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COMPOUND NUMBER: UK-432,097

PROTOCOL NO.: A3971013

PROTOCOL TITLE: A Phase II, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of UK- 432,097 Dry Powder for Inhalation in Adults With Moderate to Severe Chronic Obstructive Pulmonary Disease

Study Centers: A total of 19 centers took part in the study and subjects randomized to study treatment: 4 in Australia, 4 in Canada, 2 in the Netherlands, 4 in Poland and 5 in the United Kingdom.

Study Initiation and Final Completion Dates: 13 March 2007 to 16 July 2008

The study was terminated prematurely.

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To evaluate the efficacy and safety/tolerability of UK-432,097 (It is an adenosine A_{2a} receptor agonist that has been shown to inhibit the inappropriate activation of human inflammatory cells, in particular the neutrophil, which are believed central to chronic obstructive pulmonary disease [COPD] pathogenesis, and thus has been developed as a potential inhaled anti-inflammatory agent for COPD) dry powder for inhalation (DPI) in adults with moderate to severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage II-III).

Secondary Objectives:

- To explore the efficacious dose range for UK-432,097 DPI in COPD and provide information for Phase 2b dose ranging study(ies).

- To evaluate the time course of response to UK-432,097 DPI.

- To evaluate the washout/persistence of UK-432,097 DPI effects on lung function and symptoms for 2 weeks after stopping the drug.

- To evaluate the pharmacokinetic-pharmacodynamic (PK-PD) relationship between dose and/or systemic UK-432,097 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 and safety of UK-432,097 DPI in adult subjects with moderate to severe COPD (GOLD stages II-III).

The study comprised 9 clinic visits: a Screening Visit, 2 visits during the run-in phase (Week -2 and Week -1), a Baseline/randomization Visit (Week 0) at the start of the double-blind treatment phase, 4 visits during the double-blind treatment phase (Weeks 1, 2, 4, and 6) and a Follow-up Visit (Week 8) following a 2-week washout (run out) phase.

At the beginning of the double-blind treatment phase (Week 0), subjects were randomized to receive either UK-432,097 DPI (150 µg, 450 µg or 1350 µg) twice daily (BID) or matching placebo. Subjects who discontinued during the period from randomization (Week 0) to Follow-up (Week 8) were not replaced.

An interim analysis for efficacy (futility) was performed based on the primary efficacy endpoint, mean change from Baseline in trough forced expiratory volume in 1 second (FEV_1) at Week 6. This interim analysis was scheduled when a minimum of 80 subjects had completed 6 weeks of double-blind treatment and was based on the primary efficacy variable. The study could only be stopped for futility at the interim analysis; it could not be stopped for superiority.

The schedule of study activities is presented in Table 1.

Table 1. Study Schedule Flow Chart

	Screen	Run-in		Double-Blind Treatment					Follow-Up/ET[a]
Study Week	**-4 to -3**	**-2**	**-1**	**0 Baseline**	**1**	**2[b]**	**4[b]**	**6[b] End of Treatment**	**8[b]**
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	X
Physical examination	X			X[c]	X[c]		X[c]	X[c]	X
Blood pressure/pulse rate[d]	X			X[e]	X	X	X	X[e]	X
Review inclusion/exclusion criteria (and FEV_1 randomization criteria Week 0)	X	X	X	X					
Dispense short acting bronchodilators	X	X		X		X	X	X	
Inhaler device, AM2 and paper diary training	X			X					
Review of adverse events		X	X	X	X	X	X	X	X
Chest X-ray (if none within 12 months)	X								
12-Lead resting ECG[f]	X			X[e]	X	X	X	X[e]	X
HBsAg, HBcAB and anti-hepatitis C virus serology	X								
Lab safety tests (hematology, chemistry), FSH for amenorrheic women aged 40-60 years[g]	X			X	X	X		X	X[h]
Whole blood for de-identified pharmacogenomic sampling[i]				X					
Routine urinalysis	X			X		X		X	X[h]
Blood sample for biomarker/RNA analysis[i]				X				X	
Baseline/transition dyspnea index				BDI		TDI	TDI	TDI	
Spirometry/trough	X	X	X	X		X	X	X[j]	X
Randomization				X					
Study drug administered during clinic visit				X	X	X	X	X	
Spirometry, post-study drug[k]				X		X	X	X	
Salbutamol (albuterol) administered at clinic visit[l]	X	X	X	X				X	
Spirometry, post-salbutamol (albuterol)[m]	X	X	X	X				X	
PK, pre-dosing with study drug[n]				X	X	X	X	X	
PK, post-dosing with study drug[o]				X	X	X	X	X[p]	X[q]
Study drug dispensed				X		X	X		
Study drug return and accountability						X	X	X	
Provide paper diary and AM2[r]	X	X	X	X		X	X	X	
Daily diary collection and review (PEFR, symptoms, bronchodilator use)		X	X	X		X	X	X	X
Global impression of change and global rating of change								X	

Table 1. Study Schedule Flow Chart

AM2 = Asthma Monitor, BDI = Baseline Dyspnea Index, ECG = electrocardiogram, ET = early termination, FEV_1 = forced expiratory volume in 1 second, FSH = follicle-stimulating hormone, HBsAg = hepatitis B surface antigen, HBcAB = hepatitis B core antibody, PEFR = peak expiratory flow rate, PK = pharmacokinetic, RNA = ribonucleic acid; TDI = Transition Dyspnea Index.

