A controlled trial of 6 weeks’ treatment with a novel inhaled PDE\textsubscript{4} inhibitor in COPD

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Abstract

Anti-inflammatory drugs are lacking in COPD and inhibitors of the phosphodiesterase type-4 (PDE4) enzyme have been suggested as an interesting class of drugs to treat inflammation in COPD. We report the findings of a Phase II trial of a novel inhaled PDE4-inhibitor.

Three doses of the compound UK-500,001 were tested, 0.1mg, 0.4mg and 1mg twice daily (BID), in a double-blind placebo-controlled 6 week trial in 209 patients with moderate or severe COPD. The primary efficacy parameter was trough FEV$_1$ after 6 weeks of treatment, and secondary endpoints included other lung function endpoints, and symptom scores assessed at 2 weekly intervals. The study was stopped following a planned interim analysis for futility.

No effect was observed at any dose after 6 weeks of treatment on the primary efficacy parameter, other measures of lung function or symptom scores. However, after the first 2 weeks of treatment, there was an improvement in the 1mg BID dose group compared to placebo on a number of outcome measures. The drug was well tolerated although PDE4-inhibitor related side effects were observed, especially in the highest dose group.

Our findings question the role of inhaled PDE4-inhibitors in COPD.

Word count: 191
Introduction

COPD is a chronic inflammatory disease of the airways, in the majority of cases caused by tobacco smoking (1).

Inhibitors of the phosphodiesterase type-4 (PDE$_4$) enzyme have been developed as anti-inflammatory agents for the use in COPD. It is hypothesized that selective PDE$_4$ inhibition will improve lung function by attenuating the production of inflammatory mediators that are important in the pathophysiology of COPD. Trials of oral formulations of cilomilast and roflumilast have shown clinical efficacy, evidenced by improvements in trough FEV$_1$ in studies of ≥ 6 weeks duration, but dosing has been limited by PDE$_4$ mediated side effects, especially from the gastrointestinal tract (2-4). UK-500,001 is an isoform selective, sub-type non-selective (PDE4A IC$_{50}$ 1.9nM, PDE4B IC$_{50}$ 1.01nM and PDE4D IC$_{50}$ 3.78nM), PDE$_4$ inhibitor developed as an inhaled anti-inflammatory agent for the maintenance treatment of COPD. UK-500,001 has been developed as a dry powder for inhalation (DPI) with the premise that topical administration of a PDE$_4$ inhibitor to the lung may reduce the propensity for side effects while maintaining equivalent or possibly introducing even greater, levels of clinical efficacy than that observed with oral agents. In vitro studies had shown the compound to effectively inhibit mediator release from human isolated neutrophils and peripheral blood mononuclear cells; UK-500,001 was similar to roflumilast in terms of PDE$_4$ enzyme potency and whole cell mediator release assays (5). In animal studies inhaled UK-500,001 inhibited lipopolysaccharide-induced neutrophilia and tumor necrosis factor-α accumulation in bronchoalveolar lavage fluid in rats in a dose dependent manner. Also, the compound inhibited histamine induced
bronchoconstriction in anesthetised rabbits and guinea-pigs, the latter in a
dose dependant manner (6).

The primary purpose of this study was to evaluate the efficacy and safety /
tolerability of UK-500,001 DPI in patients with COPD. The doses in the study
were intended to explore the dose range in anticipation of subsequent larger
scale efficacy and tolerability studies. The maximum dose (1mg BID) was
selected based on the maximum tolerated dose (MTD) determined in phase I
clinical studies, adjusted due to pharmacokinetic differences observed in
smokers and elderly subjects and the lower doses selected based on those
predicted to be efficacious in preclinical in vivo models.

**Methods**

*Study design*

This was a multi-centre, 6 week, randomized, double blind, placebo-
controlled, parallel group study in adult patients with moderate to severe
COPD as defined by GOLD stages II-III. The study comprised 8 clinic visits; a
screening visit, 2 visits during the run-in phase (week –2 and week -1), a
baseline visit with randomisation (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. The study is registered on the publicly accessible database
www.clinicaltrials.gov (NCT00263874).

