (ITT Population)

Visit	Adjusted Means			
	UK-500,001			Double-Blind Placebo
	0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Week 1	-1.313	4.654	5.259	4.268
Week 2	-0.645	-3.063	4.937	-2.580
Week 3	-3.932	-3.107	2.067	0.198
Week 4	-1.532	-4.413	1.645	-2.040
Week 5	1.611	-4.691	1.317	-2.482
Week 6	-1.544	-11.059	2.091	-3.722
Week 7	-3.034	-7.879	3.946	-6.051
Week 8	-8.195	-8.930	-0.655	-3.447

BID = twice a day, ITT = intent-to-treat, PEFR = peak exploratory flow rate.

Table 21. Daily Symptoms Diary: Adjusted Mean Change From Baseline in Weekly Rescue Bronchodilator (Puffs) Usage by Treatment and Week (ITT Population)

Visit	Adjusted Means			
	UK-500,001			Double-Blind Placebo
	0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
Week 1	0.024	-0.161	-0.119	0.097
Week 2	0.042	-0.059	-0.027	0.336
Week 3	0.129	0.021	0.060	0.345
Week 4	0.223	0.048	0.172	0.444
Week 5	0.327	-0.087	0.217	0.533
Week 6	0.476	0.170	0.278	0.463
Week 7	0.603	0.221	0.230	0.793
Week 8	0.823	0.352	0.286	0.881

BID = twice a day, ITT = intent-to-treat.

The treatment comparisons for global impression of change clinician score (GICCS) and global impression of change subject score (GICSC) at Week 6 for the ITT population are summarized in Table 22. There was no statistically significant improvement in the disease condition observed in global impression of change (clinician) assessment at the End of the Study, however there was a trend towards greater improvement in the 1.0 mg BID group compared to placebo. There was a statistically significant difference between the 1 mg BID group and placebo in the global impression of change (subject) assessment.

Table 22. Treatment Comparison Versus Placebo* at Week 6 (ITT Population)

Assessments, n (%)	UK-500,001		
	0.1 mg BID	0.4 mg BID	1.0 mg BID
GICCS			
Odds ratio (SE)	0.601 (0.239)	0.712 (0.288)	1.187 (0.495)
P-value	0.100	0.201	0.341
90% confidence interval	(0.313, 1.155)	(0.366, 1.385)	(0.598, 2.355)
GICSC			
Odds ratio (SE)	1.030 (0.403)	0.939 (0.372)	2.359 (0.969)
P-value	0.470	0.437	0.018
90% confidence interval	(0.541, 1.959)	(0.490, 1.800)	(1.200, 4.636)

* Using the Bonferroni-Holm step-down procedure to control the overall Type I error rate at 5% (1-sided testing). Only significant p-values (as defined by Bonferroni-Holm procedure) were reported.
BID = twice a day, GICCS = global impression of change clinician score, GICSC = global impression of change subject score, ITT = intent-to-treat, n = number of subjects, SE = standard error.

There were no statistically significant differences between any of the UK-500,001 treatment groups and placebo at Week 6 in the primary or secondary analyses (with the exception of the GICSC). In addition, the magnitudes of treatment effects were small and not deemed to be clinically significant. However, there were a number of analyses that showed a clinically meaningful and statistically significant treatment effect at Week 2.

Safety Results:

AEs: The incidence of all-causality treatment-emergent AEs is given in Table 23 and the incidence of the treatment-related treatment-emergent AEs is given in Table 24.

A number of subjects reported COPD exacerbations, however the incidence of COPD exacerbations reported reflects only those AEs reported specifically as COPD exacerbation by the Investigator. Headache was the most frequently reported treatment-related AE followed by diarrhea. This is consistent with findings in earlier studies in healthy volunteers and could be considered to be related to phosphodiesterase type 4 inhibition. Dizziness and diarrhea were reported as treatment-related AEs in the UK-500,001 treatment groups but not in the double-blind placebo group. The majority of treatment-related AEs were reported as mild in severity. There were 2 COPD exacerbations reported as treatment-related during the study, in 1 subject this was recorded as a severe exacerbation (0.4 mg BID group) of and in the second subject recorded as moderate (1.0 mg BID group).

Table 23. Incidence of Treatment-Emergent Adverse Events (All-Causalities)

