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

Sanjeeva Dissanayake [a,*], Meena Jain [b,1], Birgit Grothe [a], Tammy McIver [c,1], Alberto Papi [d]

[a] Medical Sciences, Mundipharma Research Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0AB United Kingdom
[b] Medical Affairs, Napp Pharmaceuticals Limited, Cambridge Science Park, Milton Road, Cambridge, United Kingdom
[c] Clinical Data Management and Statistics, Mundipharma Research Limited, Cambridge Science Park, Milton Road, Cambridge, United Kingdom
[d] Research Centre on Asthma and COPD, University of Ferrara, Ferrara, Italy

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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.
Trial registration: ClinicalTrials.gov identifier: NCT00734318; EudraCT number: 2007-001633-34.

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

* Corresponding author.
E-mail addresses: sanjeeva.dissanayake@mundipharma-rd.eu (S. Dissanayake), meena_jain1@hotmail.com (M. Jain), birgit.grothe@mundipharma-rd.eu (B. Grothe), tammy2mclver@gmail.com (T. McIver), ppa@unife.it (A. Papi).
[1] Address at the time this analysis was conducted.

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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.

awakening free nights, asthma control days, rescue medication use, asthma exacerbations and asthma quality of life questionnaire (AQLQ) scores.

2.2. Statistical analysis

Analysis of all endpoints was based on the ITT population. The ITT population included all randomised patients who received at least one dose of study treatment and had at least one post-dose primary efficacy variable (FEV_1) measurement.

Change from baseline in pre-dose FEV_1, 2-h post-dose FEV_1, morning and evening PEFR, asthma symptom scores, percentage of symptom-free days, sleep disturbance scores, percentage of awakening-free nights, percentage of asthma control days, percentage of rescue medication-free days and AQLQ scores at the end of treatment were analysed using Analysis of Covariance (ANCOVA) with treatment as a factor, asthma severity and baseline value as covariates and centre as a random effect. 12-h serial FEV_1 AUC at Day 0 and end of treatment were analysed using ANCOVA with asthma severity and pre-dose FEV_1 as covariates. Missing values were imputed using the last observation carried forward.

The proportion of patients experiencing any asthma exacerbations and severe asthma exacerbations were analysed using Fisher's exact test.

The following *post-hoc* analyses were also performed: analysis of annualized exacerbation rates using a negative binomial model with treatment as a factor and length of exposure as an offset variable; analysis of the proportion of patients achieving an increase (improvement) in AQLQ score of ≥0.5 units using a logistic regression model with treatment as a factor, and overall AQLQ score at Day 0 as a covariate; and subgroup analysis of all endpoints according to FEV_1% predicted category at baseline (≤60%, >60%), the dichotomy which provided the basis for stratified randomisation.

3. Results and discussion

3.1. Patients

At the end of the 2-week run-in period (on fluticasone 250 μg b.i.d.), 309 patients were randomised to the two doses of fluticasone/formoterol with stratification according to % predicted FEV_1 (≤60% or >60%).

The two fluticasone/formoterol treatment groups (155 patients allocated to 100/10 μg b.i.d.; 154 to 500/20 μg b.i.d.) were well balanced in terms of demographics and baseline asthma characteristics. Similarly characteristics of the FEV_1 ≤60% subgroup (77 patients allocated to 100/10 μg b.i.d.; 79 to 500/20 μg b.i.d) were similar in each treatment group as were those of the FEV_1 >60% subgroup (78 patients allocated to 100/10 μg b.i.d.; 75 to 500/20 μg b.i.d) (Tables 1 and 2).

3.2. Spirometric efficacy parameters

The co-primary endpoints of the change in pre- and 2-h post-dose FEV_1 at study end from pre-dose FEV_1 at baseline demonstrated numerically greater effects with the high versus low dose of fluticasone/formoterol (Fig. 1). However, the between-group differences were neither statistically significant nor clinically relevant (pre-dose FEV_1 0.04 L, (95% CI –0.07, 0.16; p = 0.437); 2-h post-dose FEV_1 0.01 L (95% CI –0.10, 0.12; p = 0.840)). Regarding other spirometric endpoints (the change in morning and evening diary PEFR at study end from baseline and FEV_1 $AUC_{0–12}$ at day 0 and day 56) there was again no difference between high and low fluticasone/formoterol dose groups (Fig. 1). The 95% confidence intervals for these differences were more or less symmetrically distributed around the line of unity essentially illustrating the similarity of spirometric effects with both dose levels (Fig. 1).

