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Efficacy, safety, and dose response of glycopyrronium administered by metered dose inhaler using co-suspension delivery technology in subjects with intermittent or mild-to-moderate persistent asthma: A randomized controlled trial

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ABSTRACT

Objectives: This randomized, double-blind, placebo-controlled, cross-over, Phase II dose-ranging study investigated the efficacy and safety of GP MDI (glycopyrronium administered by metered dose inhaler formulated using co-suspension delivery technology) compared with an open-label active comparator, salmeterol dry powder inhaler (SAL DPI), in subjects with intermittent or mild-to-moderate persistent asthma.
Methods: Subjects were randomized to receive five of seven treatments (GP MDI 28.8, 14.4, 7.2, 3.6, and 1.9 μg, placebo MDI, and SAL DPI 50 μg), each for a 14-day period. The primary endpoint was peak change from baseline in forced expiratory volume in 1 s (FEV_1) on Day 15. Secondary endpoints included additional lung function parameters and symptoms (Asthma Control Questionnaire-5). Safety was monitored throughout.
Results: Of 248 subjects randomized, 211 completed the study. All doses of GP MDI resulted in significant improvements in the primary endpoint compared with placebo MDI in a dose-ordered fashion (range 85–155 mL, $p < .0001$), without appreciable differences between the two highest doses of GP MDI (28.8 and 14.4 μg) and SAL DPI 50 μg. Improvements in secondary lung function endpoints and symptoms were generally dose-ordered, with GP MDI 28.8 μg showing the greatest improvements. Similar results were observed when endpoints were analyzed based on subjects' background use of inhaled corticosteroids (yes/no). All GP MDI doses were well tolerated with no evidence of a dose-related effect on adverse events.
Conclusions: The results of this study suggest that GP MDI could offer an important treatment option for maintenance therapy of asthma, and warrants further investigation in Phase III clinical trials.

1. Introduction

Asthma is a chronic respiratory condition that affects approximately 358 million people worldwide (2015) [1], with prevalence as high as 18% in some countries [2]. Symptoms of asthma include wheeze, shortness of breath, chest tightness, and cough. There is also variable expiratory airflow limitation in patients with asthma and chronic airway inflammation is usually apparent [2]. Asthma severity can vary over time, and patients may experience symptom-free periods as well as exacerbations, which is some cases can become life-threatening [2].

Asthma management focuses on controlling symptoms and minimizing exacerbation risk by using a combination of medications,

Abbreviations: ACQ-5, Asthma Control Questionnaire-5; AE, adverse event; $AUC_{0–3}$, area under the curve from time 0–3 h post-dose; BID, twice daily; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; ECG, electrocardiogram; FDC, fixed dose combination; FEV_1, forced expiratory volume in 1 s; GP, glycopyrronium; ICS, inhaled corticosteroid; IWRS, Interactive Web Response System; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LSM, least squares mean; MDI, metered dose inhaler; MedDRA, Medical Dictionary for Regulatory Activities; mITT, modified intent-to-treat; PEFR, peak expiratory flow rate; SABA, short-acting β_2-agonist; SAL, salmeterol; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event

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treatment of modifiable risk factors, and non-pharmacologic therapies and strategies [2]. Current treatment guidelines advocate a stepwise approach to asthma management, based on the level of disease control achieved at each stage [2,3]. The first-line of asthma therapy generally involves treatment with a short-acting β_2-agonist (SABA) administered on an as-needed basis, and regular maintenance therapy with a low dose of an inhaled corticosteroid (ICS). For patients who remain symptomatic despite treatment with an ICS and an as-needed SABA, adding a long-acting β_2-agonist (LABA) can result in greater control than an increase in ICS dose alone [2]. However, despite the availability of efficacious ICS/LABA combination therapies, many patients have suboptimal asthma control [4,5]. Accumulating evidence shows that the addition of a long-acting muscarinic antagonist (LAMA) may be of clinical benefit to patients who remain symptomatic despite therapy with an ICS [6,7], particularly for those who remain symptomatic despite treatment with an ICS/LABA [8–10]. Clinical studies of tiotropium (a LAMA) in patients with asthma that is poorly controlled despite treatment with an ICS/LABA demonstrated treatment-associated improvements in lung function [8–10] and an increased time to the first severe exacerbation relative to an ICS/LABA alone [10]. Tiotropium was approved in Europe in 2014 as add-on maintenance treatment in adults with asthma treated with high-dose ICS/LABA and a history of severe exacerbations [11,12], and in the USA in 2015 as long-term, once-daily maintenance treatment in patients ≥12 years of age with asthma (this indication was expanded in 2017 to include patients ≥6 years of age with asthma) [13–15].