a. ET = Early Termination Visit for subjects who discontinued the study prior to Week 8.
b. Visit window ±3 days.
c. Only a brief physical exam was required. Full physical exams were required at Screening and Week 8 or ET Visit if earlier than Week 8.
d. Vital signs (blood pressure and pulse) at Weeks 0, 1, and 6 were collected 10-15 minutes before and 3 hours after study drug dosing (before ECG or PK sample); at Weeks 2 and 4 they were collected 3 hours after study drug dosing, at Screening and Week 8 at the beginning of the visit, prior to blood sample, or spirometry.
e. Blood pressure, pulse, and ECG were performed in triplicate at Weeks 0 and 6.
f. ECGs at Weeks 0 and 6 were obtained 10-15 minutes before and 3 hours after study drug dosing (after vital signs and before PK sample); at Weeks 1, 2, and 4 they were obtained 3 hours after study drug dosing (after vital signs and before PK sample); at Screening and Week 8 together with vital signs at the beginning of the visit, prior to blood sampling, or spirometry.
g. Blood sample for FSH for amenorrheic women aged 40-60 years was collected at Screening only.
h. Blood and urine were collected and analyzed if early termination. If follow-up, samples were only collected if abnormalities were detected in results obtained at Week 6.
i. Performed on a voluntary basis only.
j. At Week 6 only, a replicate was collected through spirometry measurements 30-60 minutes after initial spirometry assessment and before administration of study drug.
k. Post-study drug spirometry was performed 15-30 minutes after dosing with study drug.
l. Salbutamol (albuterol) was administered 30 minutes after dosing (after all spirometry related to study drug was complete).
m. Post-salbutamol (albuterol) spirometry was performed 15-30 minutes after salbutamol (albuterol) dosing.
n. Pre-dose PK samples were collected before study drug dosing.
o. At Weeks 0, 1, 2, 4, and 6 post-dose PK samples were collected 1-2 hours and 3-4 hours after study drug dosing.
p. At Week 6 only an additional PK sample was collected 6-8 hours and 24-26 hours after study drug dosing (selected centers only).
q. Selected centers only. Was not required at ET visit.
r. Asthma Monitor AM2 device provided at Screening only for use throughout the study.

Number of Subjects (Planned and Analyzed): A total of 240 subjects were planned to be randomized to study treatment. In actuality, a total of 288 subjects were screened, and of these, 87 subjects were analyzed and assigned to 1 of the 4 treatment groups: 150 µg, 450 µg, or 1350 µg of UK-432,097, or placebo in a 1:1:2:1 ratio. There were 17 subjects in the 150 ug group, 18 in the 450 ug group, 35 in the 1350 ug group, and 17 in the placebo group.

Diagnosis and Main Criteria for Inclusion: Male or female subjects between, and including, the ages of 40 and 80 years. Subjects with a diagnosis, for at least 6 months, of moderate to severe COPD (GOLD) and who meet the criteria for Stage II-III disease. Subjects must have a smoking history of at least 10 pack-years. Subjects must have stable disease for at least 1 month prior to screening. Subjects with more than 2 exacerbations of COPD in the preceding year were excluded. Subjects excluded with a history of a lower respiratory tract infection or significant disease instability during the month proceding Screening or during the time between Screening and randomization. Subjects were excluded because of history or presence of respiratory failure, cor pulmonale or right ventricular failure

Study Treatment: The study drug (150 µg, 450 µg, 1350 µg, or placebo) was administered by inhalation BID via the single pin monodose capsule inhaler device: 3 capsules in the morning and 3 capsules in the evening, at approximately 12-hour intervals. UK-432,097 was supplied as capsules containing either 150 µg or 450 µg of UK-432,097 DPI. Matching placebo capsules contained 100% lactose.

Efficacy Endpoints:

Primary Efficacy Endpoint:

- Change from Baseline in trough (prior to administration of study drug) FEV_1 at Week 6.

Secondary Efficacy Endpoints:

- Change from Baseline in trough FEV_1, forced expiratory volume in 6 seconds (FEV_6), forced vital capacity (FVC) and inspiratory capacity (IC) at Weeks 2 and 4 and at Week 8 (2 weeks after the completion of therapy).
- Change from Baseline in trough FEV_6, FVC, and IC at Week 6.
- Change from Baseline in post-study drug FEV_1, FEV_6, FVC, and IC at Weeks 2, 4, and 6.
- Change from Baseline in post-bronchodilator FEV_1, FEV_6, FVC, and IC at Week 6.
- Change from Baseline in dyspnea (Baseline dyspnea index/transition dyspnea index [BDI/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).

- Clinical Global Impression of Change and Patient Global Impression of Change at Week 6.

Safety Evaluations:

- Adverse events (AEs).
- Laboratory safety data.
- Change in vital signs (pulse & blood pressure) and electrocardiogram (ECG) post-study drug.
- Acute change in FEV_1 post-study drug compared to pre-study drug.

Statistical Methods: The sample size calculation was based on mean change from Baseline in trough FEV_1 at Week 6, which was the primary efficacy endpoint. Two hundred and eight completing subjects (assuming all doses at final analysis) were required to detect at least 1 dose with at least 0.075 L improvement over placebo. Assuming a discontinuation rate of 15%, 240 subjects in total were to be randomized. Prior to the futility interim analysis an unequal allocation of doses was used for the first part of the study, with fewer subjects receiving the 2 lower doses of UK-432,097(1:1:2 ratio of active doses).

The objective was to estimate the likelihood of any dose achieving a 0.075 L treatment effect over placebo. The primary analysis modeled the dose-response curve for the change from Baseline in trough FEV_1 at Week 6 using a normal dynamic linear model (NDLM). The estimated dose response and 95% credible interval at each dose was presented together with the posterior probabilities of each dose of UK-432,097 giving an improvement of at least 0.075 L over placebo. A probability of 50% or more was considered a clinical and statistical meaningful effect.

For secondary endpoints each dose of UK-432,097 was formally compared to placebo in a hierarchical order (i.e., descending dose). Continuous efficacy variables (spirometry, mean weekly diary scores) were analyzed using a longitudinal mixed effects model with baseline value, treatment, week and treatment by week as fixed effects terms. Subject was fitted as a random effect, and the covariance structure across time points was estimated from the data. TDI total focal scores at Weeks 2, 4, and 6 were included with the BDI score at Week 0 as a covariate. The proportional odds logistic regression was used to assess the clinician and subject Global Impression of Change scores with treatment fitted as a categorical variable. The analysis included center as a covariate. The significance of individual terms in the model was tested using Type III (Wald) tests and the presence of a treatment x center interaction was investigated.