*Study subjects*

Inclusion criteria were age 40-80 years, a smoking history of at least 10 pack-
years, a body mass index < 35 kg/m² and total body weight > 40 kg, moderate
or severe COPD according to GOLD criteria for at least 6 months with stable
disease for at least 1 month prior to screening, and informed written consent.
Exclusion criteria included a history of > 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 or a history of a lower respiratory tract infection or
significant disease instability during the month preceding study entry.
Other exclusion criteria were adult asthma, other chronic respiratory
disorders, a history or presence of respiratory failure, cor pulmonale or right
ventricular failure, or home oxygen therapy.

Study treatment
At the beginning of the double-blind treatment phase (week 0), patients were
randomized to receive either UK-500,001 DPI (0.1mg, 0.4mg, 1mg) BID or
matching placebo delivered via a single pin monodose capsule inhaler device
(Miat/Plastiape). A maximum tolerated dose (MTD) approach was used for
dose selection. Phase I studies indicated that 2mg BID was the MTD in
healthy volunteer studies however a study in smokers and elderly patients
showed modestly increased systemic exposure. Given this modest increase in
smokers and elderly subjects, both characteristics of COPD, the top dose of
1mg BID was selected. Patients were randomized to the treatment groups
0.1mg BID: 0.4mg BID : 1 mg BID : placebo in the ratio 1:1:1:1. Patients used
ipratropium bromide MDI 40µg QID as maintenance therapy and salbutamol
MDI for rescue use throughout the study. No other COPD medications were
allowed.
**Study Endpoints**

The primary endpoint was mean change from baseline in trough forced expiratory volume in 1 second (FEV₁) at week 6. Pulmonary function was measured at each visit according to American Thoracic Society standards (7) using the same spirometer (Masterscope CT, Viasys Healthcare GmbH, Hoechberg, Germany) in each centre. Measurements were made before use of study medication and bronchodilators; in addition, measurements were made after inhaling 200µg salbutamol at baseline and at the end of study. Centralized over-read / interpretation was performed for all lung function parameters to ensure consistent quality and reproducibility.

Secondary endpoints were other spirometric measures (FVC, FEV₆), inspiratory capacity (IC) and peak expiratory flow rate at week 2, 4, 6 and 8, Mahler dyspnoea index (BDI/TDI) at weeks 2, 4 and 6, COPD symptoms (breathlessness, sputum production and cough) and bronchodilator use recorded daily by the patient and Global Impression of Change (by both clinician and patient) at end of study. Adverse events (AEs) were recorded at each study visit as well as ECGs, lab data and vital signs.

**Interim analysis**

A pre-specified interim analysis for efficacy was performed based on the primary efficacy parameter. This analysis was triggered when 66 patients in the 1mg and placebo dose groups had completed double-blind treatment. The analysis compared the 1mg BID and placebo treated groups only, using a group sequential approach. The study could only be stopped for futility at the interim analysis; not for efficacy. If futility was not triggered, the study could complete recruitment and proceed to a final analysis.
Sample size determination

The sample size calculation was based on the primary efficacy endpoint, and the study was designed using group sequential methodology, allowing for an interim analysis for futility (comparing the 1mg BID dose group and placebo). Assuming a true difference between the 1mg BID treatment group and placebo of 0ml, then the study was designed such that the probability of stopping the study for futility was approximately 70%, based on a one-sided 5% level significance test and a Pocock stopping boundary. Further, if the study was not stopped at the interim it was required that the final analysis should have at least an 80% power to detect a difference in mean change from baseline in trough FEV₁ at week 6 of 75ml, based on a one-sided 5% significance level. The study was designed with an estimated standard deviation (SD) of 114ml, which resulted in a planned interim after 18 patients had completed in each treatment group, with a final study size of 200 randomised patients. However, emerging data from other studies suggested that the SD estimate may have been too low, so a blinded sample size re-estimation was performed after 30 patients had completed double-blind treatment. This resulted in a revised SD estimate of 173ml. In order to retain the statistical properties of the study as outlined, the subject numbers were revised with a planned interim analysis after 33 patients had completed in each treatment group. If the study did not stop at the interim analysis, the final study size was correspondingly increased to 324 patients. A drop out rate of no more than 11% was assumed throughout.