System Organ Class and MedDRA Preferred Term	UK-500,001			Double-Blind Placebo BID, N=53
	0.1 mg BID, N=53 n (%)	0.4 mg BID, N=55 n (%)	1.0 mg BID, N=48 n (%)	n (%)
Blood and lymphatic system disorders	0	0	0	1 (1.9)
Anaemia	0	0	0	1 (1.9)
Cardiac disorders	0	1 (1.8)	1 (2.1)	1 (1.9)
Aortic valve incompetence	0	1 (1.8)	0	0
Atrioventricular block second degree	0	0	1 (2.1)	0
Tachycardia	0	0	0	1 (1.9)
Endocrine disorders	0	0	0	1 (1.9)
Goitre	0	0	0	1 (1.9)
Eye disorders	1 (1.9)	2 (3.6)	1 (2.1)	0
Conjunctivitis	1 (1.9)	0	0	0
Eye irritation	0	1 (1.8)	0	0
Eye pruritus	0	1 (1.8)	0	0
Glaucoma	0	0	1 (2.1)	0
Gastrointestinal disorders	3 (5.7)	5 (9.1)	5 (10.4)	2 (3.8)
Abdominal pain upper	0	0	1 (2.1)	0
Change of bowel habit	0	1 (1.8)	0	0
Diarrhoea	2 (3.8)	4 (7.3)	3 (6.3)	1 (1.9)
Dry mouth	0	0	0	1 (1.9)
Dyspepsia	0	0	1 (2.1)	0
Dysphagia	0	0	1 (2.1)	0
Faeces discoloured	0	1 (1.8)	0	0
Gastrooesophageal reflux disease	0	1 (1.8)	0	0
Hyperchlorhydria	0	0	1 (2.1)	0
Nausea	1 (1.9)	0	1 (2.1)	0
General disorders and administration site conditions	2 (3.8)	2 (3.6)	0	1 (1.9)
Crepitations	1 (1.9)	1 (1.8)	0	1 (1.9)
Fatigue	0	1 (1.8)	0	0
Oedema peripheral	1 (1.9)	0	0	0
Hepatobiliary disorders	0	0	0	1 (1.9)
Cholelithiasis	0	0	0	1 (1.9)
Infections and infestations	5 (9.4)	11 (20.0)	6 (12.5)	8 (15.1)
Abdominal wall infection	0	0	0	1 (1.9)
Acute sinusitis	0	0	0	1 (1.9)

Table 23. Incidence of Treatment-Emergent Adverse Events (All-Causalities)

System Organ Class and MedDRA Preferred Term	UK-500,001			Double-Blind Placebo BID, N=53
	0.1 mg BID, N=53 n (%)	0.4 mg BID, N=55 n (%)	1.0 mg BID, N=48 n (%)	n (%)
Bronchitis	1 (1.9)	0	1 (2.1)	0
Bronchitis acute	0	1 (1.8)	0	0
Cystitis	0	1 (1.8)	0	0
Gastroenteritis	0	0	0	1 (1.9)
Infection	0	0	0	1 (1.9)
Influenza	0	2 (3.6)	0	2 (3.8)
Lower respiratory tract infection	0	0	0	1 (1.9)
Lung infection	1 (1.9)	0	0	1 (1.9)
Nasopharyngitis	1 (1.9)	1 (1.8)	2 (4.2)	0
Pneumonia	1 (1.9)	2 (3.6)	0	0
Respiratory tract infection	0	0	1 (2.1)	0
Rhinitis	2 (3.8)	0	0	1 (1.9)
Sinusitis	0	0	1 (2.1)	0
Upper respiratory tract infection	0	2 (3.6)	1 (2.1)	2 (3.8)
Urinary tract infection	0	2 (3.6)	0	1 (1.9)
Injury, poisoning and procedural complications	0	1 (1.8)	0	1 (1.9)
Contusion	0	0	0	1 (1.9)
Muscle strain	0	1 (1.8)	0	0
Investigations	0	0	2 (4.2)	4 (7.5)
Abdominal bruit	0	0	0	1 (1.9)
Blood glucose increased	0	0	0	1 (1.9)
Cardiac murmur	0	0	0	1 (1.9)
Gamma-glutamyltransferase increased	0	0	1 (2.1)	0
Hepatic enzyme increased	0	0	0	1 (1.9)
Intraocular pressure increased	0	0	1 (2.1)	0
Metabolism and nutrition disorders	0	1 (1.8)	0	1 (1.9)
Hyperkalaemia	0	0	0	1 (1.9)
Hypoglycaemia	0	1 (1.8)	0	0
Musculoskeletal and connective tissue disorders	0	3 (5.5)	0	0
Arthralgia	0	1 (1.8)	0	0
Back pain	0	1 (1.8)	0	0
Musculoskeletal pain	0	1 (1.8)	0	0

Table 23. Incidence of Treatment-Emergent Adverse Events (All-Causalities)