Table 2
Baseline Symptom-Related 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 % symptom-free days at Day 0 (SD)	16.14 (22.91)	21.38 (26.32)
- FEV_1 ≤60% predicted subgroup	17.18 (23.37)	21.52 (26.18)
- FEV_1 >60% predicted subgroup	15.05 (22.51)	21.25 (26.63)
Mean % asthma control days at Day 0 (SD)	9.00 (16.73)	9.95 (16.95)
- FEV_1 ≤60% predicted subgroup	7.78 (14.97)	7.33 (15.21)
- FEV_1 >60% predicted subgroup	10.29 (18.43)	12.25 (18.06)
Mean % awakening-free nights at Day 0 (SD)	46.10 (37.37)	50.23 (38.19)
- FEV_1 ≤60% predicted subgroup	45.21 (37.20)	46.75 (38.96)
- FEV_1 >60% predicted subgroup	47.04 (37.78)	53.66 (37.35)
Mean % rescue medication-free days at Day 0 (SD)	15.68 (21.03)	15.67 (20.77)
- FEV_1 ≤60% predicted subgroup	15.37 (21.19)	14.10 (20.66)
- FEV_1 >60% predicted subgroup	16.00 (21.00)	17.22 (20.89)
Mean asthma symptom scores at Day 0 (SD)	1.17 (0.61)	1.10 (0.63)
- FEV_1 ≤60% predicted subgroup	1.15 (0.63)	1.11 (0.59)
- FEV_1 >60% predicted subgroup	1.19 (0.58)	1.06 (0.62)
Mean sleep disturbance scores at Day 0 (SD)	0.65 (0.57)	0.58 (0.54)
- FEV_1 ≤60% predicted subgroup	0.63 (0.52)	0.62 (0.57)
- FEV_1 >60% predicted subgroup	0.67 (0.62)	0.54 (0.53)
Mean AQLQ scores at Day 0 (SD)	4.42 (0.89)	4.56 (0.93)
- FEV_1 ≤60% predicted subgroup	4.47 (0.93)	4.55 (0.92)
- FEV_1 >60% predicted subgroup	4.34 (0.83)	4.55 (0.94)

Day 0: baseline; SD: standard deviation; AQLQ: Asthma Quality of Life Questionnaire.
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.

