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PROPRIETARY DRUG NAME/INN: UK-369,003 MR

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

NATIONAL CLINICAL TRIAL NO.: 00163098

PROTOCOL NO.: A3711028

PROTOCOL TITLE: A Multi-Centre, Multinational, Randomised, Double-Blind, Placebo-Controlled, Proof of Concept Trial to Assess the Effects of a Subject-Optimised Dose of UK-369,003 Modified Release on Exercise Capacity in Subjects With Pulmonary Hypertension Associated With Chronic Obstructive Pulmonary Disease

Study Centres: There were 25 centres (11 in Argentina, 5 in Australia, 2 in the United Kingdom, 2 in Germany and 5 in India) of 37 who recruited subjects

Study Initiation and Completion Dates: 30 November 2004 to 15 December 2005

Phase of Development: Phase 2

Study Objectives:

The *primary* objective was to evaluate the effects of UK-369,003 modified release (MR) on exercise capacity as measured by change from baseline in distance walked during the 6-minute walk test (6MWT) after 12 weeks of treatment in subjects with pulmonary hypertension (PH) associated with chronic obstructive pulmonary disease (COPD)

The *secondary* objectives were:

- To evaluate the effects of UK-369,003 MR on health related quality of life (HRQoL) as measured by the St George's Respiratory Questionnaire (SGRQ)
- To evaluate the effects of UK-369,003 MR on exertional dyspnea as measured by the Borg dyspnea score
- To evaluate the safety and tolerability of UK-369,003 MR in subjects with COPD associated PH
- To evaluate the effects of UK-369,003 MR on resting arterial partial pressure of oxygen/partial pressure of oxygen in arterial blood (PaO_2)

- To evaluate the effects of UK-369,003 MR on the maximum oxygen desaturation (SaO_2) during the 6MWT (and up to 5 minutes after the end of the 6MW)
- To evaluate the effects of UK-369,003 MR on spirometry
- To investigate the population pharmacokinetic (PK) parameters in these subjects
- To investigate the effects of UK-369,003 MR on time to clinical worsening

METHODS

Study Design: This was a multinational, multi-centre, double-blind, parallel-group, placebo-controlled study to assess the effects of a subject-optimized dose of UK-369,003 MR on exercise capacity (as measured by the 6MWT after 12 weeks of treatment) in subjects with PH associated with COPD. For each subject the study consisted of a screening visit, 7 study visits including a baseline visit (Day 0) and 6 treatment phase visits (Visits 1 to 6, *i.e.* Weeks 1, 2, 4, 8 and 12), and a follow-up visit 30 to 40 days after the last dose of study drug. Unscheduled visits could occur at any time for down titrating study drug due to toleration problems or due to a need to follow-up subjects regarding their SaO_2 and PaO_2 levels.

Screening procedures were carried out and subjects were randomized to study medication once an echocardiogram established a transtricuspid pressure gradient (TTPG) of at least 30 mmHg (equating to a right ventricular systolic pressure (RVSP) of approximately 35 mmHg). Right heart catheterisation was offered to the subjects if an adequate echo signal was not obtained, or TTPG was ≥ 25 mmHg and < 30 mmHg, and where there was suspicion on clinical grounds that PH could be present. Subjects who gave consent for the catheterisation procedure were then randomized provided the mean pulmonary arterial pressure (mPAP) was ≥ 20 mmHg and all other inclusion exclusion criteria were satisfied. Although not consistent with the traditional value used to define PAH (> 25 mmHg), it was felt these subjects would still have pulmonary vascular disease.

At the end of the baseline visit (Day 0), subjects meeting the inclusion criteria were randomly assigned in a 1:1 ratio to receive either UK-369,003 MR or placebo orally once a day. Subjects were also allowed to take the usual medications that they normally took to treat their COPD. Investigators were allowed to down-titrate subjects to 50 mg at any time if they did not tolerate 100 mg, or if there were any safety concerns. Subjects unable to tolerate 50 mg after initially being randomized were withdrawn from the study.

Number of Patients (Planned and Analyzed):

Planned: It was planned that approximately 136 subjects would be equally randomized in order to achieve 102 evaluable subjects.

*Analyzed***:** A total of 358 subjects were screened, 143 were assigned to study treatment (72 subjects on UK-369,003 MR and 71 subjects on placebo) and 123 completed the study.