Mean values were reported by treatment group at each time point along with 95% confidence intervals. One-sided tests at the 5% level of significance were applied for all secondary analyses. Based on the mixed model, adjusted means were presented by treatment group and week, together with contrasts between each dose group and placebo and 95% 1-sided confidence intervals for each week.

The full-analysis-set (FAS) was considered the primary analysis data set and included all randomized subjects who had completed at least 2 weeks of dosing and had at least 1 valid FEV_1 measurement during the active double-blind phase of the study.

Safety data were evaluated using descriptive statistics.

RESULTS

Subject Disposition and Demography: In total, 288 subjects were screened. Of these, 87 subjects were assigned to 1 of the 4 treatment groups. Twelve subjects discontinued the study. One subject in the UK-432,097 1350 µg treatment group discontinued from the study because of a treatment-related AE ('supraventricular extrasystoles'). The most common reason for study discontinuation not related to the study drug was subjects were no longer willing to participate in the study.

Six subjects were not included in the FAS. All subjects contributed data for the AE, vital signs, and ECG analyses; whereas 3 subjects were not analyzed for laboratory analyses.

Table 2 summarizes subject disposition and subjects analyzed.

Table 2. Subject Disposition and Subjects Analyzed

Number of Subjects	UK-432,097 150 µg BID	UK-432,097 450 µg BID	UK-432,097 1350 µg BID	Double-Blind Placebo BID
Screened: 288				
Assigned to study treatment:	17	18	35	17
Treated	17	18	35	17
Completed	15	16	29	15
Discontinued	2	2	6	2
Related to study drug				
Adverse event	0	0	1	0
Not related to study drug				
Adverse event	0[a]	2	0	1
Laboratory abnormality	1[a]	0	0	0
Subject no longer willing to participate	1	0	5	0
Other	0	0	0	1
Analyzed for efficacy				
Full analysis set	16	17	32	16
Analyzed for safety				
Adverse events[b]	17	18	34	16
Laboratory data	17	17	33	17
Vital signs	17	18	35	17
Electrocardiogram	17	18	35	17

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
ALP = alkaline phosphatase, BID = twice daily, CRF = case report form.

a. Data presented in this table were based on the subject summary page of the CRF. Records for 1 subject on the AE page showed that the subject discontinued due to 'blood ALP increased.' However, on the subject summary page this was recorded as a discontinuation due to a laboratory abnormality. One further subject in the UK-432,097 150 µg dose group discontinued due to the AE increased blood ALP. This was recorded on the subject's summary page of the CRF as a discontinuation due to 'not meeting the entrance criteria,' and was therefore not included in the source table

b. The number of subjects evaluable for adverse events was 87. Two subjects had no adverse events, and as such no adverse event page was data based.

Demographic characteristics are summarized in Table 3. In all treatment groups, there were more male than female subjects with the percentage of male subjects ranging from 64.7% to 74.3%. The mean age was approximately 65 years in all treatment groups. All subjects were white.

Table 3. Subject Demographics

	UK-432,097 150 µg BID N=17	UK-432,097 450 µg BID N=18	UK-432,097 1350 µg BID N=35	Double-Blind Placebo BID N=17
Gender, N (%)				
Male	12 (70.6)	13 (72.2)	26 (74.3)	11 (64.7)
Female	5 (29.4)	5 (27.8)	9 (25.7)	6 (35.3)
Age (years)				
Mean (SD)	65.0 (6.4)	66.7 (7.0)	65.7 (9.5)	65.2 (7.8)
Range	51-75	53-77	45-80	46-78
Weight (kg)				
Mean (SD)	75.5 (17.2)	82.2 (12.4)	77.2 (13.6)	77.4 (14.6)
Range	48.0-104.0	65.0-113.0	43.0-96.0	55.0-101.0
Height (cm)				
Mean (SD)	171.4 (8.8)	172.9 (8.3)	170.2 (7.2)	169.4 (8.1)
Range	152.0-182.0	157.0-186.0	150.0-182.0	153.0-185.0
Lung function characteristics				
% predicted FEV_1				
Mean (SD)	49.35 (10.608)	49.72 (14.893)	48.93 (11.386)	46.41 (10.912)
FEV_1 (L)				
Mean (SD)	1.42 (0.453)	1.45 (0.574)	1.38 (0.403)	1.30 (0.473)
% FEV_1 reversibility				
Mean (SD)	1.86 (8.856)	-1.73 (6.810)	2.06 (12.321)	-3.01 (9.021)
Duration of COPD since first diagnosis (years)				
Mean	6.3	6.6	9.0	5.2
Range	1.3-31.0	0.5-28.0	1.333.0	0.6-20.0

BID = bis in die (twice daily), COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, N = number of treated subjects in respective treatment group, SD = standard deviation.

Efficacy Results:

Primary Efficacy Endpoints:

Change From Baseline in Trough (Prior to Administration of Study Drug) Forced Expiratory Volume in 1 Second (FEV_1) at Week 6.

The summary of the NDLM analysis of trough FEV_1 at Week 6 is shown in Table 4. In all 4 treatment groups, trough FEV_1 decreased from Baseline after 6 weeks of treatment. The NDLM estimated change from Baseline showed that the trough FEV_1 decreased with increasing doses of UK-432,097. The decrease was lowest in the placebo treatment group. The NDLM estimated difference from placebo was negative for all UK-432,097 dose groups, but the 95% credible interval of the effect included the 0-value. None of the doses met the criterion of a >20% posterior probability for an improvement of at least 0.075 L.