Another LAMA, glycopyrronium (GP), is currently approved as monotherapy and as a fixed-dose combination (FDC) with a LABA in patients with chronic obstructive pulmonary disease (COPD) [16–18]. The efficacy of GP administered by metered dose inhaler (GP MDI) and formulated using innovative co-suspension delivery technology, in patients with COPD is well established [19–24]. The co-suspension delivery technology allows administration of single, double, or triple therapies with consistent dose delivery [25,26].

This Phase II dose-ranging study is the first to evaluate the efficacy and safety profile of GP MDI using co-suspension technology in adults with asthma. The primary objective of the study was to evaluate the efficacy of GP MDI on lung function versus placebo MDI and an active comparator, salmeterol (SAL) dry powder inhaler (DPI), in subjects with intermittent asthma or mild-to-moderate persistent asthma.

2. Materials and methods

2.1. Study design

This was a double-blind, randomized, placebo-controlled, incomplete block, cross-over Phase II study conducted in subjects with intermittent or mild-to-moderate persistent asthma at 45 sites in the USA (NCT02433834). Subjects received one of seven possible treatments twice daily (BID) over each 14-day treatment period, for a total of five separate treatment periods. The treatments were GP MDI 28.8, 14.4, 7.2, 3.6, and 1.9 μg, placebo MDI (equivalent to glycopyrrolate 36, 18, 9, 4.5, or 2.4 μg), and open-label SAL DPI 50 μg (Fig. 1; all GP MDI doses are ex-actuator).

Subjects were allocated to one of 24 pre-defined treatment sequences at randomization using an Interactive Web Response System (IWRS), all of which included GP MDI 14.4 μg and GP MDI 7.2 μg, 75% of which included placebo MDI and/or SAL DPI 50 μg, and 50% of which included GP MDI 28.8 μg, GP MDI 3.6 μg, and/or GP MDI 1.9 μg. The incomplete block design allowed fewer subjects to be allocated to treatments that were not expected to demonstrate adequate efficacy, i.e. GP MDI 3.6 and 1.9 μg, but would further characterize the dose response relationship in this population. Study personnel had access to the IWRS, which managed the distribution of clinical supplies. All MDI treatments were provided blinded (in equivalently labelled foil pouches), and SAL DPI was provided as open-label. After the study had commenced, the protocol was amended, and the target number of randomized subjects was increased from 200 to 224. Additional subjects were randomized due to the potential for increased variability that initial drug supplies may have introduced because of a change in the MDI storage requirements.

Randomization was stratified according to background ICS use (ICS or non-ICS). Subjects receiving ICS therapy prior to study entry were switched to budesonide DPI 180 or 360 μg (Pulmicort® Flexhaler®) [27] BID for the study duration, based on whether their previous ICS treatment was at either a low dose or at a medium/high dose, respectively [28]. Subjects receiving non-ICS maintenance therapy prior to study entry were allowed to continue that therapy. Subjects were not allowed to use inhaled anticholinergics for at least 2 weeks prior to screening. The use of sponsor-provided Ventolin® HFA (salbutamol) inhalation aerosol as rescue medication was permitted on an as-needed basis for the duration of the study. Consumption of xanthine-containing foods and beverages (e.g., coffee, tea, chocolate, and cola) was prohibited for at least 6 h prior to, and for the duration of, each study visit. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation/Good Clinical Practice and applicable regulatory requirements.

2.2. Study population

The study population included subjects 18–70 years of age (inclusive) who had been diagnosed with intermittent or mild-to-moderate persistent asthma at least 6 months prior to screening. All subjects had a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) ≥60% and ≤90% of predicted normal value at screening (calculated using the Third National Health and Nutrition Examination Survey reference equations) [29], and demonstrated β_2-agonist reversibility, defined as an FEV_1 increase of ≥12% and ≥200 mL 30–60 min after the inhalation of four puffs of salbutamol. Following the first treatment period, subjects were required to meet baseline FEV_1 eligibility criteria, defined as a pre-dose FEV_1 within 20% of the baseline FEV_1 value determined at randomization, at the beginning of each subsequent treatment period. The study population included subjects receiving ICS as maintenance therapy and those who were not in order to capture a broad, and typical, range of subjects with asthma. Those who were receiving ICS were required to have been on a stable dose for at least 4 weeks prior to screening.

Subjects with life-threatening asthma, defined as a history of significant episode(s) requiring intubation within the 12 months prior to screening, were excluded from participation in the study. Subjects with worsening of asthma (involving an emergency department visit, hospitalization, or use of oral/parenteral corticosteroids) during the 6 weeks prior to screening were also excluded. Other exclusion criteria included current evidence or diagnosis of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis, emphysema, COPD, or respiratory abnormalities other than asthma. Current or former smokers who had stopped smoking during the 6 months prior to enrollment, or with a smoking history of > 10 pack-years, were excluded from study participation. Subjects who were receiving chronic treatment with oral/systemic corticosteroids or antibiotics, or were using inhaled anticholinergics in the 2 weeks prior to screening, depot or intra-articular corticosteroids within 3 months of screening, or parenteral and oral corticosteroids for an asthma exacerbation during the 6 weeks prior to screening were not eligible.

