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A controlled trial of 6 weeks' treatment with a novel inhaled PDE_4 inhibitor in COPD

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Abstract

Anti-inflammatory drugs are lacking in COPD and inhibitors of the phosphodiesterase type-4 (PDE_4) 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 PDE_4-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 PDE_4-inhibitor related side effects were observed, especially in the highest dose group.

Our findings question the role of inhaled PDE_4-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 $\geq$ 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 bronchioalveolar 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/m^2 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 (FEV_1) 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, FEV_6), 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 FEV_1 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 treatement 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 FEV_1, there was a tendency to a response after 2 weeks in the 1 mg group on several parameters including FEV_6, 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 FEV_1 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, beta$_2$-agonists on prolonged exposure (14).

In conclusion, the inhaled isotype non-specific, selective PDE$_4$ 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, PDE$_4$ 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 PDE$_4$-inhibitors in COPD, although it will require future studies with other inhaled PDE4 inhibitors to fully test this hypothesis.

Investigators:

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Table 1

Baseline characteristics for the 209 included patients.

Treatment	UK-500,001 (0.1mg BID)	UK-500,001 (0.4mg BID)	UK-500,001 (1mg BID)	Placebo
N	53	55	48	53
Gender				
Male (%)	37 (70)	44 (80)	33 (69)	38 (72)
Age				
Mean (range)	65 (45-80)	63 (43-78)	62 (46-79)	65 (45-78)
Weight (kg)				
Mean	68.5	74.8	76.6	72.9
Smoking				
Smoker	25	14	16	24
Ex-smoker	28	41	32	29
FEV_1 (L)				
Mean (SD)	1.37 (0.46)	1.45 (0.47)	1.53 (0.48)	1.43 (0.49)
FEV_1%pred				
Mean (SD)	51.0 (14.6)	49.3 (12.3)	53.9 (14.2)	52.2 (14.2)
Reversibility (%)				
Mean (SD)	16.2 (15.0)	14.1 (14.8)	14.0 (14.1)	13.7 (16.4)

Table 2. Change from baseline in secondary effect parameters.

	UK500,001 0.1 mg BID	UK500,001 0.4 mg BID	UK500,001 1.0 mg BID	Placebo
Trough FEV_6 (L)	-0.050	-0.040	-0.007	-0.015
Trough FVC (L)	-0.095	-0.065	-0.025	-0.023
Trough IC (L)	0.070	0.012	-0.012	0.020
Breathlessness score	0.066	0.037	-0.062	0.014
Cough score	0.100	-0.077	-0.120	0.080
Sputum score	0.023	0.126	0.038	-0.006

FEV_6 – 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

Adverse Reaction	UK-500,001			Placebo
	0.1mg (n=53)	0.4mg (n=55)	1.0mg (n=48)	
Any	16 (30.2%)	25 (45.5%)	17 (35.4%)	23 (43.4%)
Diarrhoea	2 (3.8%)	4 (7.3%)	3 (6.3%)	1 (1.9%)
Headache	3 (5.7%)	1 (1.8%)	6 (12.5%)	1 (1.9%)
Respiratory Disorders	6 (11.3%)	10 (18.2%)	5 (10.4%)	7 (13.2%)

Figure legends

Figure 1.