System Organ Class and MedDRA Preferred Term	UK-500,001			Double-Blind Placebo BID, N=53
	0.1 mg BID, N=53 n (%)	0.4 mg BID, N=55 n (%)	1.0 mg BID, N=48 n (%)	n (%)
Nervous system disorders	5 (9.4)	1 (1.8)	6 (12.5)	2 (3.8)
Dizziness	2 (3.8)	0	1 (2.1)	0
Dysgeusia	1 (1.9)	0	0	0
Headache	3 (5.7)	1 (1.8)	5 (10.4)	1 (1.9)
Sinus headache	0	0	0	1 (1.9)
Psychiatric disorders	0	1 (1.8)	0	0
Insomnia	0	1 (1.8)	0	0
Renal and urinary disorders	0	0	0	1 (1.9)
Haematuria	0	0	0	1 (1.9)
Respiratory, thoracic and mediastinal disorders	6 (11.3)	10 (18.2)	5 (10.4)	7 (13.2)
Bronchospasm	1 (1.9)	0	0	0
Chronic obstructive pulmonary disease	2 (3.8)	7 (12.7)	4 (8.3)	4 (7.5)
Cough	2 (3.8)	2 (3.6)	0	0
Dyspnoea	1 (1.9)	0	1 (2.1)	2 (3.8)
Epistaxis	0	0	0	1 (1.9)
Foreign body aspiration	0	1 (1.8)	0	0
Pharyngeal ulceration	0	1 (1.8)	0	0
Pharyngolaryngeal pain	0	1 (1.8)	0	0
Rhinorrhoea	1 (1.9)	0	0	0
Wheezing	0	0	1 (2.1)	0
Skin and subcutaneous tissue disorders	1 (1.9)	0	1 (2.1)	1 (1.9)
Dermatitis allergic	0	0	1 (2.1)	0
Rash	0	0	0	1 (1.9)
Skin reaction	1 (1.9)	0	0	0
Vascular disorders	1 (1.9)	1 (1.8)	0	0
Flushing	0	1 (1.8)	0	0
Hypertension	1 (1.9)	0	0	0
Total preferred term events	27	43	31	36

Included data up to 7 days after last dose of study drug.
MedDRA (version 9.1) coding dictionary applied.
BID = twice a day, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects evaluable for adverse events; n = number of subjects meeting specified criteria.

Table 24. Incidence of Treatment-Emergent Adverse Events (Treatment-Related)

System Organ Class and MedDRA Preferred Term	UK-500,001			Double-Blind Placebo BID, N=53
	0.1 mg BID, N=53 n (%)	0.4 mg BID, N=55 n (%)	1.0 mg BID, N=48 n (%)	n (%)
Cardiac disorders	0	0	0	1 (1.9)
Tachycardia	0	0	0	1 (1.9)
Eye disorders	0	1 (1.8)	0	0
Eye pruritus	0	1 (1.8)	0	0
Gastrointestinal disorders	1 (1.9)	3 (5.5)	1 (2.1)	1 (1.9)
Abdominal pain upper	0	0	1 (2.1)	0
Change of bowel habit	0	1 (1.8)	0	0
Diarrhoea	1 (1.9)	2 (3.6)	1 (2.1)	0
Dry mouth	0	0	0	1 (1.9)
Dysphagia	0	0	1 (2.1)	0
Faeces discoloured	0	1 (1.8)	0	0
Gastrooesophageal reflux disease	0	1 (1.8)	0	0
General disorders and administration site conditions	0	1 (1.8)	0	0
Fatigue	0	1 (1.8)	0	0
Infections and infestations	1 (1.9)	1 (1.8)	1 (2.1)	1 (1.9)
Nasopharyngitis	1 (1.9)	1 (1.8)	0	0
Sinusitis	0	0	1 (2.1)	0
Upper respiratory tract infection	0	0	0	1 (1.9)
Investigations	0	0	1 (2.1)	0
Intraocular pressure increased	0	0	1 (2.1)	0
Musculoskeletal and connective tissue disorders	0	2 (3.6)	0	0
Arthralgia	0	1 (1.8)	0	0
Musculoskeletal pain	0	1 (1.8)	0	0
Nervous system disorders	4 (7.5)	0	5 (10.4)	1 (1.9)
Dizziness	1 (1.9)	0	1 (2.1)	0
Dysgeusia	1 (1.9)	0	0	0
Headache	2 (3.8)	0	4 (8.3)	1 (1.9)
Respiratory, thoracic and mediastinal disorders	1 (1.9)	3 (5.5)	2 (4.2)	3 (5.7)
Chronic obstructive pulmonary disease	0	1 (1.8)	1 (2.1)	0
Cough	1 (1.9)	0	0	0
Dyspnoea	0	0	1 (2.1)	2 (3.8)
Epistaxis	0	0	0	1 (1.9)

Table 24. Incidence of Treatment-Emergent Adverse Events (Treatment-Related)

System Organ Class and MedDRA Preferred Term	UK-500,001			Double-Blind Placebo BID, N=53 n (%)
	0.1 mg BID, N=53 n (%)	0.4 mg BID, N=55 n (%)	1.0 mg BID, N=48 n (%)	
Pharyngeal ulceration	0	1 (1.8)	0	0
Pharyngolaryngeal pain	0	1 (1.8)	0	0
Wheezing	0	0	1 (2.1)	0
Vascular disorders	0	1 (1.8)	0	0
Flushing	0	1 (1.8)	0	0
Total preferred term events	7	14	13	7

Included data up to 7 days after last dose of study drug.
MedDRA (version 9.1) coding dictionary applied.
BID = twice a day, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects evaluable for adverse events; n = number of subjects meeting specified criteria.