Table 4. Trough FEV_1 (L) at Week 6: Mean Change from Baseline at Week 6 and Summary of NDLM Analysis (FAS Population)

	UK-432,097 150 µg BID	UK-432,097 450 µg BID	UK-432,097 1350 µg BID	Double-Blind Placebo BID
Baseline	1.40	1.48	1.41	1.33
(SD)	(0.45)	(0.57)	(0.39)	(0.48)
Raw mean change from Baseline	-0.0123	-0.0526	-0.0457	-0.0460
(SD)	(0.2041)	(0.1812)	(0.1766)	(0.1634)
Number of subjects in NDLM analysis	15	17	29	15
NDLM estimated change from Baseline	-0.0190	-0.0492	-0.0613	-0.0103
(SE)	(0.0393)	(0.0393)	(0.0335)	(0.0221)
95% credible interval of dose	-0.0963, 0.0604	-0.1276, 0.0289	-0.1275, 0.0036	-0.0540, 0.0327
NDLM estimated difference from placebo	-0.0087	-0.0389	-0.0510	-
95% credible interval of effect over placebo	-0.0943, 0.0774	-0.1299, 0.0471	-0.1298, 0.0290	-
Posterior probability of effect >0 ml	0.4025	0.1844	0.1040	-
Posterior probability of effect >75 ml	0.0284	0.0056	0.0009	-

BID = twice daily, FAS = full analysis set, FEV_1 = forced expiratory volume in 1 second, NDLM = normal dynamic linear model, SD = standard deviation, SE = standard error.

Secondary Efficacy Endpoints:

Change From Baseline in Trough Forced Expiratory Volume in 1 Second (FEV_1) at Weeks 2, 4, and 8: The change from Baseline in trough FEV_1 at Weeks 2, 4 and 8 is summarized in Table 5.

Table 5. Change From Baseline in Trough FEV_1 at Weeks 2, 4, and 8

	UK-432,097 150 µg BID N=16 Mean±SD	UK-432,097 450 µg BID N=17 Mean±SD	UK-432,097 1350 µg BID N=32 Mean±SD	Double-Blind Placebo BID N=16 Mean±SD
n	16	17	32	16
Baseline	1.40±0.45	1.48±0.57	1.41±0.39	1.33±0.48
n	16	17	32	16
Change at Week 2	-0.01±0.10	-0.10±0.11	0.01±0.13	0.01±0.18
n	15	17	30	16
Change at Week 4	-0.08±0.19	-0.06±0.15	-0.02±0.17	-0.01±0.12
n	14	16	27	16
Change at Week 8	0.03±0.23	-0.07±0.18	0.04±0.23	-0.05±0.17

BID = twice daily, FEV_1 = forced expiratory volume in 1 second, N = number of subjects, n = number of subjects meeting prespecified criteria, SD = standard deviation.

Change From Baseline in Trough Forced Expiratory Volume in 6 Seconds (FEV_6) at Weeks 2, 4, 6 and 8: The change from Baseline in trough FEV_6 at Weeks 2, 4, 6 and 8 is summarized in Table 6.

Table 6. Change From Baseline in Trough FEV_6 at Weeks 2, 4, 6, and 8

	UK-432,097 150 µg BID N=16 Mean±SD	UK-432,097 450 µg BID N=17 Mean±SD	UK-432,097 1350 µg BID N=32 Mean±SD	Double-Blind Placebo BID N=16 Mean±SD
n	16	17	32	16
Baseline	2.66±0.73	2.80±0.81	2.75±0.69	2.54±0.73
n	16	17	32	16
Change at Week 2	-0.02±0.22	-0.08±0.18	-0.01±0.20	0.03±0.19
n	15	17	30	16
Change at Week 4	-0.12±0.24	0.03±0.19	-0.05±0.23	-0.01±0.13
n	14	17	29	15
Change at Week 6	-0.00±0.25	0.01±0.30	-0.06±0.22	-0.05±0.18
n	14	16	27	16
Change at Week 8	0.10±0.34	-0.05±0.31	0.04±0.30	-0.09±0.26

BID = twice daily, FEV_6 = forced expiratory volume in 6 seconds, N = number of subjects, n = number of subjects meeting prespecified criteria, SD = standard deviation.

Change From Baseline in Trough Forced Vital Capacity (FVC) at Weeks 2, 4, 6 and 8: The change from Baseline in trough FVC at Weeks 2, 4, 6 and 8 is summarized in Table 7.

Table 7. Change From Baseline in Trough FVC at Weeks 2, 4, 6, and 8

	UK-432,097 150 µg BID N=16 Mean±SD	UK-432,097 450 µg BID N=17 Mean±SD	UK-432,097 1350 µg BID N=32 Mean±SD	Double-Blind Placebo BID N=16 Mean±SD
n	16	17	32	16
Baseline	3.11±0.85	3.43±1.16	3.24±0.91	3.01±0.94
n	16	17	32	16
Change at Week 2	-0.07±0.30	-0.09±0.30	-0.04±0.25	0.09±0.31
n	15	17	30	16
Change at Week 4	-0.14±0.34	0.14±0.21	-0.02±0.32	0.05±0.21
n	14	17	29	15
Change at Week 6	0.01±0.32	0.01±0.33	-0.01±0.31	0.02±0.17
n	14	16	27	16
Change at Week 8	0.14±0.46	0.02±0.40	0.07±0.33	-0.05±0.28

BID = twice daily, FVC = forced vital capacity, N = number of subjects, n = number of subjects meeting prespecified criteria, SD = standard deviation.

Change From Baseline in Trough Inspiratory Capacity (IC) at Weeks 2, 4, 6, and 8: The change from Baseline in trough IC at Weeks 2, 4, 6, and 8 is summarized in Table 8.

Table 8. Change From Baseline in Trough IC at Weeks 2, 4, 6 and 8

	UK-432,097 150 µg BID N=16 Mean±SD	UK-432,097 450 µg BID N=17 Mean±SD	UK-432,097 1350 µg BID N=32 Mean±SD	Double-Blind Placebo BID N=16 Mean±SD
n	16	17	32	16
Baseline	2.44±0.63	2.81±0.78	2.53±0.59	2.41±0.82
n	16	17	32	16
Change at Week 2	0.03±0.27	-0.06±0.38	-0.03±0.30	-0.10±0.24
n	15	17	30	16
Change at Week 4	-0.05±0.18	-0.03±0.38	-0.15±0.28	-0.06±0.25
n	14	17	29	15
Change at Week 6	-0.03±0.23	-0.08±0.40	-0.14±0.28	-0.09±0.32
n	14	16	27	16
Change at Week 8	0.07±0.22	0.01±0.44	-0.10±0.33	-0.05±0.26

BID = twice daily, IC = inspiratory capacity, N = number of subjects, n = number of subjects meeting prespecified criteria, SD = standard deviation.