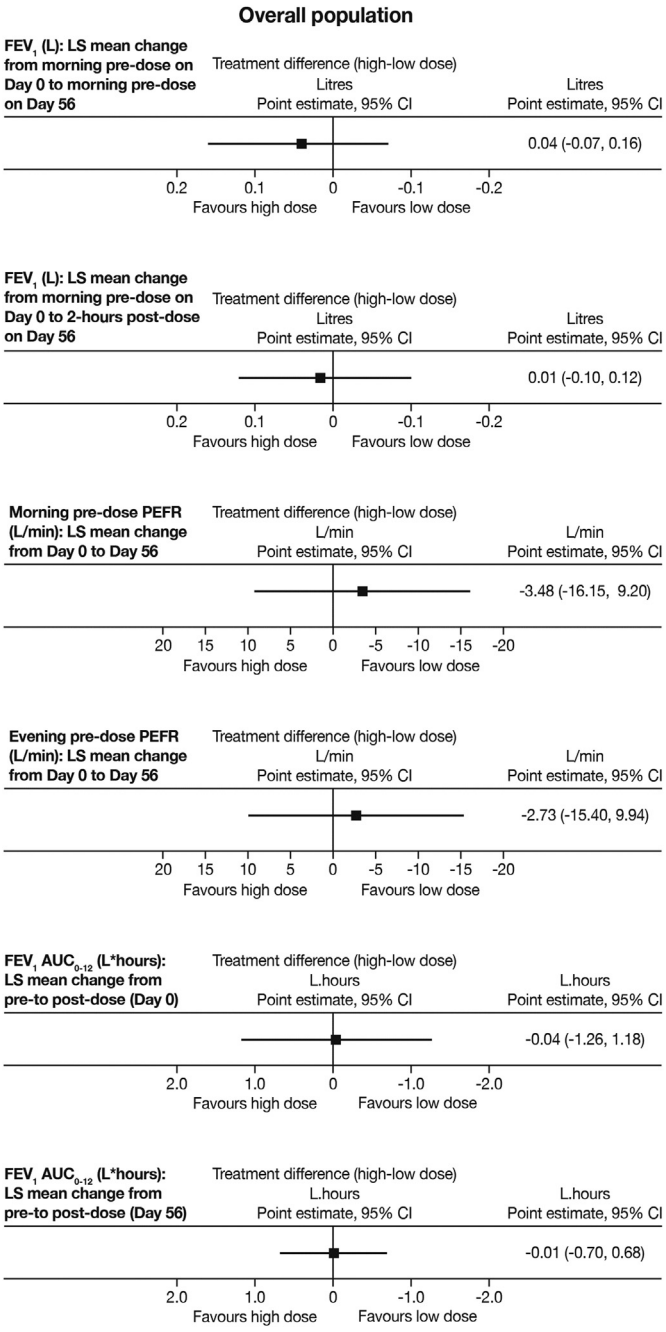

Fig. 1. Spirometric treatment differences (95% CIs) between high and low dose fluticasone/formoterol pMDI (Overall ITT population). LS = Least Squares; Day 0 = Baseline; CI = Confidence Interval; AUC = Area Under the Curve.

Subgroup analysis of the above spirometric endpoints with the population dichotomised according to % predicted FEV_1 at baseline also failed to demonstrate statistically or clinically significant differences between the low and high fluticasone/formoterol dose, or any consistent trends (Fig. 2 and Table S1).

3.3. Symptom-related efficacy parameters

Results for symptom-related endpoints in the study are summarised in Fig. 3.

Although the study was not powered to evaluate treatment differences for symptom-based endpoints, statistically significant differences (at the 5% level) were noted for the change in sleep disturbance scores (–0.12 units; p = 0.005) and the change in the percentage of awakening free nights (9.87%; p = 0.002), (Fig. 3) in favour of high dose fluticasone/formoterol. A numerical difference in favour of the high dose was observed for asthma symptom scores, symptom-free days, AQLQ scores and the annualized rate of exacerbations. Consistent treatment effect differences across almost all symptom-based endpoints, and the distribution of the associated 95% confidence intervals illustrated in Fig. 3, suggested an overall benefit in favour of high dose fluticasone/formoterol.

Subgroup analyses of the symptom-related endpoints according to percentage predicted FEV_1 at baseline (≤60% and >60%) were undertaken, as for the spirometric endpoints (see Fig. 4 and Tables S2–S4).

These subgroup analyses showed that overall treatment effect differences between the fluticasone/formoterol high and low doses for the symptom-related endpoints were consistently more evident in the "severe" FEV_1 subgroup. In the latter subgroup the differences were statistically significant for change in sleep disturbance scores, change in percent of awakening-free nights and change in AQLQ scores and were close to being statistically significant for 3 other endpoints (change in asthma symptom scores [p = 0.085], annualized rate of asthma exacerbations [p = 0.064], and the proportion of subjects attaining an increase in AQLQ ≥ 0.5 units [p = 0.080]). By contrast in the "moderate" subgroup, other than for nocturnal symptoms, there was no difference between high and low doses of fluticasone/formoterol for the symptom-based endpoints. Overall, for all 11 symptom-based endpoints treatment effect differences between high and low dose fluticasone/formoterol were greater in the "severe" than in the "moderate" subgroup. Notably, baseline symptom scores were similar in these two subgroups.

3.4. Safety

There was no evidence of an adverse qualitative or quantitative dose-related effect on safety. Adverse events were reported in 19.5% and 18.7% of the fluticasone/formoterol high and low dose groups, respectively. The most common adverse events were nasopharyngitis (1.9% and 1.3%, respectively), pharyngitis (1.3% and 1.3%, respectively) and asthma (1.9% and 1.9%, respectively). Two patients in each dose group (1.3%) reported severe asthma exacerbations as adverse events. There were no reports of biochemical or clinically overt adrenal axis suppression. No subjects in either group experienced serious adverse events. Six patients in the high dose group withdrew due to a lack of efficacy (3.9%) compared to 18 (11.6%) in the low dose group (difference –7.7% [95% CI: –13.6, –1.8]; p = 0.018). Clinical laboratory evaluations were unremarkable: effects upon glucose and potassium revealed no consistent differences between treatment groups.