2.3. Efficacy assessments

The primary efficacy endpoint was the peak change from baseline in FEV_1 on Day 15, within 3 h of study drug administration. Secondary endpoints included the change from baseline in morning pre-dose trough FEV_1 on Day 15, the FEV_1 area under the curve from time 0–3 h post-dose (AUC_{0-3}) on Day 15, the change from baseline in average

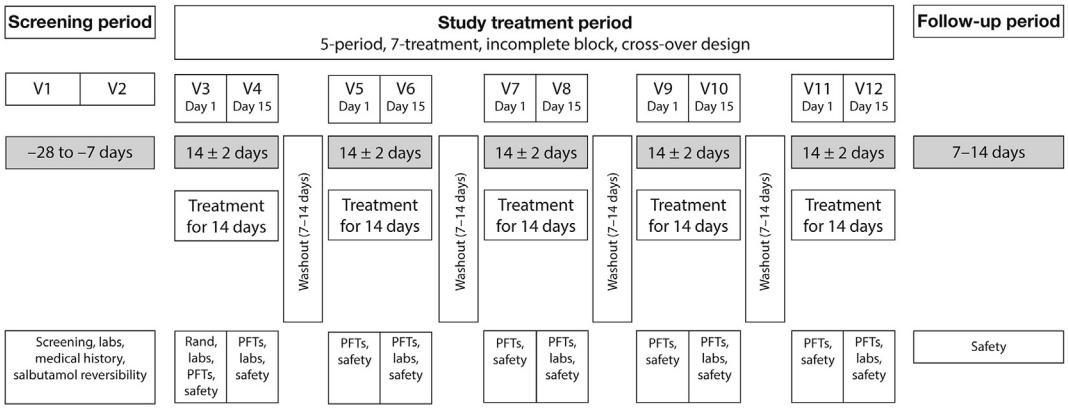

Fig. 1. Study design. Each subject received 14 days of study treatment with each of their assigned treatments for a total of five separate treatment periods. Treatments: GP MDI 28.8, 14.4, 7.2, 3.6, and 1.9 μg, open-label SAL DPI 50 μg, placebo MDI. DPI, dry powder inhaler; GP, glycopyrronium; labs, laboratory parameters; MDI, metered dose inhaler; PFT, pulmonary function test; rand, randomization; SAL, salmeterol; V, visit.

daily pre- and post-dose peak expiratory flow rate (PEFR) over 14 days, the change from baseline in average daily rescue medication use over 14 days, and the change from baseline in Asthma Control Questionnaire-5 (ACQ-5) on Day 15. The ACQ-5 summary score represents the mean of five questions relating to asthma control over the preceding 7-day period (scored from 0 = no impairment to 6 = maximum impairment), with a score ≤1 denoting very good control of asthma [30,31].

Spirometry assessments were conducted during the screening period and at the beginning and end of each randomized treatment period at the following times: 60 and 30 min prior to study drug administration, and at 15 and 30 min, and 1, 2, and 3 h after dosing (Fig. 1). Subjects were also provided with an eDiary to record morning and evening asthma symptoms, morning and evening pre- and post-dose PEFR (immediately before and 30 min after dosing), and daily use of rescue medication (number of actuations). Subjects were required to demonstrate eDiary compliance of ≥70% in the 7 days preceding randomization in order to qualify for randomization into the study.

2.4. Safety assessments

Medical history was taken at screening. A complete physical examination was performed at screening and at the final study visit, or the premature discontinuation visit as applicable. Vital signs were assessed at screening and at all subsequent visits (at pre-dose, within 1 h of in-clinic dosing, and at 30 min post-dose). A 12-lead electrocardiogram (ECG) was also obtained at the screening visit and at 60 and 30 min prior to study drug administration, and at 30 min and 3 h post-dose on the day of randomization. On subsequent visits, ECG recordings were taken within 1 h prior to drug administration and at 30 min and 3 h post-dose. Finally, clinical laboratory assessments, which included hematology and chemistry parameters, were measured at screening and on subsequent visits (prior to dosing). Samples were analyzed by a local or central laboratory according to standardized, validated assays.

Adverse events (AEs) were monitored throughout the study. Paradoxical bronchospasm (defined as a reduction in FEV_1 of at least 20% from the pre-dose value, with associated asthma symptoms of wheezing, shortness of breath and/or cough) and dry mouth were considered AEs of special interest.