Change From Baseline in Post-Study Drug Forced Expiratory Volume in 1 Second (FEV_1) at Weeks 2, 4 and 6: The change from Baseline in post-study drug FEV_1 at Weeks 2, 4 and 6 is summarized in Table 9.

Table 9. Change From Baseline in Post-Study Drug FEV_1 at Weeks 2, 4, and 6

	UK-432,097 150 µg BID N=16 Mean±SD	UK-432,097 450 µg BID N=17 Mean±SD	UK-432,097 1350 µg BID N=32 Mean±SD	Double-Blind Placebo BID N=16 Mean±SD
n	16	17	32	16
Baseline	1.40±0.45	1.48±0.57	1.41±0.39	1.33±0.48
n	16	16	30	16
Change at Week 2	0.02±0.11	-0.10±0.16	-0.02±0.11	0.03±0.20
n	14	16	29	16
Change at Week 4	-0.07±0.15	-0.04±0.10	-0.02±0.15	-0.01±0.15
n	13	16	27	15
Change at Week 6	-0.06±0.23	-0.04±0.18	-0.04±0.15	-0.03±0.20

BID = twice daily, FEV_1 = forced expiratory volume in 1 seconds, N = number of subjects, n = number of subjects meeting prespecified criteria, SD = standard deviation.

Change From Baseline in Post-Study Drug Forced Expiratory Volume in 6 Seconds (FEV_6), Forced Vital Capacity (FVC) and Inspiratory Capacity (IC) at Weeks 2, 4, and 6:

Data for these outcomes were not analyzed, as the study was terminated due to futility based on results of the interim analysis.

Change From Baseline in Post-Bronchodilator Forced Expiratory Volume in 1 Second (FEV_1) at Week 6: The change from Baseline in post-bronchodilator FEV_1 at Week 6 is summarized in Table 10.

Table 10. Change From Baseline in Post-Bronchodilator FEV_1 at Week 6

	UK-432,097 150 µg BID N=13 Mean±SD	UK-432,097 450 µg BID N=16 Mean±SD	UK-432,097 1350 µg BID N=27 Mean±SD	Double-Blind Placebo BID N=14 Mean±SD
Baseline	0.32±0.20	0.29±0.19	0.26±0.18	0.24±0.15
Change at Week 6	0.06±0.14	0.03±0.19	-0.02±0.19	-0.06±0.14

BID = twice daily, FEV_1 = forced expiratory volume in 1 seconds, N = number of subjects, SD = standard deviation.

Change From Baseline in Post-Bronchodilator Forced Expiratory Volume in 6 Seconds (FEV_6), Forced Vital Capacity (FVC) and Inspiratory Capacity (IC) at Week 6:

Data for these outcomes were not analyzed, as the study was terminated due to futility based on results of interim analysis.

Change From Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) at Weeks 2, 4 and 6:

None of the UK-432,097 treatments showed a statistically significant difference in comparison with placebo. The change from Baseline in dyspnea at Weeks 2, 4 and 6 is summarized in Table 11.

Table 11. Change From Baseline in Dyspnea BDI/TDI at Weeks 2, 4, and 6

	UK-432,097 150 µg BID N=16 Mean±SD	UK-432,097 450 µg BID N=17 Mean±SD	UK-432,097 1350 µg BID N=32 Mean±SD	Double-Blind Placebo BID N=16 Mean±SD
n	16	17	32	16
BDI	7.1±1.9	7.6±2.1	7.2±2.1	7.1±2.0
n	16	17	32	16
TDI at Week 2	-0.2±1.9	0.8±1.9	0.2±1.1	1.3±2.4
n	15	17	31	16
TDI at Week 4	0.5±2.8	0.2±1.7	-0.3±1.9	0.3±2.2
n	14	16	29	15
TDI at Week 6	-0.6±2.3	0.9±3.1	0.1±2.4	1.0±1.9

BID = twice daily, BDI = baseline dyspnea index, N = number of subjects, SD = standard deviation, TDI = transition dyspnea index.

Change From Baseline of Chronic Obstructive Pulmonary Disease (COPD) Symptoms: The change from Baseline in COPD symptoms is summarized in Table 12.

Table 12. Change From Baseline in COPD Symptom Score at Weeks 1, 2, 3, 4, 5, 6, 7, and 8