4. Conclusions

To our knowledge, this is only the second clinical study to explicitly compare the effects of two dose levels of a fixed dose combination ICS/LABA upon spirometric and patient-centred outcomes in asthmatic patients, and the first to assess dose–response in subgroups of patients with moderate and severe airways obstruction. Aubier et al. reported a six month, open-label study comparing budesonide/formoterol 400/12 μg b.i.d. versus 200/6 μg b.i.d. administered as maintenance and reliever therapy [3]. Comparative data for different dose levels of budesonide and formoterol in combination [4–7] and for a fixed combination of mometasone/formoterol [8] are also available from four further studies although none of these include inferential comparisons between treatment groups in which different dose levels are used. No comparable data are available for other ICS/LABA combinations such as fluticasone propionate/salmeterol or beclometasone/

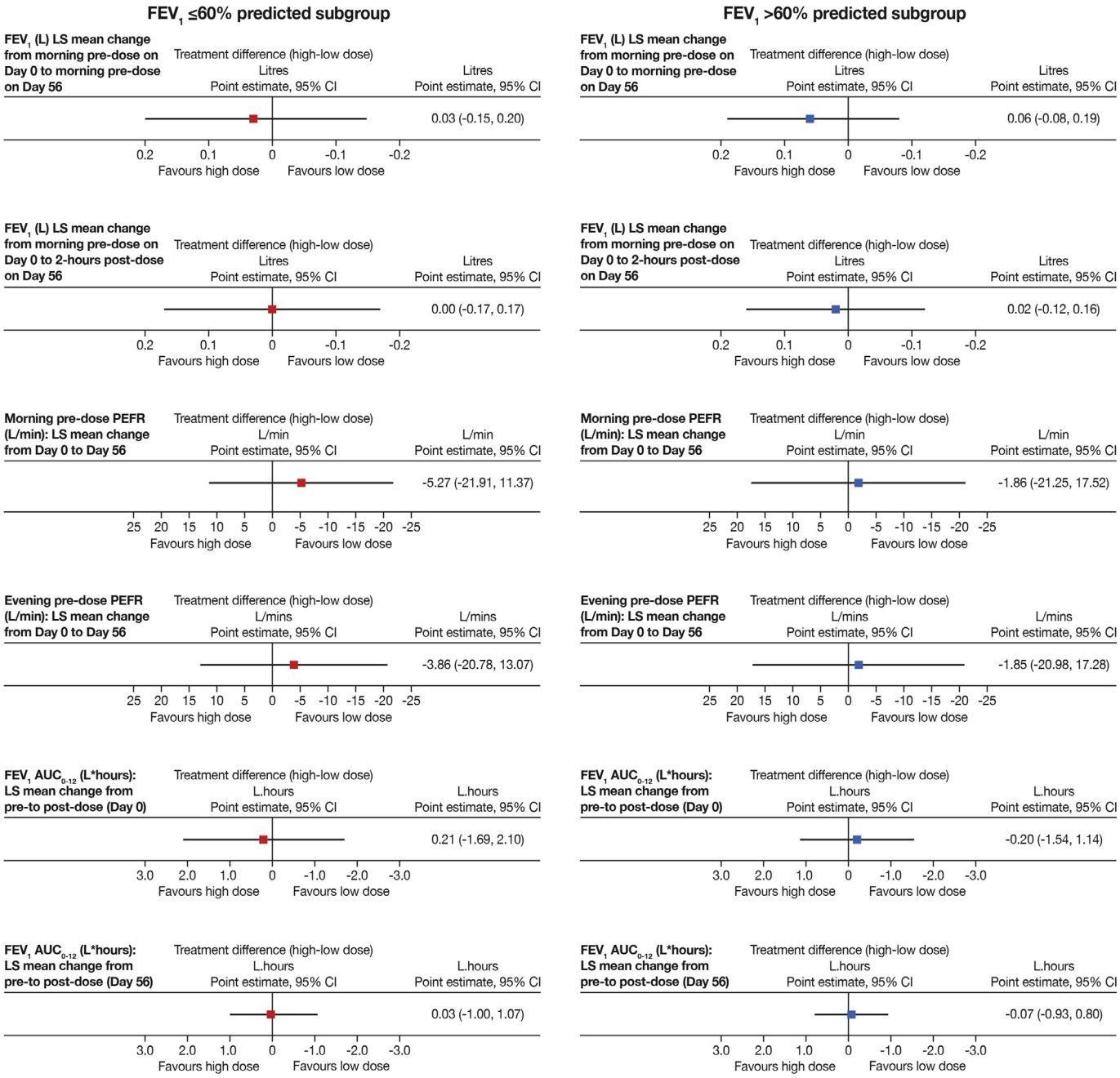

Fig. 2. Spirometric treatment differences (95% CIs) between high and low dose fluticasone/formoterol pMDI dichotomised by percentage predicted FEV_1 at baseline (ITT population). LS = Least Squares; Day 0 = Baseline; CI = Confidence Interval; AUC = Area Under the Curve.

formoterol. In the present study the top and bottom daily dose levels of the fluticasone/formoterol dose range were evaluated, since multiple previous studies have shown minimal pairwise differences in effect between contiguous dose levels of ICS and β_2-agonist monotherapies in asthma [10–16].

A potential criticism of this study is its short duration. However, with corticosteroid-based therapy improvement of lung function and symptom control in asthma is typically rapid, occurring within one to two weeks [17]. Treatment effects other than airways hyperresponsiveness are generally (near-) maximal within 1–3 months in most patients, and several long-term studies have demonstrated that key conventional endpoints, such as lung function effects and symptom scores, are sustained but do not usually improve substantially beyond improvements seen at 1–2 months with ICS monotherapy or ICS/LABA combinations [18–20]. Furthermore treatment *differences* for lung function, symptoms and rescue medication use between different ICS/LABAs or between ICS/LABAs and ICSs are typically static over 2–12 months or increase modestly but in the same direction as that seen at early time points [19,20]. In a similar manner treatment differences in event based outcomes (such as exacerbations) are either static or increase in magnitude in the same direction between 2 and 12 months [20,21]. In view of these observations the treatment differences observed over 8 weeks in our study have reasonable predictive value over the longer-term.

Randomisation in our study was stratified by percent predicted FEV_1, which provided a simple means for a dichotomised subgroup analysis of "moderate" and "severe" patients. The lack of any consistent evidence of dose–response for standard