2.5. Statistical analyses

The primary endpoint analysis was performed on the modified intent-to-treat (mITT) population, which included all subjects who received treatment, had post-treatment efficacy data from at least two treatment periods, and did not have a major protocol violation that would preclude the use of data from these periods. The primary efficacy endpoint was analyzed using a mixed model with treatment, baseline FEV_1, period, ICS user subgroup, and treatment-by-subgroup interaction as covariates. Baseline FEV_1 values were calculated as the average of the pre-dose values from Day 1 of all treatment periods. Intra-subject correlation across treatment periods was modelled by including subject as a random effect. A two-sided α level of 0.05 was used to compare GP MDI with placebo MDI, and Type I error was controlled using a pre-specified sequential approach. A sample size of 180 subjects was estimated to provide at least 97% power to detect a 100-mL difference in peak FEV_1 in the comparison of GP MDI with placebo. Within the ICS use subgroups, each pairwise comparison of GP MDI with placebo to detect the same 100-mL difference was powered to at least 79%. Non-inferiority comparisons (1-sided, $\alpha = 0.025$) of GP MDI with the comparator SAL DPI 50 μg used a margin of 100 mL and employed a sequential approach to control Type I error.

The analysis of secondary efficacy endpoints used a similar approach to that of the primary endpoint. FEV_1 $AUC_{0–3}$ was calculated using the trapezoidal rule, using all observed data. All AUC values were normalized by dividing the AUC by the time from the first to the last non-missing value (typically 3 h). Daily pre- and post-dose PEFR were calculated as the mean of the respective morning and evening measurements for a given day. For eDiary parameters, baseline values were derived from non-missing values from the last 7 days prior to randomization. During treatment, the average of the non-missing daily values over each week and over the last week of treatment within each period was taken.

Safety parameters were analyzed in the safety population, which included all subjects who were randomized and received at least one dose of study treatment. Changes from baseline for clinical safety laboratory measurements, where baseline was defined as the last available pre-dose value prior to randomization, were analyzed descriptively. AEs were recorded at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

3. Results

3.1. Study population

In total, 248 subjects were randomized and received treatment (safety population) and, of these, 222 (89.5%) were eligible for inclusion in the mITT population. A total of 210 subjects completed Day 15 assessments in all five treatment periods between 27 May 2015 and 26 March 2016. One subject who did not complete the Day 15 assessments of the last treatment period was categorized as completing the study. Hence, 211 subjects (85.1%) completed the study, with rates of

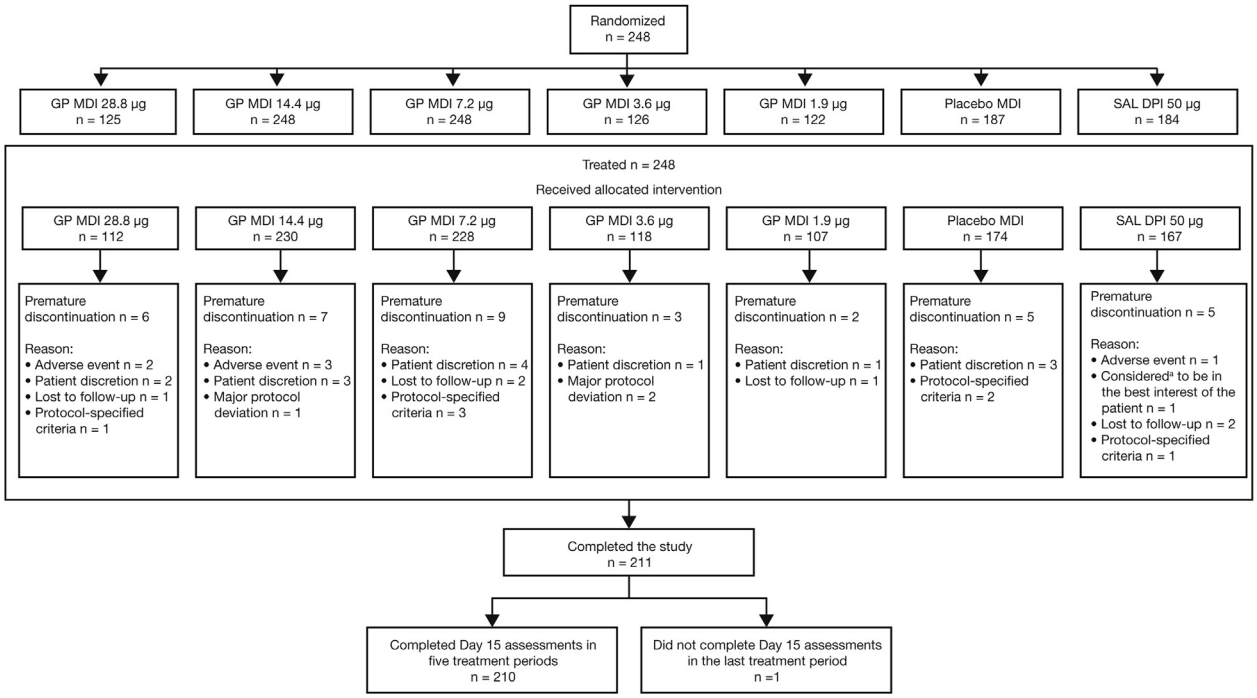

Fig. 2. Subject disposition. [a]Considered by the investigator. One subject did not complete the Day 15 assessment of the last treatment period in the placebo MDI group. DPI, dry powder inhaler; GP, glycopyrronium; MDI, metered dose inhaler; SAL, salmeterol.

premature discontinuation similar across treatments (Fig. 2).