Patients with a baseline value and at least one 'on treatment' value recorded were included in the analyses.
Results

A total of 209 of an intended 324 patients, 152 men and 57 women, were entered into the study at 26 clinical centres. The pre-specified interim analysis for efficacy was performed based on the primary efficacy endpoint as mentioned above. The analysis was performed after 150 patients had completed double-blind treatment and the study was stopped for futility at this analysis. There was no adverse safety signal and patients who were already in the double blind phase of the study were informed of these findings and could either withdraw or continue to study completion. Therefore results contained here reflect the final analysis for all 209 patients entered in the trial, not those obtained at the interim analysis for futility.

Table 1 shows the characteristics of all randomized subjects in each treatment group. These data confirm that the subjects recruited into the trial were indeed GOLD stage II-III patients with a baseline post-bronchodilator FEV$_1$ of ~ 50% of predicted in each group, and a mean reversibility (to 400µg salbutamol) of ~15%, indicating room for improvement with an effective anti-inflammatory treatment in these patients. Comparison of the demographics across the treatment groups did not show any significant imbalance.

There was no statistically significant difference between the change from baseline in trough FEV$_1$ at week 6 for any dose compared to placebo, mean changes 0 ml (p=0.51), -18 ml (p=0.71), and 37 ml (p=0.14), for the 0.1, 0.4 and 1mg doses, respectively.

Mean change from baseline in trough FEV$_1$ in comparison with placebo at weeks 2, and 4 did not differ either for the 0.1 and 0.4mg doses, although
there was a statistically significant (p=0.0001) change of 119 mL compared to placebo after 2 weeks in the 1 mg group, as shown in Figure 2. There were no statistically significant differences between any dose and placebo on any other secondary efficacy parameters at week 6; some of these findings are shown in Table 2. As for FEV₁, there was a tendency to a response after 2 weeks in the 1 mg group on several parameters including FEV₆, FVC, Mahler dyspnea index and breathlessness on symptom scoring. This is illustrated in Figure 3 for breathlessness supported by the TDI score > 1 point difference at week 2 for 1.0mg compared to placebo. Further analyses were performed to assess the robustness of these conclusions, including analyses of patients who completed the study with no major protocol deviations, and analyses that examined whether smoking status, baseline reversibility or % predicted FEV₁ affected the efficacy outcomes. All of these analyses were consistent with the results described above.

Compared to placebo, there was a slightly higher incidence of treatment-related AEs reported in the 0.4 and 1 mg treatment groups; however, discontinuations due to AEs were similar across all groups. The most frequently occurring AEs are shown in table 3. There were 2 serious AEs; 1 patient on 1 mg of active drug experienced gastrointestinal effects requiring hospitalisation, and 1 patient on 0.4 mg of active drug was admitted to hospital due to pneumonia. There were no differences in exacerbation rates across the treatment groups; 10-15% of subjects experienced an exacerbation during the study.
Discussion

This study of a novel inhaled PDE$_4$ inhibitor showed no effect of treatment on spirometric measures and symptoms scores in patients with moderate and severe COPD. Given the previous reports on efficacy of oral PDE$_4$ inhibitors this finding is surprising and disappointing from patients’ outlook. All negative trials should be interpreted with caution to ensure that study design and methodology has not led to wrong conclusions (8). The study was adequately powered to detect clinically significant changes in trough FEV$_1$, the observed SD (157ml) was less than the expected SD (173ml), and a number of sensitivity analyses confirmed the results from the primary analyses. There is no reason to believe that patients included should be less responsive to patients in previous trials of PDE$_4$-inhibitors, given they are of comparable baseline disease severity (2) and showed significant reversibility to bronchodilator therapy. In addition, the 6 week treatment duration has been long enough to show clinical benefit in terms of improvements of trough FEV$_1$ in studies of oral PDE$_4$-inhibitors. Thus, we do not think that the study methodology or design is to blame for the lack of effect on the primary or secondary efficacy variables at week 6.