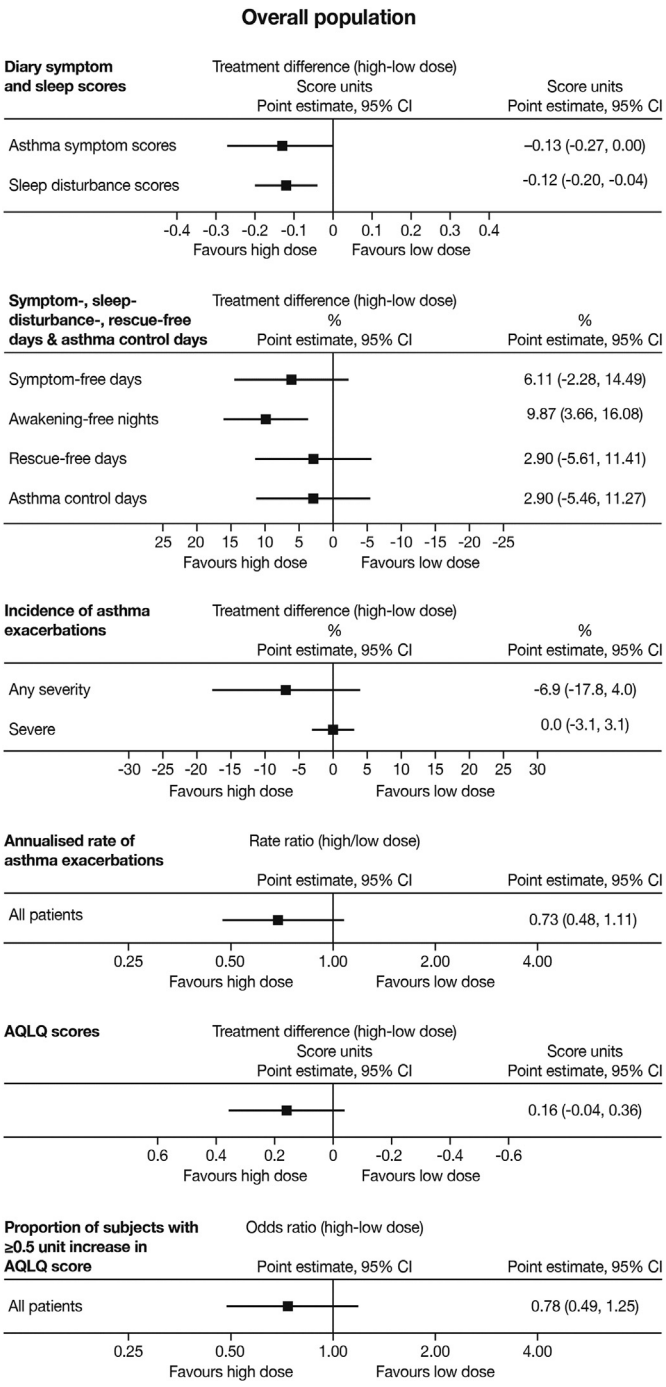

Fig. 3. Symptom-related treatment differences (95% CIs) between high and low dose fluticasone/formoterol pMDI (Overall ITT population). AQLQ = Asthma Quality of Life Questionnaire; CI = Confidence Interval.

spirometric endpoints in the overall population in our study echoes the shallow and inconsistent spirometric dose–response reported in the literature for all classes of inhaled drugs used to treat obstructive lung disease [5,10,12,22,23]. Nonetheless a similar lack of any dose–response in the "severe" subgroup was perhaps surprising particularly given the extent of airways obstruction (mean 51.4% predicted FEV_1) which might have been expected to manifest as a right shift of the dose–response curve.

The contrast with the pattern observed across multiple symptom-based endpoints in our study was noteworthy. Significant differences at the 5% level between high and low doses of fluticasone/formoterol or trends in favour of the high dose were noted for a number of symptom-related endpoints although the study was not formally powered to evaluate these outcomes. Overall dose-dependent directional consistency was evident across 10 of 11 symptom-based endpoints.

Support for the observed pattern of treatment effects in our study is available from FACET [5,6]. Interpretation of the FACET data is complicated by the fact that the authors did not present a pairwise comparison of high versus low dose levels of budesonide/formoterol. Nonetheless, the symptom-related dose–response trends in our study largely echo those apparent in FACET; in FACET high dose budesonide/formoterol afforded consistent incremental benefits in terms of lower day- and night-time symptom scores, improved health status, and lesser rescue medication use, whilst the exacerbation rate was approximately halved with the high (800/24 μg) versus low dose (200/24 μg) dose of budesonide/formoterol. As in our study, in FACET there was no apparent dose–response for FEV_1. Other published studies evaluating two dose levels of budesonide and formoterol or mometasone and formoterol in combination show less evidence of dose–response than FACET [3,4,7,8]; however, all these studies evaluated dose-levels separated by only a two-fold multiple of one or both components which reinforces our rationale for comparing fluticasone/formoterol over the widest available dose range in the present study. Dose–response patterns in earlier ICS/LABA studies and the wider literature suggest that the five-fold increase in fluticasone dose is primarily responsible for treatment effect differences in our study compared to the two-fold increase in formoterol dose. Interestingly however, Aubier and colleagues observed that post-bronchodilator PEFR and post-bronchodilator FEV_1 at baseline were somewhat stronger predictors of patients likely to benefit with a higher (400/12 μg) versus lower (200/6 μg) dose of budesonide/formoterol than the corresponding pre-bronchodilator indices [3]. This may suggest that a component of dose–response in Aubier's study (in which an 18% reduction in time to exacerbations and exacerbation rate were reported), and in our own study, is due to the two-fold multiple of formoterol in the high versus low dose groups.