	UK-432,097 150 µg BID N=16 Mean±SD	UK-432,097 450 µg BID N=17 Mean±SD	UK-432,097 1350 µg BID N=31 Mean±SD	Double-Blind Placebo BID N=16 Mean±SD
n	16	17	31	16
Cough: Baseline	1.09±0.50	0.77±0.75	1.11±0.67	1.06±0.61
n	16	17	31	16
Cough: change at Week 1	-0.08±0.46	0.11±0.48	0.07±0.41	0.10±0.50
n	16	15	31	16
Cough: change at Week 2	-0.10±0.43	0.13±0.31	0.10±0.53	-0.01±0.41
n	15	17	31	16
Cough: change at Week 3	-0.06±0.51	0.15±0.32	0.07±0.48	0.15±0.41
n	14	17	30	16
Cough: change at Week 4	-0.04±0.30	0.07±0.38	-0.03±0.46	0.18±0.39
n	15	17	30	16
Cough: change at Week 5	-0.13±0.38	0.04±0.44	0.10±0.73	0.00±0.43
n	15	17	30	15
Cough: change at Week 6	-0.10±0.36	0.04±0.43	0.07±0.77	-0.02±0.40
n	15	16	30	15
Cough: change at Week 7	-0.16±0.38	-0.08±0.57	0.00±0.64	0.07±0.31
n	15	16	28	15
Cough: change at Week 8	-0.15±0.37	0.00±0.56	-0.15±0.60	0.07±0.47
n	16	17	31	16
Breathlessness: Baseline	1.31±0.59	1.30±0.60	1.15±0.75	1.27±0.54
n	16	17	31	16
Breathlessness: change at Week 1	-0.24±0.45	-0.10±0.31	-0.05±0.23	0.00±0.32
n	16	15	31	16
Breathlessness: change at Week 2	-0.13±0.48	-0.11±0.29	0.00±0.33	-0.01±0.38
n	15	17	31	16
Breathlessness: change at Week 3	-0.12±0.57	-0.15±0.33	0.02±0.33	0.13±0.41
n	14	17	30	16
Breathlessness: change at Week 4	-0.18±0.50	-0.16±0.50	-0.07±0.28	0.18±0.34
n	15	17	30	16
Breathlessness: change at Week 5	-0.14±0.47	-0.22±0.50	-0.06±0.33	0.13±0.40
n	15	17	30	15
Breathlessness: change at Week 6	-0.12±0.56	-0.03±0.50	-0.05±0.34	0.12±0.47
n	15	16	30	15
Breathlessness: change at Week 7	-0.06±0.43	-0.21±0.48	0.01±0.36	0.10±0.43
n	15	16	28	15
Breathlessness: change at Week 8	-0.04±0.49	-0.13±0.51	-0.04±0.49	0.08±0.45
n	16	17	31	16
Sputum: Baseline	1.00±0.62	0.76±0.79	0.95±0.59	0.90±0.61
n	16	17	31	16
Sputum: change at Week 1	-0.07±0.26	0.10±0.36	0.04±0.39	0.04±0.41
n	16	15	31	16
Sputum: change at Week 2	-0.05±0.20	0.17±0.37	0.14±0.54	0.05±0.52
n	15	17	31	16
Sputum: change at Week 3	-0.08±0.32	0.20±0.37	0.15±0.52	0.05±0.41
n	14	17	30	16
Sputum: change at Week 4	0.01±0.21	0.15±0.36	0.06±0.51	0.01±0.47
n	15	17	30	15
Sputum: change at Week 5	0.06±0.23	0.15±0.33	0.07±0.48	-0.04±0.44

Table 12. Change From Baseline in COPD Symptom Score at Weeks 1, 2, 3, 4, 5, 6, 7, and 8

	UK-432,097 150 µg BID N=16 Mean±SD	UK-432,097 450 µg BID N=17 Mean±SD	UK-432,097 1350 µg BID N=31 Mean±SD	Double-Blind Placebo BID N=16 Mean±SD
n	15	17	30	15
Sputum: change at Week 6	0.09±0.09	0.10±0.46	0.10±0.61	-0.02±0.51
n	15	15	30	15
Sputum: change at Week 7	0.08±0.23	-0.02±0.39	0.07±0.56	0.03±0.51
n	15	15	28	15
Sputum: change at Week 8	0.07±0.27	-0.06±0.40	0.02±0.47	-0.03±0.55

BID = twice daily, COPD = chronic obstructive pulmonary disease, N = number of subjects, n = number of subjects meeting prespecified criteria, SD = standard deviation.

Change From Baseline of Rescue Bronchodilator Use: The change from Baseline of rescue bronchodilator use is summarized in Table 13.

Table 13. Change From Baseline in Rescue Bronchodilator Use at Weeks 1, 2, 3, 4, 5, 6, 7, and 8

	UK-432,097 150 µg BID N=14 Mean±SD	UK-432,097 450 µg BID N=15 Mean±SD	UK-432,097 1350 µg BID N=27 Mean±SD	Double-Blind Placebo BID N=15 Mean±SD
n	14	15	27	15
Baseline	2.87±2.91	3.32±2.99	2.97±2.83	3.46±3.26
n	14	15	27	15
Change at Week 1	-0.24±0.51	-0.17±0.53	-0.19±0.61	-0.41±1.11
n	13	13	27	15
Change at Week 2	-0.26±0.58	-0.14±0.67	-0.08±0.85	0.01±1.09
n	13	14	27	15
Change at Week 3	-0.12±0.63	-0.10±0.79	0.03±0.95	0.17±1.31
n	13	14	26	15
Change at Week 4	-0.19±0.56	-0.01±0.99	-0.08±0.99	0.07±1.00
n	13	14	26	15
Change at Week 5	-0.44±0.98	-0.22±1.39	0.21±1.32	0.13±0.93
n	13	14	24	14
Change at Week 6	-0.39±1.17	0.15±1.16	0.26±1.52	0.30±1.10
n	13	13	26	14
Change at Week 7	-0.20±1.05	-0.01±1.81	0.38±1.41	0.24±0.99
n	13	13	25	14
Change at Week 8	-0.17±1.31	0.02±1.51	0.30±1.47	0.40±1.17

BID = twice daily, N = number of subjects, n = number of subjects meeting prespecified criteria, SD = standard deviation.

Change From Baseline of Peak Expiratory Flow Rate (PEFR): The change from Baseline of PEFR is summarized in Table 14.

Table 14. Change From Baseline in Morning and Evening PEFR at Weeks 1, 2, 3, 4, 5, 6, 7, and 8