Serious AEs (SAEs): All reported SAEs occurring during the study and at the end of the treatment are summarized in Table 25.

Six (6) subjects experienced treatment-emergent SAEs. Of these 4 subjects experienced SAEs during the pre-treatment run-in period, and 1 subject experienced a SAE 2 weeks after the drug had been discontinued.

There were 2 SAEs which were reported during the post-randomization dosing period. One (1) SAE (abdominal pain upper) reported in 1 subject (1.0 mg BID group) was considered to be treatment-related and this subject subsequently withdrew from the study due to diarrhea. One (1) SAE (pneumonia) which led to permanent discontinuation from the study was reported for 1 subject.

Table 25. Summary of Serious Adverse Events

Serial Number	Serious Adverse Event	Investigator Causality	Suspect Drug (Total Daily Dose at Onset)	Action Taken	Outcome
1	Constipation	Other	UK-500,001 (0.8 mg/day)	Post-therapy: drug previously discontinued	Recovered
2	Abdominal pain upper	Study drug	UK-500,001 (2 mg/day)	No Action Taken	Recovered
3	Pneumonia	Other illness	UK-500,001 (0.8 mg/day)	Permanently discontinued	Recovered
4	Pneumothorax	Disease under study	Pre-randomization (unknown)	No Action Taken	Recovered
5	Cardiac arrest	Other	Pre-randomization (unknown)	No Action Taken	Death
6	Bronchitis acute	Disease under study	Pre-randomization (unknown) Ipratropium (0.042 mg/day) Salbutamol (unknown)	No Action Taken No Action Taken No Action Taken	Recovered

Permanent Discontinuations Due to AEs: The permanent discontinuations due to AEs are summarized in Table 26. There were 11 subjects who discontinued due to AEs, out of which 3 subjects discontinued due to treatment-related AEs.

Table 26. Permanent Discontinuations Due to Adverse Events

Serial Number	MedDRA Preferred Term	Treatment at Onset	Severity/Outcome	Causality
1	Dyspnoea	UK-500,001 (0.1 mg BID)	Moderate/still present	Other illness-subject had a cold
2	Bronchitis	UK-500,001 (0.1 mg BID)	Moderate/still present	Other-infection (unknown etiology)
	COPD	UK-500,001 (0.1 mg BID)	Moderate/still present	Other-bronchitis
3	Diarrhoea	UK-500,001 (0.4 mg BID)	Mild/resolved	Study drug
	GORD	UK-500,001 (0.4 mg BID)	Moderate/ resolved	Study drug
4	COPD	UK-500,001 (0.4 mg BID)	Mild/still present	Other-exacerbation of COPD
5	Pneumonia	UK-500,001 (0.4 mg BID)	Moderate/ resolved	Other illness-bacterial infection
6	COPD	UK-500,001 (0.4 mg BID)	Moderate/still present	Other illness-bacterial infection
7	COPD	UK-500,001 (0.4 mg BID)	Moderate/resolved	Disease under study
8	COPD	UK-500,001 (0.4 mg BID)	Severe/resolved	Study drug
9	Diarrhoea	UK-500,001 (1.0 mg BID)	Moderate/still present	Study drug
	Dysphagia	UK-500,001 (1.0 mg BID)	Moderate/still present	Study drug
10	A-V block second degree	UK-500,001 (1.0 mg BID)	Moderate/still present	Other illness-pre-existing A-V block first degree
11	Glaucoma	UK-500,001 (1.0 mg BID)	Moderate/resolved	Concomitant treatment-ipratropium

A-V = atrioventricular, BID = twice a day, COPD = chronic obstructive pulmonary disease, GORD = gastro-oesophageal reflux disease, MedDRA = Medical Dictionary for Regulatory Activities.

Dose Reductions or Temporary Discontinuations Due to Adverse Events: One (1) subject in the double-blind placebo group had a temporary discontinuation due to a mild AE of tachycardia. The AE was considered to be related to the study drug and treatment was stopped temporarily until resolution when treatment was recommenced. There were no discontinuations due to abnormal laboratory test results.

Death: There was 1 death reported during this study. The subject died prior to randomization of the study drug due to a cardiac arrest. The day of death (study day) was not available.

Clinical Laboratory Tests: Regardless of baseline values, the incidence of laboratory abnormalities was low among all treated groups. A similar proportion of subjects in each treatment group experienced laboratory abnormalities, ranging from 33-55% across treatment groups. There were no drug-related trends.

Median changes in laboratory parameter values from Baseline to last observation were small and comparable among treatment groups. There were no clinically significant median changes from Baseline to last observation for any laboratory value (Table 27).