Treatment differences between high and low dose fluticasone/formoterol in our study were modest for a number of symptom-based endpoints in the overall population and for some of these, such as rescue-free days and asthma control days, were clearly not of a clinically relevant magnitude. For other endpoints however dose comparisons hinted at more meaningful differences. These differences were accentuated in the "severe" subgroup: for every symptom-based endpoint the difference between dose levels was greater in the "severe" than in the "moderate" subgroup. Thus in the "severe" subgroup, treatment effect differences appeared to be relatively large for some of the endpoints assessed: with high versus low dose fluticasone/formoterol the exacerbation rate was 45% lower, the odds of an AQLQ "response" (≥0.5 unit increase) was almost twice as high, there was a 43% relative increase in awakening-free nights and 21% relative increase in symptom-free days. Even in the "severe" subgroup however, there was little evidence of a meaningful reduction in rescue medication use, whilst the increase in asthma control days still appeared to be of borderline utility (a 14% relative increase).

From a practical perspective our data suggest that patients with the most compromised lung function are those in whom dose escalation is most likely to be worthwhile in the event of partial control with low dose fluticasone/formoterol treatment, and that symptomatic gains may largely relate to exacerbation risk reduction, health status improvement and less sleep disturbance. Confirmation of these hypotheses is required in future studies.

Statistical significance at the 5% level was only demonstrated for a few symptom-based endpoints. This is because the comparison between high and low dose fluticasone/formoterol was