Diagnosis and Main Criteria for Inclusion: The target population was subjects aged ≥ 40 and ≤ 75 years, having COPD, having a smoking history, who had forced expiratory volume

in 1 second (FEV_1) < 80% predicted and FEV_1/forced vital capacity (FVC) < 70% at screening, who had symptom limited exercise capacity with a 6MW distance of ≥ 100 metres and ≤ 450 metres and who did not desaturate to a SaO_2 < 75% during or 5 minutes after this walk at screening visit, were included in the study.

Study Treatment: Subjects received 50 mg of UK-369,003 MR or placebo tablets orally once a day. After 1 week of therapy they were up-titrated to 100 mg provided there were no toleration or safety concerns in which case they were either withdrawn or maintained on 50 mg. Subjects then remained on the 100 mg dose for the duration of the study but they were allowed to down-titrate to 50 mg at any time during the study if they were unable to tolerate the 100 mg dose.

Efficacy Evaluations: The 6MWT was carried out at screening, baseline (Day 0) and Week 4, 8 and 12 visits. The distance a subject could walk in 6 minutes was measured. The primary endpoint was the change in the distance walked during the 6MWT at Week 12 from the baseline visit. The minimum SaO_2 that occurred during and up to 5 minutes after the end of the 6MWT was recorded. The subjects were asked to score their dyspnea on the Borg dyspnea score at the completion of the 6MWT. HRQoL was measured by the SGRQ administered before the 6MWT at baseline (Day 0) and Week 8 and 12 visits. FEV_1 % predicted was calculated according to the centre's usual practice and FEV_1/FVC ratio documented.

Pharmacokinetic and Other Evaluations: Blood samples (6 mL blood to provide at least 2.5 mL plasma) for population PK were collected in non-beaded heparinised tubes from all subjects at Visits 1 (Day 1), 2 (Week 1) and 6 (Week 12). Other analyses were conducted to determine the effect of UK-369,003 on levels of plasma biomarkers such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and big endothelin (ET). A 9 mL blood sample for pharmacogenomics was to be collected into a plastic ethylenediaminetetraacetic acid tube at the screening visit along with other blood samples for the clinical study.

Safety Evaluations: The investigators obtained and recorded on the data collection tool all observed or volunteered adverse events (AEs), the severity (mild, moderate, or severe) of the events, and the investigator's opinion of the relationship to the study treatment. All serious adverse events (SAEs) were to be reported immediately to the sponsor. All clinically important abnormal laboratory tests occurring during the study were repeated at appropriate intervals. Heart rate and blood pressure were to be recorded at every visit. A 12-lead electrocardiogram was recorded after resting for 5 minutes supine, at screening, Week 1 and 12 visits. Echocardiographic investigations from each individual centre were performed at screening on the same machine and by the same operator to the extent possible.

Statistical Methods:

Efficacy:

The primary endpoint was evaluated using a 2-sample t-statistic stratified by severity of airways obstruction at baseline as measured by FEV_1 (% predicted) [< 50%; ≥ 50%] and use

of theophylline [Yes; No] at baseline. Testing was conducted 1-sided at the prespecified α-level of 0.05 and estimates were constructed with 90% confidence intervals.

The same 1-sided testing procedure was used for the analysis of the secondary end points. Spirometry (FEV_1 (% predicted) and FEV_1/FVC), resting PaO_2, and SaO_2 were analyzed using a stratified t-test as for the primary end point; the time to clinical worsening was analyzed using a stratified log-rank test (subjects with no documentation of clinical worsening were included in the analysis as censored observations); the Borg dyspnea score and SGRQ were analyzed using a stratified Wilcoxon test (Van-Elteren).

Tertiary endpoints comprised the correlation of baseline FEV_1 (% predicted), PaO_2, SaO_2, minimum SaO_2 and biomarkers ANP, BNP and ET with baseline 6MWT distance and Week 16 change from baseline in 6MWT distance.

No adjustments for multiplicity were made because there was no interim analysis and the analysis of the secondary and tertiary endpoints was regarded as exploratory.

Safety:

Safety and demographic data were summarized using "Worldwide Safety Standards for Clinical Trials" version 3.0. Statistical hypothesis testing was not performed on any safety assessments.

