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An evaluation of comparative treatment effects with high and low dose fluticasone propionate/formoterol combination in asthma

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ABSTRACT

Background: Despite extensive use of inhaled corticosteroid/long-acting β_2-agonist combinations in asthma, limited data evaluating dose–response for this combination class are available. The benefits of dose escalation and nature of patient subgroups likely to benefit are thus ill-defined.
Method: In this randomised, double-blind, 8-week study the effects of two dose levels (100/10 and 500/20 μg b.i.d.) of a fixed combination of fluticasone/formoterol (***flutiform***®) were compared in 309 patients. Treatment effects upon spirometric and symptom-based endpoints were examined in the overall population and in two subgroups defined *a priori* by % predicted FEV_1 at baseline (≥40–≤60% ["severe" airways obstruction] and >60–≤80% ["moderate" airways obstruction]).
Results: No dose–response was evident for spirometric outcomes (FEV_1, FEV_1 AUC_{0-12}, PEFR) either overall or in either subgroup. At variance with the spirometric data, statistically significant dose-dependent differences were seen for nocturnal outcomes and consistent numerical differences were found across multiple symptom-based outcomes (symptom scores, sleep scores, rescue medication use, asthma control days, AQLQ scores, exacerbations); greater effects were noted with the higher dose of fluticasone/formoterol. Between-group differences for the overall population were driven by treatment effect differences in the "severe" subgroup.
Conclusion: In this exploratory comparison a high dose of fluticasone/formoterol in asthmatic patients appears to provide additional improvement in symptom-based rather than spirometric outcomes. Additional benefits from high versus low dose treatment are most likely in patients with severe airway obstruction, although the doses at which ceiling effects are attained may vary between individuals.
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1. Background

Clinical development of fixed combination drugs for asthma, such as fluticasone propionate/salmeterol or budesonide/formoterol, has historically involved extrapolation of the dose levels approved (or shown to be effective) for the monoproducts to derive an appropriate fixed combination dose. In pivotal phase 3 studies, a single dose level of the fixed combination has then been compared to equivalent doses of one or more of the constituent monoproducts [1,2]. As a result of such practice, reflecting the fact that regulatory authorities have not previously required head-to-head dose level comparisons to support a proposed dose range for the combination, there are few data directly comparing different dose levels of an inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) despite the use of this class in asthma management for approximately 15–20 years. Indeed no published data are available in asthmatic subjects regarding the comparative clinical effects of fluticasone/salmeterol, beclometasone/formoterol or fluticasone furoate/vilanterol at different dose levels; whilst only one study has directly compared different dose levels of budesonide/formoterol [3] alongside three further budesonide/formoterol studies in which two dose levels were evaluated albeit not directly compared [4–7]. A single further study evaluating two dose levels of mometasone/formoterol is available again without a direct pairwise analysis [8]. As a result of this sparse evidence base the feasibility of demonstrating dose–response is

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uncertain and there is little guidance for prescribers as to when dose escalation of an ICS/LABA may be warranted. In recent years however, European regulatory authorities have become increasingly interested in dose–response data suggesting that the provision of such data will increase which in turn may allow more informed treatment decisions to be made.

In this paper we present the results of a *post hoc* analysis in which two dose levels of ***flutiform***®, an ICS/LABA comprising fluticasone propionate and formoterol fumarate in combination (fluticasone/formoterol) in a pressurised metered-dose inhaler were compared in an exploratory manner. The study has been previously reported [9] but here we focus solely on the comparison of fluticasone/formoterol dose levels, in an attempt to shed light on dose–response for ICS/LABAs and provide insights into the utility of current regulatory guidelines.

2. Methods

The details of the study protocol and main findings have been published elsewhere [9]. Briefly, this was a double-blind, double-dummy, parallel-group study. Adults (≥18 years) with a history of asthma characterized by ICS treatment with ≥500 μg fluticasone or equivalent, a pre-bronchodilator FEV_1 of ≥40% to ≤80% predicted, and FEV_1 reversibility of ≥15% post-salbutamol were eligible for inclusion. Patients discontinued their usual asthma medications and entered a 2-week open-label run-in period in which they were given fluticasone 250 μg twice daily (b.i.d.) (*Flixotide*®, GlaxoSmithKline, UK). Patients uncontrolled at the end of this run-in (i.e., who required rescue medication for at least 3 days, *and* had at least 1 night with sleep disturbance or at least 3 days with asthma symptoms during the last 7 days of the run-in period) were randomised *inter alia* to 8 weeks treatment with one of two doses of fluticasone/formoterol (500/20 μg or 100/10 μg b.i.d.; *flutiform*® hydrofluoroalkane [HFA] pMDI) via a spacer (*AeroChamber Plus*®, Trudell Medical International, UK). This comparison therefore entailed a five-fold difference in ICS and a two-fold difference in LABA dose. Randomisation was stratified by % predicted FEV_1 at baseline (≥40–≤60% versus >60–≤80%) which provided a straightforward basis for a dichotomised subgroup analysis by baseline FEV_1 severity.