Subject demographics and baseline clinical characteristics for the mITT population are summarized in Table 1 (according to ICS user subgroup) and in Supplementary Table 1 (according to treatment group). Overall, the majority of subjects were female (64.0%) and the mean age was 46.0 (standard deviation ± 13.8) years (Supplementary Table 1). The mean duration of asthma was similar across treatments, ranging from 25.5 to 28.9 years, and the majority of subjects had mild persistent asthma (range 40.0–48.6% across treatments) or moderate persistent asthma (range 34.6–40.0%). When stratified according to ICS use, slightly more than half of the subjects were using an ICS at screening (122 subjects; 55.0%). In general, a higher proportion of ICS users (53.3%) had moderate persistent asthma compared with non-ICS users (15.0%), and rescue medication use was higher in the ICS user subgroup than in the non-ICS user subgroup (mean of 2.06 vs 1.54 puffs per day; Table 1). All subjects in the mITT population demonstrated reversibility to salbutamol.

3.2. Lung function

3.2.1. FEV_1 – peak change from baseline

All doses of GP MDI were associated with significant improvements in the peak change from baseline in FEV_1 on Day 15 compared with placebo ($p < .0001$), ranging from 85 to 155 mL in the overall population (Fig. 3A; Table 2). The peak change from baseline in FEV_1 for each GP MDI dose was larger in the ICS user subgroup compared with the non-ICS user subgroup, but the magnitude of improvement versus placebo observed in both groups was similar. In the overall population, and in the ICS user and non-ICS user subgroups, numerical dose ordering was observed across GP MDI doses (Fig. 3B and C). Comparison with the active comparator SAL DPI 50 µg showed no appreciable difference to GP MDI 28.8 and 14.4 µg (least squares mean [LSM] differences [95% confidence interval; CI] of −1 [–39, 37] mL, −24 [–55, 7] mL, respectively). Non-inferiority to SAL DPI 50 µg using a clinical margin of 100 mL was also demonstrated for the GP MDI 7.2 and 3.6 µg doses (LSM differences [95% CI] of −33 [–64, −2] mL, and −48 [–85, −11] mL respectively); however, the improvements were larger for SAL DPI and the 95% CIs excluded zero.

3.2.2. Morning pre-dose trough FEV_1

Compared with placebo, all doses of GP MDI led to numerical improvements in morning pre dose trough FEV_1 on Day 15, which reached statistical significance for the three highest GP MDI doses (Fig. 4A; Table 2).

In all subjects, the highest dose of GP MDI, 28.8 µg BID, showed a placebo-adjusted improvement of 85 mL in morning pre-dose trough FEV_1, while a 71 mL placebo-adjusted improvement was observed with SAL DPI 50 µg. The same trend was observed in the ICS user and non-ICS user subgroups, with significant improvements following treatment with GP MDI 28.8, 14.4, and 7.2 µg treatments (Fig. 4B and C; Table 2). Changes from baseline were generally greater in the ICS user subgroup (LSM range 34–104 mL) than in the non-ICS user subgroup (LSM range −12 to 43 mL) at each dose level. In the ICS user subgroup, placebo-adjusted treatment effects with GP MDI 28.8 µg exceeded the clinical margin of 100 mL (placebo-adjusted improvement of 105 mL).

3.2.3. FEV_1 $AUC_{0–3}$

Consistent with the primary endpoint, peak change from baseline in FEV_1 on Day 15, all doses of GP MDI were associated with statistically significant improvements in FEV_1 $AUC_{0–3}$ change from baseline relative to placebo on Day 15, irrespective of ICS use, ranging from 75 to 153 mL in the overall population (all $p < .0001$; Supplementary Table 2). The improvement observed following the highest dose of GP MDI, 28.8 µg, was similar to that associated with SAL DPI 50 µg (LSM differences vs placebo of 153 mL for GP MDI 28.8 µg and 152 mL for SAL DPI 50 µg; $p < .0001$ for both comparisons).