	UK-432,097 150 µg BID N=16 Mean±SD	UK-432,097 450 µg BID N=17 Mean±SD	UK-432,097 1350 µg BID N=32 Mean±SD	Double-Blind Placebo BID N=16 Mean±SD
n	16	17	32	16
Morning PEFR: Baseline	220.0±113.0	236.4±121.4	213.6±72.6	191.0±77.8
n	16	17	32	16
Morning PEFR: change at Week 1	-3.6±17.5	3.5±17.8	2.1±13.9	1.1±23.0
n	16	17	32	16
Morning PEFR: change at Week 2	-5.0±21.0	-6.0±18.6	-1.3±21.3	0.7±27.2
n	15	17	31	16
Morning PEFR: change at Week 3	-8.8±27.5	-6.2±17.8	1.9±26.4	2.6±22.4
n	15	17	31	16
Morning PEFR: change at Week 4	-5.9±24.2	-2.8±18.4	3.3±31.2	2.8±28.9
n	15	17	30	16
Morning PEFR: change at Week 5	-13.4±27.2	-4.4±21.5	-9.4±27.5	5.7±31.0
n	15	17	30	15
Morning PEFR: change at Week 6	-10.5±27.2	-4.9±21.0	-3.9±36.6	-6.1±26.8
n	15	16	29	15
Morning PEFR: change at Week 7	-8.3±22.1	-0.0±24.3	1.2±33.7	-2.8±26.7
n	15	16	27	15
Morning PEFR: change at Week 8	-9.5±26.8	-6.8±29.4	0.4±30.2	0.8±23.1
n	16	17	32	16
Evening PEFR: Baseline	242.9±111.8	269.3±123.1	250.0±78.7	207.1±88.2
n	16	17	32	16
Evening PEFR: change at Week 1	5.5±20.5	-0.2±16.8	3.2±19.7	5.2±19.5
n	16	17	32	16
Evening PEFR: change at Week 2	4.8±27.1	-8.7±19.6	0.4±25.9	8.5±37.8
n	15	17	31	16
Evening PEFR: change at Week 3	0.1±16.2	-17.0±28.6	1.6±22.9	7.6±27.7
n	15	17	31	16
Evening PEFR: change at Week 4	-1.5±21.5	-13.7±19.3	-0.7±23.6	1.6±28.5
n	15	17	30	16
Evening PEFR: change at Week 5	-5.4±23.6	-14.2±24.7	-8.6±27.0	9.5±36.7
n	15	17	30	15
Evening PEFR: change At Week 6	-5.5±26.8	-13.6±23.2	-7.3±27.7	-4.5±40.2
n	15	16	30	15

Table 14. Change From Baseline in Morning and Evening PEFR at Weeks 1, 2, 3, 4, 5, 6, 7, and 8

	UK-432,097 150 µg BID N=16 Mean±SD	UK-432,097 450 µg BID N=17 Mean±SD	UK-432,097 1350 µg BID N=32 Mean±SD	Double-Blind Placebo BID N=16 Mean±SD
Evening PEFR: change at Week 7	0.8±23.7	-10.7±21.6	-6.0±30.7	-1.0±34.5
n	15	16	28	15
Evening PEFR: change at Week 8	-2.6±21.9	-16.0±23.4	-3.4±30.6	-5.9±41.9

BID = twice daily, N = number of subjects, n = number of subjects meeting prespecified criteria, PEFR = peak expiratory flow rate, SD = standard deviation.

Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) at Week 6:

The odds ratio was not significantly in favor of treatment. The CGI-C is summarized in Table 15 and PGI-C is summarized in Table 16.

Table 15. Number of Subjects With Categorical Scores on the CGI-C

	UK-432,097 150 µg BID	UK-432,097 450 µg BID	UK-432,097 1350 µg BID	Double-Blind Placebo BID
N	14	16	29	15
Very much improved	0	0	0	1
Much improved	0	2	2	2
Minimally improved	5	4	9	4
No change	5	7	14	6
Minimally worse	2	3	4	2
Much worse	2	0	0	0
Very much worse	0	0	0	0

BID = twice daily, CGI-C = Clinical Global Impression of Change, N = number of subjects.

Table 16. Number of Subjects With Categorical Scores on the PGI-C

	UK-432,097 150 µg BID	UK-432,097 450 µg BID	UK-432,097 1350 µg BID	Double-Blind Placebo BID
N	14	16	29	15
Very Much Improved	0	0	0	0
Much Improved	2	2	3	2
Minimally Improved	3	4	7	6
No Change	7	8	15	5
Minimally Worse	1	1	2	2
Much Worse	1	0	1	0
Very Much Worse	0	1	1	0

BID = twice daily, N = number of subjects, PGI-C = Patient Global Impression of Change.

Safety Results:

Treatment-emergent nonserious AEs (all causalities and treatment-related) by system organ class (SOC) and preferred term that occurred in >5% of subjects in either treatment groups are summarized in Table 17.

The most commonly reported all causality AEs were in the SOC 'infections and infestations.' The only AE occurring in at least 2 subjects in any treatment group was nasopharyngitis.

Of the treatment-related AEs, the SOC in which an AE was most frequently reported was 'respiratory, thoracic and mediastinal disorders.'

The majority of the AEs was mild or moderate in intensity and resolved by the end of the study.

There were no deaths and serious adverse events among subjects who participated in this study.

No major findings were obtained in the clinical laboratory, vital signs or ECG analyses.

Table 17. Disclosure for Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term in >5% of Subjects

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v7.1) Preferred Term	UK-432,097 150 µg BID			UK-432,097 450 µg BID			UK-432,097 1350 µg BID			Double-Blind Placebo BID		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of Subjects:												
Evaluable for adverse events	17			18			35			17		
With adverse events	11 (64.7)			8 (44.4)			11 (31.4)			10 (58.8)		
Cardiac disorders	0	0	0	0	0	0	0	0	0	1 (5.9)	1	1
Atrioventricular block first degree	0	0	0	0	0	0	0	0	0	1 (5.9)	1	1
Eye disorders	0	0	0	1 (5.6)	1	1	0	0	0	1 (5.9)	1	0
Eye swelling	0	0	0	1 (5.6)	1	1	0	0	0	0	0	0
Vision blurred	0	0	0	0	0	0	0	0	0	1 (5.9)	1	0
Gastrointestinal disorders	0	0	0	0	0	0	2 (5.7)	2	2	2 (11.8)	2	1
Dry mouth	0	0	0	0	0	0	2 (5.7)	2	2	0	0	0
Nausea	0	0	0	0	0	0	0	0	0	1 (5.9)	1	1
Vomiting	0	0	0	0	0	0	0	0	0	1 (5.9)	1	0
General disorders and administration site conditions	2 (11.8)	4	3	0	0	0	0	0	0	1 (5.9)	1	0
Chest pain	2 (11.8)	3	2	0	0	0	0	0	0	0	0	0
Influenza like illness	0	0	0	0	0	0	0	0	0	1 (5.9)	1	0
Oedema peripheral	1 (5.9)	1	1	0	0	0	0	0	0	0	0	0
Infections and infestations	3 (17.6)	5	0	6 (33.3)	6	0	7 (20.0)	7	0	2 (11.8)	2	0
Infective exacerbation of chronic obstructive airways disease	0	0	0	2 (11.1)	2	0	2 (5.7)	2	0	0	0	0
Lower respiratory tract infection	0	0	0	1 (5.6)	1	0	1 (2.9)	1	0	0	0	0
Nasopharyngitis	1 (5.9)	1	0	3 (16.7)	3	0	3 (8.6)	3	0	1 (5.9)	1	0
Pharyngitis	0	0	0	0	0	0	0	0	0	1 (5.9)	1	0
Sinusitis	1 (5.9)	1	0	0	0	0	0	0	0	0	0	0
Upper respiratory tract infection	1 (5.9)	1	0	0	0	0	1 (2.9)	1	0	0	0	0
Urinary tract infection	1 (5.9)	2	0	0	0	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	1 (5.9)	1	0	1 (5.6)	1	0	0	0	0	1 (5.9)	1	0
Muscle strain	1 (5.9)	1	0	0	0	0	0	0	0	1 (5.9)	1	0
Skin laceration	0	0	0	1 (5.6)	1	0	0	0	0	0	0	0
Investigations	3 (17.6)	3	1	1 (5.6)	1	0	0	0	0	0	0	0
Blood alkaline phosphatase increased	2 (11.8)	2	0	0	0	0	0	0	0	0	0	0
Electrocardiogram QT prolonged	1 (5.9)	1	1	0	0	0	0	0	0	0	0	0
Forced expiratory volume decreased	0	0	0	1 (5.6)	1	0	0	0	0	0	0	0