CONSORT diagram

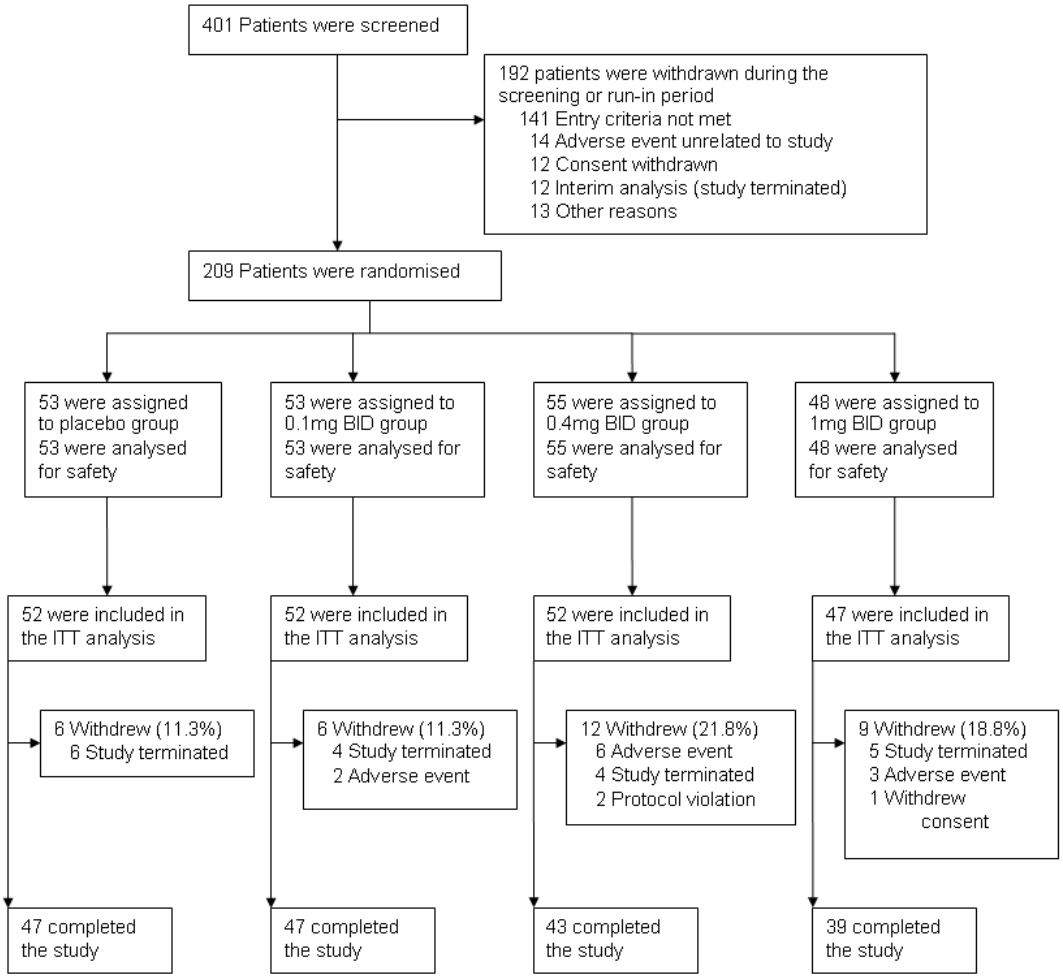


Figure 2.

Mean change from baseline in trough FEV_1 at weeks 2, 4 and 6 for the 4 treatment groups.

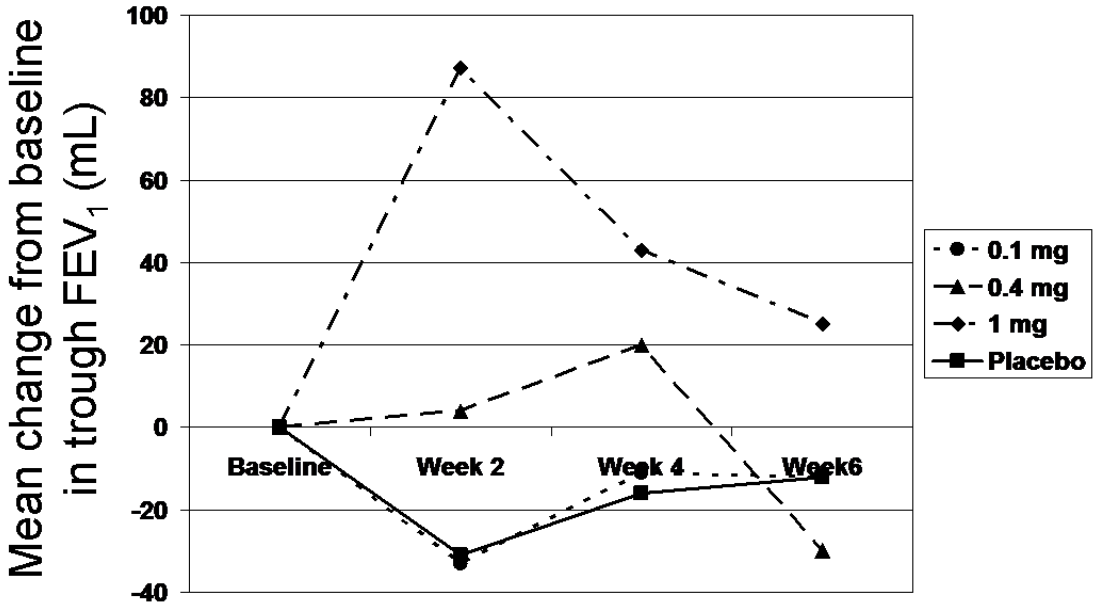
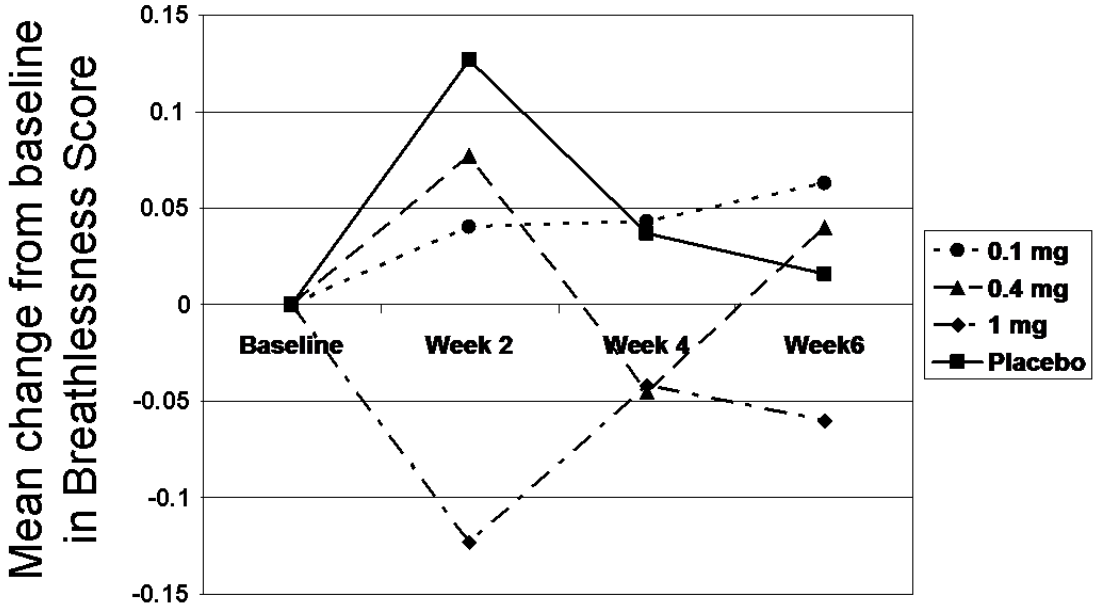


Figure 3.

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


Mean change from baseline in Breathlessness Score
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
Baseline
Week 2
Week 4
Week6
0.1 mg
0.4 mg
1 mg
Placebo