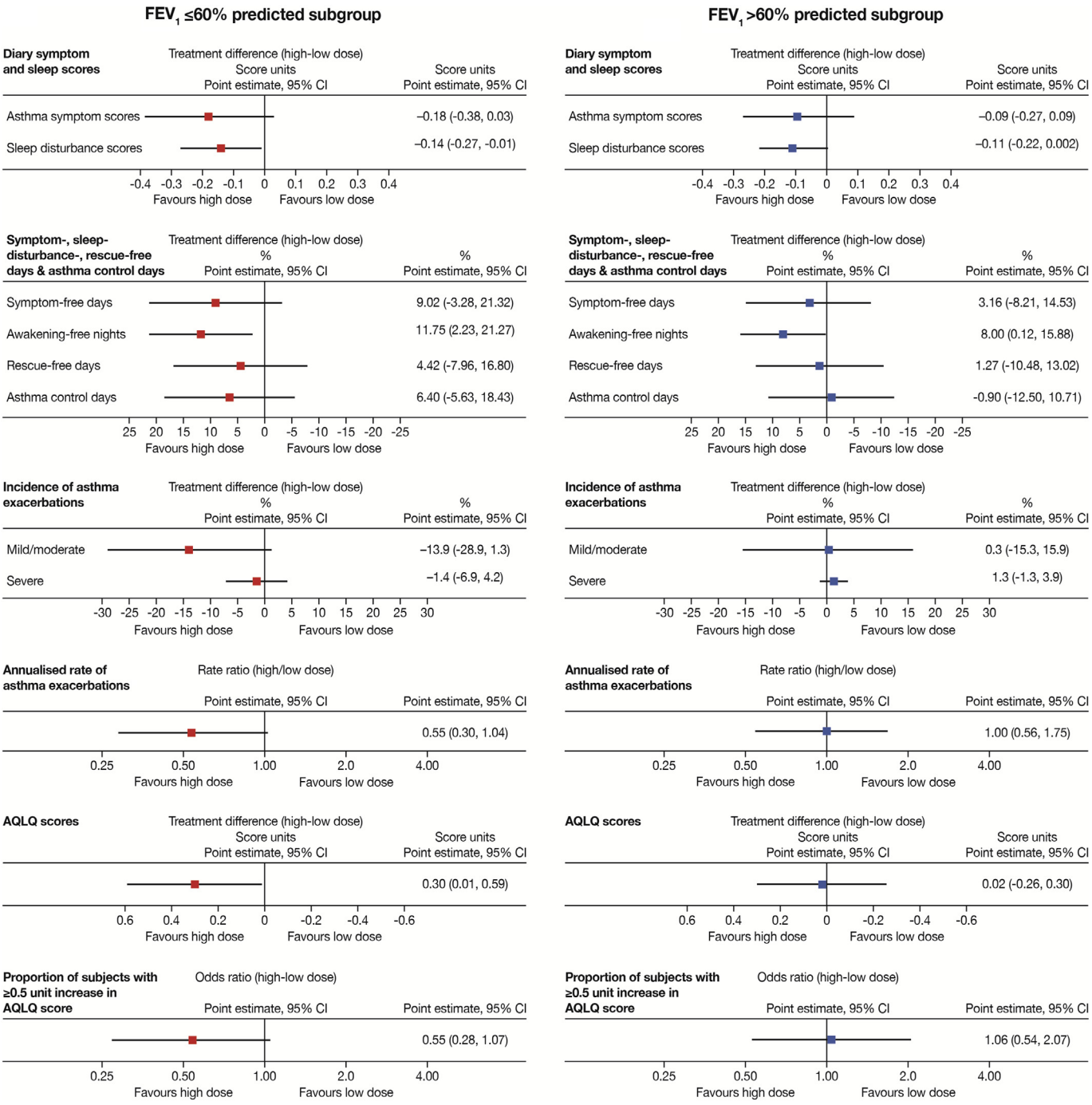

Fig. 4. Symptom-related treatment differences (95% CIs) between high and low dose fluticasone/formoterol pMDI dichotomised by percentage predicted FEV_1 at baseline (ITT population). AQLQ = Asthma Quality of Life Questionnaire; CI = Confidence Interval.

exploratory and not formally powered to evaluate treatment effect differences for symptom-based endpoints. In this context it is important to understand the meaning of a result such as the exacerbation rate ratio of 0.55 ($p = 0.064$) seen with high versus low dose treatment in the "severe" subgroup. Whilst failing to satisfy the conventional, and arbitrary, 5% false positive threshold (i.e., associated with $p = 0.05$) a result such as this (which implies a 6.4% probability that the observed difference happened by chance) is still meaningful to generate a hypothesis for evaluation in future studies. With a larger sample size several borderline statistical results would likely have become significant at the 5% level.

Notably, a dose–response is not evident for standard lung function indices but appears to exist for symptom-related endpoints. Differing patterns of dose–response for these different endpoints may be reflective of different mechanisms. While FEV_1 and PEFR mainly reflect large airways responses, clinical outcomes such as nocturnal asthma [24], exacerbations [25,26] and asthma control [27,28] have been previously related to dysfunction of the peripheral airway zone. It is thus tempting to speculate that while the central lung is readily saturable with low doses of inhaled drug, high doses may provide additional benefit in severe patients by increasing drug deposition in the peripheral compartment.