3.2.4. Pre- and post-dose PEFR (eDiary)

In the overall population, treatment with all doses of GP MDI resulted in improvements in LSM daily pre-dose PEFR over 14 days relative to placebo (improvements ranging from 8.32 to 23.54 L/min [$p < .0001$ for the 28.8, 14.4, 7.2, and 3.6 µg doses; $p = .0888$ for the 1.9 µg dose]; Supplementary Table 3). Treatment with SAL DPI 50 µg also led to an improvement versus placebo in LSM daily pre-dose PEFR

Table 1
Subject demographics and clinical characteristics according to ICS user subgroup (mITT population).

	ICS users (n = 122)	Non-ICS users (n = 100)
Mean age, years (SD)	48.8 (13.2)	42.6 (13.9)
Male gender, n (%)	38 (31.1)	42 (42.0)
Smoking status, n (%)		
Current	0	0
Former	30 (24.6)	17 (17.0)
Never	92 (75.4)	83 (83.0)
Use of ICS at baseline[a], n (%)	122 (100)	0
ACQ-5 summary score[b], mean (SD)	1.5 (0.8)	1.3 (0.8) [n = 99][f]
Mean duration of asthma, years (SD)	29.1 (16.4)	25.1 (15.5)
Asthma severity, n (%)		
Intermittent	9 (7.4)	34 (34.0)
Mild persistent	48 (39.3)	51 (51.0)
Moderate persistent	65 (53.3)	15 (15.0)
Mean baseline FEV_1, mL (SD)	2205 (592)	2371 (581)
Mean pre-bronchodilator FEV_1, % predicted, Visit 1/Visit 2	72.5/71.8 [n = 121/121][f]	74.4/NA[g]
Reversibility to salbutamol		
Reversible[c], n (%)	122 (100)	100 (100)
Mean reversibility[d], % (SD)	23.4 (8.9)	19.2 (8.8)
Mean number of puffs of rescue medication per day at baseline (SD)[e]	2.06 (2.69)	1.54 (2.30)

ACQ-5, Asthma Control Questionnaire-5; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; mITT, modified intent-to-treat; SD, standard deviation.

[a] At baseline was defined as ongoing at the time of the first dose of study medication.

[b] The ACQ-5 score is the mean of all five questions (range 0–6).

[c] Reversible was defined as improvement in FEV_1 post-salbutamol versus pre-salbutamol of ≥12% and ≥200 mL, 30–60 min after inhalation at screening.

[d] Reversibility was defined as 100 x (post-salbutamol FEV_1 - pre-salbutamol FEV_1)/pre-salbutamol FEV_1 (for whichever screening visit had pre-dose and post-dose values that yielded the highest percent reversibility value).

[e] Subjects for whom data on change in rescue medication use were available (as shown in Supplementary Table 4).

[f] N values for group sizes are reported where different from those of the overall mITT population.

[g] Visit 2 was required only for subjects switched to budesonide DPI 180 or 360 µg during screening.

(20.49 L/min; $p < .0001$ vs placebo). Changes in LSM daily post-dose PEFR followed a similar pattern (improvements ranging from 14.35 to 30.62 L/min for all doses of GP MDI [$p \leq .0008$ vs placebo] and 27.26 L/min for SAL DPI 50 µg [$p < .0001$ vs placebo]). Improvements in PEFR following treatment with the highest dose of GP MDI (28.8 µg) were similar to those observed following SAL DPI 50 µg treatment. Similar results were observed in the ICS user subgroup and the non-ICS user subgroup (Supplementary Table 3).

3.3. Symptom control

3.3.1. Use of rescue medication

The use of rescue medication was low at baseline (< 2 puffs/day across all treatment groups; Supplementary Table 1). Nonetheless, there were small numerical reductions from baseline versus placebo in average daily rescue medication use over 14 days with all GP MDI doses and SAL DPI 50 µg, in the overall population and in the ICS user and non-ICS user subgroups (Supplementary Table 4). The largest changes were generally recorded for GP MDI 28.8 µg and SAL DPI 50 µg (Supplementary Table 4).