RESULTS

Subject Disposition and Demography: Of 358 subjects screened, 143 were assigned to study treatment and 123 completed the study. There were 215 screen failures, the majority (198) of which was due to subjects failing the entry criteria. There were 12 subjects on UK-369,003 MR group and 8 subjects on placebo, who discontinued from the study. Of the total UK-369,003 MR discontinuations, 10 were not related to the study drug and 1 of the subjects discontinued due to AEs related to the study drug. There were 72 subjects (52 males and 20 females) on UK-369,003 MR and 71 subjects (51 males and 20 females) on placebo. Age ranged from 46 to 75 years, the majority were white and none of the females were Asians. All 143 subjects were analyzed for efficacy and safety.

Efficacy Results:

Primary Evaluation:
The primary efficacy endpoint of the study was the change from the baseline in exercise capacity at Week 12 as measured by distance walked in 6 minutes. There was no statistically significant difference between UK-369,003 MR and placebo with respect to change from baseline in 6-minute walk distance for both intent-to-treat and per protocol populations. An average improvement of 6 metres was observed in favour of UK-369,003 MR (P = 0.262) when compared to placebo after 12 weeks of treatment. The treatment comparisons of the primary endpoint are summarized in Table S 1.

Table S 1. Treatment Comparisons of the Primary Endpoint (6 Minute Walk in Metres)

	UK-369,003 MR
ITT Population (Placebo N = 69)	N=62
Mean Difference (SE)	6.2 (9.7)
p-value From Stratified t-test (1-sided)	0.262
90% Confidence Interval	(-9.8, 22.2)
95% Confidence Interval	(-12.9, 25.3)

ITT = Intent-to-treat, MR = Modified release, SE = Standard error

Secondary Evaluations:
The median difference between the total SGRQ scores for UK-369,003 MR and placebo was small and not statistically significant. The median difference observed for the Borg dyspnea score at Week 12 was 0.0, the mean difference in resting PaO_2 at Week 12 was -0.12 and the change from baseline in SaO_2 was negligible as the mean difference was -0.10. There was no statistically significant change from baseline to Week 12 in FEV_1 (% predicted) for UK-369,003 MR compared to placebo. There was no statistically significant difference in time to first event for UK-369,003 MR compared to placebo.

Pharmacokinetic and Other Results: The population PK analyses were to be presented in a separate report. There was no significant change from baseline to Week 12 in the correlation of baseline biomarkers and FEV_1, PaO_2, SaO_2 with baseline 6MWT.

Safety Results: Of 143 treated subjects, 101 subjects (70.6%) reported AEs. Of the 279 treatment-emergent AEs, 71 (25.4%) were treatment-related.

The most frequently occurring AEs that were reported by more than 2 subjects are summarized in Table S2.

Table S2. Frequently Reported Adverse Events

MedDRA preferred term	Treatment-Related		All Causalities	
	UK-369,003 MR N	Placebo N	UK-369,003 MR N	Placebo N
Headache	8	4	9	5
Dizziness	3	1	3	1
Abdominal distension	3	0	3	0
Diarrhoea	2	1	4	2
Myalgia	2	1	4	2
Nausea	2	1	2	3
Hyperchlorhydria	2	1	2	1
Reflux oesophagitis	2	0	2	0
Tremor	2	0	2	0

MR = Modified release, MedDRA = Medical Dictionary for Regulatory Activities

Two deaths occurred during the study, 1 due to cardiac arrest and the other due to community acquired pneumonia, sepsis, cardiac arrest and acute respiratory failure, both were not treatment-related.

Seven subjects (3 on UK-369,003 and 4 on placebo) permanently discontinued from the study due to severe AEs.

Twenty subjects reported 43 SAEs. The majority of subjects who experienced SAEs were on placebo (13). The most common of the SAEs (19) were due to an exacerbation of the underlying disease (COPD). None of the SAEs were treatment-related. Myalgia was the only severe treatment related AE. All other AEs were reported to be mild or moderate.

CONCLUSIONS:

- There was no statistically significant difference between UK-369,003 MR and placebo with respect to change from baseline in 6MW distance. An average improvement of 6 metres was observed in favour of UK-369,003 MR (P = 0.262) when compared to placebo after 12 weeks of treatment in subjects with PH associated with COPD. There was no significant effect observed on any of the secondary points.

- UK-369,003 MR was generally well tolerated with most AEs being of mild to moderate intensity for both treatment groups. There were no clinical signs suggestive of an adverse effect on ventilation perfusion; however, ventilation or partial pressure of carbon dioxide (pCO_2) were not summarized.