Table 17. Disclosure for Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term in >5% of Subjects

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v7.1) Preferred Term	UK-432,097 150 µg BID			UK-432,097 450 µg BID			UK-432,097 1350 µg BID			Double-Blind Placebo BID		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Musculoskeletal and connective tissue disorders	2 (11.8)	3	1	1 (5.6)	2	0	1 (2.9)	1	0	0	0	0
Arthralgia	0	0	0	1 (5.6)	1	0	1 (2.9)	1	0	0	0	0
Muscle rigidity	1 (5.9)	1	1	0	0	0	0	0	0	0	0	0
Musculoskeletal stiffness	1 (5.9)	1	0	0	0	0	0	0	0	0	0	0
Neck pain	1 (5.9)	1	0	1 (5.6)	1	0	0	0	0	0	0	0
Nervous system disorders	0	0	0	1 (5.6)	1	0	1 (2.9)	1	0	0	0	0
Headache	0	0	0	1 (5.6)	1	0	1 (2.9)	1	0	0	0	0
Renal and urinary disorders	0	0	0	0	0	0	0	0	0	1 (5.9)	1	0
Obstructive uropathy	0	0	0	0	0	0	0	0	0	1 (5.9)	1	0
Respiratory, thoracic and mediastinal disorders	5 (29.4)	6	3	4 (22.2)	4	1	3 (8.6)	3	3	2 (11.8)	7	6
Chronic obstructive pulmonary disease	2 (11.8)	2	0	0	0	0	2 (5.7)	2	2	0	0	0
Cough	0	0	0	1 (5.6)	1	0	0	0	0	1 (5.9)	1	1
Dyspnoea	1 (5.9)	1	0	2 (11.1)	2	1	0	0	0	0	0	0
Epistaxis	0	0	0	0	0	0	0	0	0	1 (5.9)	4	4
Productive cough	1 (5.9)	1	1	1 (5.6)	1	0	1 (2.9)	1	1	1 (5.9)	1	0
Rhinalgia	0	0	0	0	0	0	0	0	0	1 (5.9)	1	1
Throat irritation	1 (5.9)	1	1	0	0	0	0	0	0	0	0	0
Wheezing	1 (5.9)	1	1	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	1 (5.6)	1	1	0	0	0	1 (5.9)	1	1
Eczema	0	0	0	0	0	0	0	0	0	1 (5.9)	1	1
Rash pruritic	0	0	0	1 (5.6)	1	1	0	0	0	0	0	0
Vascular disorders	1 (5.9)	1	1	0	0	0	0	0	0	1 (5.9)	1	0
Hot flush	1 (5.9)	1	1	0	0	0	0	0	0	0	0	0
Varicose vein	0	0	0	0	0	0	0	0	0	1 (5.9)	1	0

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
Includes data up to 7 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (v11.0) coding dictionary applied.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1: The number of occurrences of treatment-emergent all causalities adverse events.
n2: The number of occurrences of treatment-emergent causally related to treatment adverse events.
BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities; QT = interval longation, v = version.

In total, 5 subjects discontinued the study due to an AE; 1 subject in each of the UK432,097 150 µg and 1350 µg dose groups and in the placebo treatment group, and 2 subjects in the UK432,097 450 µg dose group (Table 18). The AE 'supraventricular extrasystoles' that led to discontinuation was assessed as treatment-related. None of these AEs was rated severe or serious.

Table 18. Permanent Discontinuations Due to Adverse Events

Treatment Group	AE Leading to Discontinuation (PT)	Severity	Outcome by End of Study	Treatment Related
UK-432,097 150 µg BID	Blood alkaline phosphatase increased	Mild	Not resolved	No
UK-432,097 450 µg BID	Infective exacerbation of chronic obstructive airways disease	Moderate	Resolved	No
	Infective exacerbation of chronic obstructive airways disease	Moderate	Resolved	No
UK-432,097 1350 µg BID	Supraventricular extrasystoles	Mild	Resolved	Yes
Double-Blind Placebo BID	Obstructive uropathy	Moderate	Not resolved	No

AE = adverse event, BID = twice daily, PT = preferred term.

CONCLUSIONS:

The objective was to estimate the likelihood of any dose achieving a 0.075 L treatment effect over placebo in the FEV_1 change from Baseline. This effect was not achieved by any of the 3 dose groups of UK-432,097 at the interim analysis. Therefore the study was terminated prematurely due to futility, and the development of the compound did not progress any further. There were no concerns regarding safety and tolerability of UK-432,097.