Table 27. Laboratory Test Data: Median Changes From Baseline to Last Observation

Parameters Units	UK-500,001									Double-Blind Placebo BID		
	0.1 mg BID			0.4 mg BID			1.0 mg BID					
	N	Baseline Median	Median Change From Baseline	N	Baseline Median	Median Change From Baseline	N	Baseline Median	Median Change From Baseline	N	Baseline Median	Median Change From Baseline
Hemoglobin, g/dL	53	15.7	-0.2	52	16.1	-0.2	46	15.8	-0.2	53	15.8	-0.3
Hematocrit, %	53	49	-1	52	50	0	46	49.1	0	53	49	-1
RBC count, 10^6/mm^3	53	5.22	-0.06	52	5.14	-0.06	46	5.22	-0.06	53	5.08	-0.1
MCV, 10^{-15}L	53	93	0	52	93	0	46	93	0	53	94	0
MCHC, g/dL	53	33	0	52	33.2	-0.2	46	33	0	53	33.3	-0.1
Platelets, 10^3/mm^3	53	257	-2	52	263	-2	46	251	7	51	238	-4
WBC count, 10^3/mm^3	53	7.8	-0.2	52	6.9	0.1	46	6.7	0.1	53	7.3	-0.3
Lymphocytes (abs), 10^3/mm^3	53	2.2	-0.1	52	1.85	0	46	2.1	-0.05	53	2	0
Total neutrophils (abs), 10^3/mm^3	53	4.5	0	52	4.25	0.1	46	4	0.2	53	4.6	-0.1
Basophils (abs), 10^3/mm^3	53	0	0	52	0	0	46	0	0	53	0	0
Eosinophils (abs), 10^3/mm^3	53	0.3	0	52	0.2	0	46	0.1	0	53	0.2	0
Monocytes (abs), 10^3/mm^3	53	0.5	0	52	0.5	0	46	0.5	0	53	0.5	0
Total bilirubin, mg/dL	53	0.5	0	52	0.5	0	46	0.4	0	52	0.5	0
AST (SGOT), IU/L	53	25	0	52	26	-1	46	26	-1	52	26	1
ALT (SGPT), IU/L	53	21	0	52	24	1	46	24	-1	52	22	0
Gamma GT, IU/L	53	28	-3	52	29	1	46	31	-1	53	32	0
Alkaline phosphatase, IU/L	53	80	0	52	83	-2	46	76	-1	52	81	1
Total protein, g/dL	53	7.2	0	52	7.2	0	46	7.2	0	53	7	0
Albumin, g/dL	53	4.5	0	52	4.4	0	46	4.5	0	53	4.4	-0.1
BUN, mg/dL	53	35.1	-0.5	52	35.3	0	46	34.1	0.6	53	34.6	0.9
Creatinine, mg/dL	53	1.1	0	52	1	0	46	1	0	53	1	0
Uric acid, mg/dL	53	4	-0.1	52	4	-0.2	46	4.5	-0.2	53	4	0
Sodium, meq/L	53	142	-1	52	142	0	46	142	0	52	142	0
Potassium, meq/L	53	4.6	-0.1	52	4.5	0	46	4.6	0	52	4.5	0
Chloride, meq/L	53	103	0	52	103	0	46	104	0	52	104	-1
Calcium, mg/dL	53	9.9	0	52	9.9	0	46	9.9	-0.1	53	9.8	0
Bicarbonate, meq/L	53	26.4	-0.4	52	26.9	-1.1	46	26.4	0.2	52	26.4	-0.8
Glucose (random), mg/dL	53	88	0	52	87	0	46	92	-2	53	90	-1

Table 27. Laboratory Test Data: Median Changes From Baseline to Last Observation

Last observation was defined as last observation while on study drug or during the lag.
Normalized data were used in the computations.
Abs = absolute; ALT = alanine transaminase, AST = aspartate aminotransferase, BID = twice a day, BUN = blood urea nitrogen, GT = glutamyl transferase, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, N = number of subjects, RBC = red blood cells, SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamate pyruvate transaminase, WBC = white blood cells.

Vital Signs and 12-Lead ECG: No clinical or statistically significant changes in vital signs were observed for any treatment group (Table 28). No significant differences were observed in ECG data between the treatment groups (Table 29). No subject had QTcF ≥500 msec in any of the 4 treatment groups. An increase of ≥60 msec from Baseline was seen in 1 subject each in the 0.1 mg BID and 0.4 mg BID groups, 2 subjects in the 1.0 mg BID group and 6 subjects in the double-blind placebo BID group.