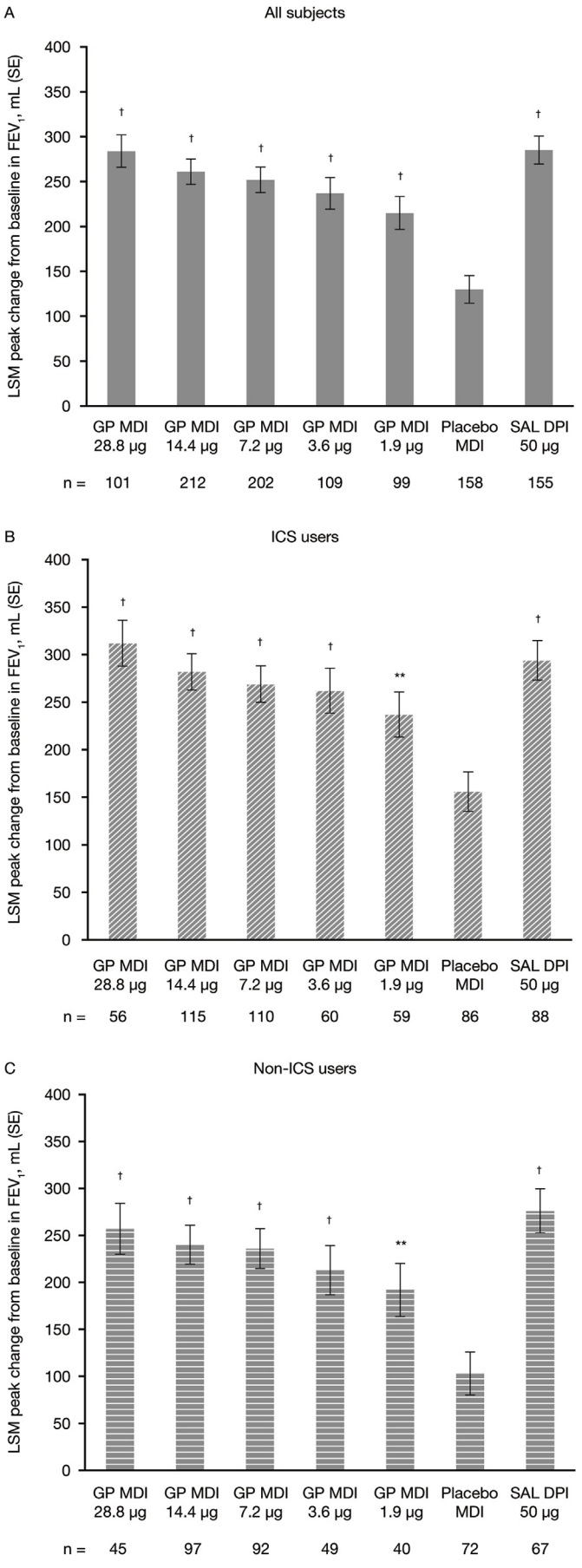

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Fig. 3. Peak change from baseline in FEV_1 on Day 15 in (A) all subjects, (B) ICS users, and (C) non-ICS users (mITT population). $^{**}p < .01$; $^{\dagger}p < .0001$ LSM difference versus placebo MDI. DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; GP, glycopyrronium; ICS, inhaled corticosteroid; LSM, least squares mean; mITT, modified intent-to-treat; MDI, metered dose inhaler; SAL, salmeterol; SE, standard error.

3.3.2. Asthma Control Questionnaire-5

As for rescue medication, baseline ACQ-5 summary scores were low (< 1.5 across all treatment groups). GP MDI was associated with small reductions from baseline in ACQ-5 summary scores (range −0.10 to −0.21) on Day 15 of treatment, with no dose-related response observed (Supplementary Table 5). When stratified according to ICS use at screening, the reductions in ACQ-5 summary scores in ICS user and non-ICS user subgroups were comparable to those reported in all subjects (data not shown).

3.4. Safety

All doses of GP MDI were generally well tolerated, and the incidence of treatment-emergent AEs (TEAEs) was low and similar across treatments, with no dose-related trends (Table 3). Dry mouth and asthma (MedDRA preferred terms) were the only TEAEs with an incidence of ≥2% in any treatment group (Table 3). Additionally, the incidence of paradoxical bronchospasm was low, mild in intensity, and similar across treatments (range 0–1.9%). The incidence of dry mouth was similar across treatments, with the highest GP MDI dose, 28.8 μg, resulting in a similar incidence as placebo MDI (8% and 7.5%, respectively), and no evidence of a dose-related trend (Table 3). The majority of events were mild or moderate in intensity.

Five subjects discontinued from the study due to TEAEs occurring during the treatment periods. Of these, two occurred during treatment with GP MDI 28.8 μg (pulmonary hypertension and right bundle branch block), three with GP MDI 14.4 μg (hypersensitivity; ventricular extrasystoles; and acute sinusitis, bronchitis, cough, and pharyngitis). An additional subject discontinued prematurely due to an AE of asthma during a washout period following treatment with SAL 50 μg. None of the events were serious or severe in intensity. One subject, following administration of placebo MDI, experienced a serious AE (viral gastroenteritis) that was not considered treatment-related, and no deaths were reported during the study. Although isolated incidences of post-baseline newly occurring or worsening potentially clinically significant laboratory values, vital signs, and ECG values were reported, the incidences of these were generally similar to those observed in the placebo MDI group, with no evidence of a dose-related response.