The findings in this study are relevant to regulatory authorities. Conventional lung function indices are the most standard, accepted primary efficacy variables [29,30] in regulatory studies intended to facilitate product approval. However, given the increased regulatory focus on assay sensitivity and a desire for a clear demonstration of dose–response, it is important that regulators are aware that this may not be feasible, at least with ICS/LABAs, using conventional spirometric endpoints in studies which are externally valid (i.e., do not specifically recruit enriched populations of selected dose–responsive patients).

In conclusion, our study suggests that treatment benefits with higher versus lower doses of fluticasone/formoterol may be identifiable for symptom-based but not spirometric parameters. Patients with more severe airways obstruction appear to be those most likely to gain additional benefit from higher treatment doses, with clinically relevant benefits primarily appearing to relate to exacerbation risk reduction, health status and sleep disturbance. These exploratory observations require confirmation in studies specifically designed and powered to assess dose–response.

Author contributions

All authors were involved in the generation and evaluation of the data for this paper. The authors co-wrote the manuscript and each has approved the final version.

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Competing interests

Dr Sanjeeva Dissanayake, Ms Birgit Grothe and Mrs Tammy McIver are employees of the study sponsor, Mundipharma Research Limited. At the time this study and the analyses presented in this publication were conducted, Dr Meena Jain was an employee of Napp Pharmaceuticals Limited, an Independent Associated Company of Mundipharma Research Limited. Professor Alberto Papi has been on Scientific Advisory Boards, has received grants and speaker fees from Mundipharma.

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Appendix A: Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pupt.2015.10.001.

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