PDE$_4$ inhibitors have been suggested as promising anti-inflammatory agents targeting the inflammation characteristic of COPD (9). Subsequently, roflumilast has been found to reduce the absolute number of neutrophils in induced sputum (10) but neither roflumilast nor cilomilast has been shown to change the percentage of neutrophils in sputum (10, 11). The 12 week study of cilomilast (11) showed a reduction of CD8+ and CD68+ T-lymphocyte subsets in bronchial biopsies. only 1 year study published to date only showed
modest changes as a result of treatment with roflumilast; i.e., a change in 
FEV$_1$ of 39 mL and no statistically significant change in exacerbations, 
although the latter was seen in a subgroup analysis of patients with very 
severe COPD (4). This somewhat modest level of efficacy is consistent with a 
number of 26 week studies which were conducted with cilomilast, made 
publicly available via New Drug Application (NDA) submissions to the FDA, 
thoroughly reviewed by Giembycz (12). However, in all clinical studies 
treatment with PDE$_4$-inhibitors has been associated with significant side 
effects, in particular gastrointestinal side effects (2-4). It seems unlikely that 
greater efficacy can be achieved with the existing oral PDE$_4$-inhibitors by 
higher doses as maximal clinical tolerability seems to have been reached with 
current dosing (4, 12).

Our findings show a clear discrepancy with studies of oral PDE$_4$ inhibitors in 
terms of the failure of UK-500,001 to show significant and maintained efficacy 
in moderate to severe COPD. The first explanation that comes to mind is that 
systemic PDE$_4$ inhibition, and hence anti-inflammatory activity, is required to 
provide clinical benefit of this class of agents in COPD. However, the 
preclinical data do not support this explanation with topical anti-inflammatory 
effects shown in animal models with inhaled UK-500,001 (5, 6). In addition we 
did detect an early (i.e. at 2 weeks) efficacy signal in the primary efficacy 
parameter supported by improvements in some secondary efficacy 
parameters with the 1mg BID dosing group. Given that this improvement was 
only seen at the highest dose and was seen across a number of endpoints, it 
would seem unlikely that this was due to a type 1 error (i.e. a false positive), 
suggesting a true efficacy signal with UK-500,001 by the inhaled route at this
timepoint and dose. Finally, the adverse event profile in the study indicates that there was also systemic PDE$_4$-inhibitor action of inhaled UK-500,001. The early efficacy signal detected also seems to rule out a second possible explanation for the overall failure of the study to detect significant and maintained efficacy, namely that UK-500,001 did not reach areas of the diseased COPD lung containing active inflammation (eg. due to mucus plugging and fixed airways obstruction leading to reduced air-flow and ventilation, well described characteristics of COPD) in high enough concentrations or reached areas of inflammation in high enough concentrations but was not retained for a sufficient period of time to produce sustained activity. It is not possible to fully exclude this as a possible explanation, although it would seem surprising that a topically administered compound can exert systemic side effects, which were prolonged in Phase I studies, without having any persistent effects in the respiratory system. Given the early (i.e. 2 week) effect of 1mg BID UK-500,001 on both primary and secondary endpoints, a perhaps more likely explanation for the lack of a maintained efficacy is the development of tachyphylaxis or tolerance on repeated dosing. Consistent with this interpretation is the clinical observation that oral PDE4 inhibitors cilomilast and roflumilast seem to show greater levels of efficacy in shorter (i.e. 6 weeks; 2,3) as opposed to longer term (i.e. 26-52 weeks; 4,12) clinical studies. To further support this explanation there is the interesting preclinical observation that increasing intracellular cyclic AMP (the main effect of PDE$_4$ inhibition) may in itself lead to up-regulation of PDE$_4$ activity either by phosphorylation or by altered gene transcription and translation (reviewed in 13), and could be part of the explanation for reduced
inflammatory cell sensitivity to, for example, beta2-agonists on prolonged exposure (14).

In conclusion, the inhaled isotype non-specific, selective PDE4 inhibitor UK-500,001 did not demonstrate efficacy at any dose, up to and including the maximum tolerated dose, in patients with moderate-severe COPD. Given that the best of the oral isotype non-specific agents described to date, have shown only modest clinical benefit in COPD in the absence of dose limiting toleration issues, an obvious attempt to improve the therapeutic index of this mechanism, with the potential to realise improved efficacy, has been delivering a selective, but isotype non-specific, PDE4 inhibitors by inhalation. This was the therapeutic rationale behind progression of UK-500,001. Thus, the findings of this study should lead to doubt about the future role of inhaled PDE4-inhibitors in COPD, although it will require future studies with other inhaled PDE4 inhibitors to fully test this hypothesis.