Table 28. Vital Signs - Changes From Baseline

Study Day of Exam/ Collection	Time Post-Dose (Hours)	Parameters	Adjusted Means			
			UK-500,001			Double-Blind Placebo BID
			0.1 mg BID	0.4 mg BID	1.0 mg BID	
Supine Systolic BP (mm Hg)						
Week 0	0.25	N	52	53	48	53
		Mean	-0.3	0.0	1.5	-2.0
		SD	7.01	8.75	6.64	6.70
		Median	0.0	0.0	0.0	0.0
		Min	-20	-20	-11	-20
		Max	17	20	25	13
Week 2	0.25	N	50	48	43	52
		Mean	-1.7	-3.2	-3.3	-1.5
		SD	12.75	14.15	12.51	14.15
		Median	-1.0	-1.0	-3.0	0.0
		Min	-30	-30	-30	-30
		Max	30	30	30	30
Week 4	0.25	N	47	44	41	47
		Mean	-3.6	-4.5	-3.3	-2.3
		SD	15.16	13.59	15.93	14.07
		Median	-5.0	-2.0	-4.0	-3.0
		Min	-30	-30	-40	-25
		Max	35	35	30	27
Week 6	0	N	47	43	38	47
		Mean	-1.9	-5.2	-3.9	-2.8
		SD	16.11	13.06	15.25	14.13
		Median	-3.0	-5.0	-2.0	-1.0
		Min	-40	-35	-45	-30
		Max	34	20	40	25
	0.25	N	47	41	39	47
		Mean	-4.7	-5.8	-3.8	-2.8
		SD	13.52	15.54	13.90	15.56
		Median	-5.0	-5.0	-6.0	-2.0
		Min	-35	-40	-50	-40
		Max	20	27	30	30
Supine Diastolic BP (mm Hg)						
Week 0	0.25	N	52	53	48	53
		Mean	-1.4	0.1	-0.7	0.5
		SD	6.83	5.46	6.29	6.69
		Median	0.0	0.0	0.0	0.0
		Min	-15	-10	-20	-17
		Max	20	11	10	20
Week 2	0.25	N	50	48	43	52
		Mean	-1.8	-2.9	-1.1	-0.2
		SD	9.41	7.13	8.95	11.11
		Median	-1.0	0.0	0.0	0.0
		Min	-25	-20	-20	-20
		Max	18	10	20	38
Week 4	0.25	N	47	44	41	47
		Mean	-1.5	-0.3	-2.2	-1.0
		SD	10.11	9.65	10.87	11.96
		Median	0.0	0.0	-2.0	0.0
		Min	-20	-25	-30	-30
		Max	20	20	20	35

Table 28. Vital Signs - Changes From Baseline

Study Day of Exam/ Collection	Time Post-Dose (Hours)	Parameters	Adjusted Means			
			UK-500,001			Double-Blind Placebo BID
			0.1 mg BID	0.4 mg BID	1.0 mg BID	
Week 6	0	N	47	43	38	47
		Mean	-0.8	-0.8	-2.3	-0.0
		SD	11.58	9.23	11.78	9.86
		Median	0.0	0.0	-1.5	0.0
		Min	-30	-20	-25	-20
		Max	26	25	30	25
	0.25	N	47	41	39	47
		Mean	-1.6	-1.0	-2.4	0.7
		SD	10.34	8.49	11.01	10.77
		Median	0.0	0.0	0.0	0.0
		Min	-31	-20	-25	-20
		Max	20	20	24	25
Supine Pulse Rate (bpm)						
Week 0	0.25	N	52	53	48	53
		Mean	-0.3	-0.2	-1.1	-0.2
		SD	4.93	5.23	5.24	5.27
		Median	0.0	0.0	-1.5	0.0
		Min	-12	-12	-11	-16
		Max	11	15	13	13
Week 2	0.25	N	50	48	43	52
		Mean	0.0	1.1	0.6	0.9
		SD	7.77	6.92	7.97	7.04
		Median	0.0	0.0	0.0	0.0
		Min	-24	-16	-15	-16
		Max	16	16	22	15
Week 4	0.25	N	47	44	41	47
		Mean	0.1	0.6	0.7	1.6
		SD	9.02	9.08	7.20	8.15
		Median	1.0	0.0	0.0	0.0
		Min	-22	-20	-16	-15
		Max	25	26	18	16
Week 6	0	N	47	43	38	47
		Mean	-0.4	0.7	-0.4	2.1
		SD	8.94	7.52	10.09	9.77
		Median	-2.0	2.0	-0.5	1.0
		Min	-20	-14	-22	-16
		Max	28	16	30	30
	0.25	N	47	41	39	47
		Mean	-0.9	-0.4	-0.9	0.4
		SD	8.32	6.89	7.96	8.37
		Median	-2.0	0.0	-3.0	-2.0
		Min	-14	-13	-12	-13
		Max	24	11	17	25

Means and medians were determined within a subject prior to summarizing across subjects.
Day was relative to first day of first treatment period (Day 1).
Note: The mean listed was the change from Baseline for all times post-dose after Baseline.
The minimum and maximum values were determined from all values recorded.
Unplanned readings were excluded from the presentation.
BID = twice a day, BP = blood pressure, Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation.