2.1. Patients

The co-primary endpoints were the mean change in morning pre-dose FEV_1 from baseline to the end of treatment; and the mean change in FEV_1 from morning pre-dose at baseline to 2 h post-morning dose at the end of treatment. Secondary efficacy endpoints of interest can be classified as "spirometric", i.e. mean 12-h FEV_1 area under the curve (AUC_{0-12}) at day 0 and day 56 (in a subset of 48% of patients) and daily morning and evening peak expiratory flow rate (PEFR); and "symptom-related", i.e. asthma symptoms scores, symptom free days, sleep disturbance scores,

Table 1
Demographic and Baseline Spirometric Characteristics for high and low dose fluticasone/formoterol pMDI dichotomised by percentage predicted FEV_1 at baseline (ITT Population).

Endpoint	Fluticasone/formoterol 500/20 μg b.i.d. (high dose)	Fluticasone/formoterol 100/10 μg b.i.d. (low dose)
N	154	155
Mean age [years (SD)]	50.5 (14.4)	48.0 (13.9)
- FEV_1 ≤60% predicted subgroup	51.1 (14.11)	48.6 (14.10)
- FEV_1 >60% predicted subgroup	49.8 (14.76)	47.4 (13.80)
Male/female [n (%)]	56 (36.4)/98 (63.6)	60 (38.7)/95 (61.3)
- FEV_1 ≤60% predicted subgroup	38 (48.1)/41 (51.9)	31 (40.3)/46 (59.7)
- FEV_1 >60% predicted subgroup	18 (24.0)/57 (76.0)	29 (37.2)/49 (62.8)
Mean duration of asthma [years(SD)]	12.7 (11.82)	13.5 (12.49)
- FEV_1 ≤60% predicted subgroup	12.8 (12.46)	12.0 (10.86)
- FEV_1 >60% predicted subgroup	12.6 (11.18)	14.9 (13.84)
Median ICS requirement pre-study [μg FP-equivalent/day (range)]	500 (250–1500)	500 (80–1500)
- FEV_1 ≤60% predicted subgroup	500 (250–1500)	500 (80–1000)
- FEV_1 >60% predicted subgroup	500 (400–1000)	500 (250–1500)
LABA co-administration pre-study [n (%)]	118 (76.6)	112 (72.3)
- FEV_1 ≤60% predicted subgroup	63 (79.7)	53 (68.8)
- FEV_1 >60% predicted subgroup	55 (73.3)	59 (75.6)
Mean FEV_1 reversibility [% (SD)]	31.6 (17.29)	30.5 (15.08)
- FEV_1 ≤60% predicted subgroup	32.9 (19.76)	31.8 (15.67)
- FEV_1 >60% predicted subgroup	30.2 (14.24)	29.2 (14.47)
Mean FEV_1 predicted at Day 0 [%(SD)]	60.0 (10.94)	60.3 (10.33)
- FEV_1 ≤60% predicted subgroup	51.00 (5.37)	51.84 (5.34)
- FEV_1 >60% predicted subgroup	69.54 (6.21)	68.66 (6.56)
Mean pre-dose FEV_1 at Day 0 [L (SD)]	1.73 (0.52)	1.81 (0.58)
- FEV_1 ≤60% predicted subgroup	1.51 (0.42)	1.54 (0.45)
- FEV_1 >60% predicted subgroup	1.97 (0.51)	2.09 (0.56)
Mean morning pre-dose PEFR at Day 0 [L/min (SD)]	310.7 (124.45)	312.7 (124.52)
- FEV_1 ≤60% subgroup	310.1 (138.56)	308.5 (138.78)
- FEV_1 >60% subgroup	311.3 (108.56)	316.8 (109.38)
Mean evening pre-dose PEFR at Day 0 [L/min (SD)]	315.5 (123.10)	321.7 (125.55)
- FEV_1 ≤60% predicted subgroup	313.7 (139.98)	317.2 (140.12)
- FEV_1 >60% predicted subgroup	317.4 (103.29)	326.1 (110.03)

Day 0: baseline; FP: fluticasone propionate; SD: standard deviation.
FEV_1 ≤60% predicted subgroup: N = 79 in fluticasone/formoterol high dose group and N = 77 in fluticasone/formoterol low dose group; FEV_1 >60% predicted subgroup: N = 75 in fluticasone/formoterol high dose group and N = 78 in fluticasone/formoterol low dose group.

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