Investigators:


inhibits TNFα, MIP1β and LTB4 release from native human blood cells.
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13. Lugnier C. Cyclic nucleotide phosphodiesterase (PDE) superfamily: A
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Pharmacol & Therapeutics 2006; 109: 366 – 398

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Table 1
Baseline characteristics for the 209 included patients.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>UK-500,001 (0.1mg BID)</th>
<th>UK-500,001 (0.4mg BID)</th>
<th>UK-500,001 (1mg BID)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>53</td>
<td>55</td>
<td>48</td>
<td>53</td>
</tr>
<tr>
<td>Gender Male (%)</td>
<td>37 (70)</td>
<td>44 (80)</td>
<td>33 (69)</td>
<td>38 (72)</td>
</tr>
<tr>
<td>Age Mean (range)</td>
<td>65 (45-80)</td>
<td>63 (43-78)</td>
<td>62 (46-79)</td>
<td>65 (45-78)</td>
</tr>
<tr>
<td>Weight (kg) Mean</td>
<td>68.5</td>
<td>74.8</td>
<td>76.6</td>
<td>72.9</td>
</tr>
<tr>
<td>Smoking Smoker</td>
<td>25</td>
<td>14</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>28</td>
<td>41</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td>FEV1 (L) Mean (SD)</td>
<td>1.37 (0.46)</td>
<td>1.45 (0.47)</td>
<td>1.53 (0.48)</td>
<td>1.43 (0.49)</td>
</tr>
<tr>
<td>FEV1%pred Mean (SD)</td>
<td>51.0 (14.6)</td>
<td>49.3 (12.3)</td>
<td>53.9 (14.2)</td>
<td>52.2 (14.2)</td>
</tr>
<tr>
<td>Reversibility (%)</td>
<td>16.2 (15.0)</td>
<td>14.1 (14.8)</td>
<td>14.0 (14.1)</td>
<td>13.7 (16.4)</td>
</tr>
</tbody>
</table>
Table 2. Change from baseline in secondary effect parameters.

<table>
<thead>
<tr>
<th></th>
<th>UK500,001 0.1 mg BID</th>
<th>UK500,001 0.4 mg BID</th>
<th>UK500,001 1.0 mg BID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough FEV&lt;sub&gt;6&lt;/sub&gt; (L)</td>
<td>-0.050</td>
<td>-0.040</td>
<td>-0.007</td>
<td>-0.015</td>
</tr>
<tr>
<td>Trough FVC (L)</td>
<td>-0.095</td>
<td>-0.065</td>
<td>-0.025</td>
<td>-0.023</td>
</tr>
<tr>
<td>Trough IC (L)</td>
<td>0.070</td>
<td>0.012</td>
<td>-0.012</td>
<td>0.020</td>
</tr>
<tr>
<td>Breathlessness score</td>
<td>0.066</td>
<td>0.037</td>
<td>-0.062</td>
<td>0.014</td>
</tr>
<tr>
<td>Cough score</td>
<td>0.100</td>
<td>-0.077</td>
<td>-0.120</td>
<td>0.080</td>
</tr>
<tr>
<td>Sputum score</td>
<td>0.023</td>
<td>0.126</td>
<td>0.038</td>
<td>-0.006</td>
</tr>
</tbody>
</table>

FEV<sub>6</sub> – Forced expiratory volume in 6 seconds, FVC – forced vital capacity, IC – inspiratory capacity.
Table 3. Adverse reactions occurring in more than 5% of patients in any treatment group

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>UK-500,001</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1mg (n=53)</td>
<td>0.4mg (n=55)</td>
</tr>
<tr>
<td>Any</td>
<td>16 (30.2%)</td>
<td>25 (45.5%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2 (3.8%)</td>
<td>4 (7.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (5.7%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td>6 (11.3%)</td>
<td>10 (18.2%)</td>
</tr>
</tbody>
</table>
Figure legends

Figure 1.
CONSORT diagram
Figure 2.
Mean change from baseline in trough FEV$_1$ at weeks 2, 4 and 6 for the 4 treatment groups.

Figure 3.
Mean change from baseline breathlessness score at weeks 2, 4 and 6 for the 4 treatment groups.