Table 29. ECG Parameters: Mean Baseline and Mean Changes From Baseline at Weeks 0 and 6

Study Day of Exam/ Collection	Time Post-Dose (Hours)	Parameters	Adjusted Means			
			UK-500,001			Double-Blind Placebo BID
			0.1 mg BID	0.4 mg BID	1.0 mg BID	
RR Interval (msec)						
Baseline		N	52	53	48	53
		Mean	820.4	828.6	815.8	869.4
		SD	174.02	163.29	230.90	175.75
		Median	823.5	827.0	861.0	880.0
		Min	72	92	76	82
		Max	1080	1092	1120	1200
Week 0	1	N	52	53	47	53
		Mean	41.5	28.8	28.7	24.8
		SD	68.06	114.87	142.45	71.45
		Median	40.0	0.0	6.0	30.0
		Min	-120	-227	-240	-114
		Max	206	540	727	220
Baseline		N	46	41	38	47
		Mean	817.0	841.7	846.2	859.6
		SD	167.89	187.17	212.81	219.01
		Median	800.0	867.0	820.0	880.0
		Min	96	104	92	96
		Max	1078	1280	1320	1250
Week 6	1	N	46	41	38	47
		Mean	33.4	21.7	37.9	33.2
		SD	70.01	51.61	72.91	132.00
		Median	40.0	6.0	36.0	0.0
		Min	-204	-120	-80	-160
		Max	174	124	280	746
Heart Rate (bpm)						
Baseline		N	52	53	48	53
		Mean	73.4	73.0	71.3	69.6
		SD	10.65	11.07	12.39	11.00
		Median	73.0	72.0	68.0	70.0
		Min	56	54	54	50
		Max	98	97	102	107
Week 0	1	N	52	53	48	53
		Mean	-3.3	-2.4	-0.9	-2.9
		SD	5.45	6.97	7.17	6.07
		Median	-3.5	-1.0	-1.0	-2.0
		Min	-15	-34	-18	-16
		Max	17	15	23	15
Baseline		N	47	41	38	47
		Mean	72.9	71.3	71.0	69.5
		SD	10.39	11.82	12.45	12.91
		Median	75.0	71.0	71.0	68.0
		Min	56	48	49	47
		Max	100	98	99	107
Week 6	1	N	47	41	38	47
		Mean	-3.2	-1.5	-2.7	-1.6
		SD	5.12	4.31	5.52	6.76
		Median	-4.0	-1.0	-3.0	-1.0

Table 29. ECG Parameters: Mean Baseline and Mean Changes From Baseline at Weeks 0 and 6

Study Day of Exam/ Collection	Time Post-Dose (Hours)	Parameters	Adjusted Means			
			UK-500,001			Double-Blind Placebo BID
			0.1 mg BID	0.4 mg BID	1.0 mg BID	
		Min	-11	-9	-16	-17
		Max	15	12	10	12
PR Interval (msec)						
Baseline		N	52	53	48	53
		Mean	156.3	163.8	161.2	152.1
		SD	22.07	30.08	33.01	24.56
		Median	160.0	160.0	160.0	160.0
		Min	120	118	112	100
		Max	219	260	320	220
Week 0	1	N	52	53	48	53
		Mean	1.9	-2.3	0.8	2.0
		SD	13.74	11.88	8.10	11.84
		Median	0.0	0.0	0.0	0.0
		Min	-56	-60	-20	-20
		Max	40	32	26	48
Baseline		N	47	41	38	46
		Mean	153.9	159.3	159.2	159.2
		SD	20.70	25.06	24.65	23.08
		Median	160.0	160.0	160.0	160.0
		Min	100	110	120	118
		Max	202	216	220	220
Week 6	1	N	47	41	38	46
		Mean	1.9	0.7	-0.6	0.1
		SD	12.05	10.00	13.71	10.28
		Median	0.0	0.0	0.0	0.0
		Min	-44	-34	-40	-33
		Max	40	24	40	40
QRS Complex (msec)						
Baseline		N	52	53	48	53
		Mean	83.9	85.0	85.3	88.3
		SD	16.02	19.85	17.37	27.80
		Median	80.0	80.0	82.5	80.0
		Min	40	17	25	40
		Max	130	136	130	234
Week 0	1	N	52	53	48	53
		Mean	0.7	2.6	-1.9	0.5
		SD	9.58	22.40	10.32	9.70
		Median	0.0	0.0	0.0	0.0
		Min	-20	-15	-47	-35
		Max	53	160	15	40
Baseline		N	47	41	38	47
		Mean	88.9	89.0	84.5	85.8
		SD	23.36	19.98	10.26	21.45
		Median	82.0	80.0	80.0	82.0
		Min	70	36	58	22
		Max	230	142	114	150
Week 6	1	N	47	41	38	47
		Mean	-4.3	-0.5	0.2	3.9

Table 29. ECG Parameters: Mean Baseline and Mean Changes From Baseline at Weeks 0 and 6

Study Day of Exam/ Collection	Time Post-Dose (Hours)	Parameters	Adjusted Means			
			UK-500,001			Double-Blind Placebo
			0.1 mg BID	0.4 mg BID	1.0 mg BID	BID
		SD	22.84	10.62	4.58	29.46
		Median	0.0	0.0	0.0	0.0
		Min	-150	-20	-10	-40
		Max	7	55	20	195
QT Interval (msec)						
Baseline		N	52	53	48	53
		Mean	375.0	378.7	380.1	379.1
		SD	29.18	30.60	33.52	32.39
		Median	378.0	377.0	385.5	380.0
		Min	320	320	292	260
		Max	440	440	446	461
Week 0	1	N	52	53	48	53
		Mean	4.2	4.4	6.8	7.4
		SD	24.39	21.02	22.98	25.17
		Median	0.0	0.0	3.0	4.0
		Min	-80	-40	-46	-40
		Max	100	80	40	87
Baseline		N	47	41	38	47
		Mean	375.5	377.0	380.5	387.1
		SD	29.99	36.00	31.56	37.35
		Median	370.0	378.0	380.0	388.0
		Min	320	315	324	312
		Max	440	480	445	481
Week 6	1	N	47	41	38	47
		Mean	7.0	5.0	2.1	0.9
		SD	15.72	19.32	17.26	21.34
		Median	4.0	0.0	0.0	0.0
		Min	-40	-40	-40	-40
		Max	60	73	40	55
QTc Interval (msec)						
Baseline		N	52	53	48	53
		Mean	410.4	412.9	410.2	403.0
		SD	25.03	24.27	28.80	25.65
		Median	411.0	414.0	414.0	407.0
		Min	316	353	280	296
		Max	467	459	466	450
Week 0	1	N	52	53	48	53
		Mean	-5.7	-1.7	3.9	2.4
		SD	24.81	21.42	21.05	30.23
		Median	-3.5	0.0	2.0	0.0
		Min	-83	-74	-46	-67
		Max	79	56	45	110
Baseline		N	47	41	38	47
		Mean	410.0	405.4	409.1	411.9
		SD	18.93	27.49	23.19	29.01
		Median	408.0	406.0	405.5	413.0
		Min	357	337	353	341
		Max	448	460	465	479

Table 29. ECG Parameters: Mean Baseline and Mean Changes From Baseline at Weeks 0 and 6

Study Day of Exam/ Collection	Time Post-Dose (Hours)	Parameters	Adjusted Means			
			UK-500,001			Double-Blind Placebo BID
			0.1 mg BID	0.4 mg BID	1.0 mg BID	
Week 6	1	N	47	41	38	47
		Mean	-0.4	1.5	-2.9	-5.1
		SD	17.52	24.96	22.46	25.01
		Median	0.0	0.0	-2.0	0.0
		Min	-63	-57	-71	-59
		Max	46	99	43	85
QTcF Interval (Fridericia's Correction) (msec)						
Baseline		N	52	53	48	53
		Mean	399.2	402.3	400.1	396.0
		SD	22.99	23.56	26.23	25.12
		Median	401.0	403.0	402.0	398.0
		Min	322	345	284	284
		Max	440	450	440	440
Week 0	1	N	52	53	48	53
		Mean	-2.7	-0.5	4.5	2.5
		SD	21.78	18.52	21.48	27.67
		Median	-0.5	0.0	1.0	0.0
		Min	-81	-43	-47	-71
		Max	83	60	47	103
Baseline		N	47	41	38	47
		Mean	398.7	396.8	399.9	403.4
		SD	20.16	26.71	21.82	27.89
		Median	396.0	397.0	397.0	401.0
		Min	345	330	360	330
		Max	440	448	437	472
Week 6	1	N	47	41	38	47
		Mean	1.3	2.3	-3.4	-2.2
		SD	15.48	21.76	19.98	23.48
		Median	0.0	0.0	-2.5	0.0
		Min	-45	-38	-60	-49
		Max	42	89	42	70

Means and medians were determined within a subject prior to summarizing across subjects.
Subjects were counted once for each treatment.
Follow-up data were excluded even if it occurred within the lag period.
Note: The mean listed was the change from Baseline (Week 0 and Week 6) for all times post-dose after Baseline.
The minimum and maximum values were determined from all values recorded.
Unplanned readings were excluded from the presentation.
BID = twice a day, ECG = electrocardiogram, Max = maximum, Min = minimum, N = number of subjects, QTc = corrected QT interval, QTcF = corrected QT interval (Fridericia's formula), SD = standard deviation.

Physical Examination: Physical examination findings were unremarkable.

FEV_1 Assessment: There was no change observed in post-study FEV_1 compared to pre-study drug at Week 0.

CONCLUSIONS: In conclusion, this appeared to be a well-designed and technically sound study in a representative population of moderate-severe COPD subjects. UK-500,001 up to dosages of 1 mg BID for 6 weeks appeared to be generally safe and well tolerated. After 6 weeks of treatment it appeared to provide no benefit compared to placebo on any assessment of efficacy.