4. Discussion and conclusions

This Phase II, randomized, cross-over, dose-ranging study examined the efficacy and safety of five doses of the inhaled LAMA, GP MDI (28.8 μg–1.9 μg), compared with placebo and open-label SAL DPI 50 μg in subjects with intermittent or mild-to-moderate persistent asthma. All doses of GP MDI, formulated using innovative co-suspension delivery technology, significantly improved peak change from baseline in FEV_1, the primary endpoint, compared with placebo in a dose-ordered fashion, with the two highest doses (28.8 μg and 14.4 μg) resulting in similar improvements as the active comparator, SAL DPI 50 μg. In addition, improvements in secondary lung function endpoints following 14 days of treatment with GP MDI were generally dose-ordered, with the greatest changes from baseline in lung function observed following the highest dose of GP MDI (28.8 μg), and the two lowest GP MDI doses (3.6 μg and 1.9 μg) not significantly improving morning pre-dose trough FEV_1 on Day 15 relative to placebo. At baseline, daily rescue medication use was low (< 2 puffs/day) and ACQ-5 scores were < 1.5 in all treatment groups. Nonetheless, consistent with the improvements in lung function, GP MDI at all doses resulted in small numerical improvements in both average daily rescue medication use and ACQ-5 scores relative to placebo.

Table 2
Peak change from baseline in FEV_1 and change from baseline in morning pre-dose trough FEV_1 on Day 15 (mITT population).

	GP MDI					Placebo MDI	SAL DPI 50 μg
	28.8 μg	14.4 μg	7.2 μg	3.6 μg	1.9 μg		
Peak change from baseline in FEV_1 on Day 15, mL							
All subjects	(n = 101)	(n = 212)	(n = 202)	(n = 109)	(n = 99)	(n = 158)	(n = 155)
LSM (SE)	284 (18)	261 (14)	252 (14)	237 (18)	215 (18)	130 (15)	285 (16)
LSM difference vs placebo MDI (SE)	155† (19)	131† (15)	123† (16)	108† (19)	85† (20)	NA	155† (17)
95% CI	117, 193	101, 162	92, 153	71, 145	47, 123	NA	122, 189
ICS users	(n = 56)	(n = 115)	(n = 110)	(n = 60)	(n = 59)	(n = 86)	(n = 88)
LSM (SE)	312 (24)	282 (19)	269 (19)	262 (24)	237 (24)	156 (21)	294 (21)
LSM difference vs placebo MDI (SE)	155† (26)	126† (21)	113† (21)	106† (25)	81** (25)	NA	137† (23)
95% CI	105, 206	85, 167	71, 154	56, 155	31, 131	NA	93, 182
Non-ICS users	(n = 45)	(n = 97)	(n = 92)	(n = 49)	(n = 40)	(n = 72)	(n = 67)
LSM (SE)	257 (27)	240 (21)	236 (21)	213 (26)	192 (28)	103 (23)	276 (23)
LSM difference vs placebo MDI (SE)	154† (29)	137† (23)	133† (23)	110† (28)	89** (30)	NA	173† (25)
95% CI	98, 210	92, 181	88, 178	55, 164	31, 147	NA	124, 223
Change from baseline in morning pre-dose trough FEV_1 on Day 15, mL							
All subjects	(n = 101)	(n = 212)	(n = 204)	(n = 109)	(n = 99)	(n = 159)	(n = 155)
LSM (SE)	73 (17)	47 (12)	42 (12)	12 (16)	18 (17)	−12 (13)	59 (14)
LSM difference vs placebo MDI (SE)	85† (20)	59*** (16)	54*** (16)	24 (20)	30 (20)	NA	71† (18)
95% CI	46, 125	27, 91	22, 86	−15, 62	−10, 70	NA	36, 106
ICS users	(n = 56)	(n = 115)	(n = 111)	(n = 60)	(n = 59)	(n = 87)	(n = 88)
LSM (SE)	104 (22)	63 (16)	54 (16)	34 (21)	48 (22)	−2 (18)	69 (18)
LSM difference vs placebo MDI (SE)	105† (27)	65** (22)	56* (22)	36 (26)	50 (26)	NA	71** (24)
95% CI	53, 158	22, 108	13, 99	−16, 87	−2, 102	NA	24, 117
Non-ICS users	(n = 45)	(n = 97)	(n = 93)	(n = 49)	(n = 40)	(n = 72)	(n = 67)
LSM (SE)	43 (25)	31 (17)	30 (18)	−10 (24)	−12 (26)	−22 (20)	50 (20)
LSM difference vs placebo MDI (SE)	65* (30)	53* (24)	52* (24)	12 (29)	10 (31)	NA	72** (27)
95% CI	7, 124	6, 100	5, 100	−45, 69	−51, 71	NA	20, 124

$^{*}p < .05$; $^{**}p < .01$; $^{***}p \leq .001$; $^{\dagger}p < .0001$ versus placebo MDI.
CI, confidence interval; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; GP, glycopyrronium; ICS, inhaled corticosteroid; LSM, least squares mean; MDI, metered dose inhaler; mITT, modified intent-to-treat; NA, not applicable; SAL, salmeterol; SE, standard error.

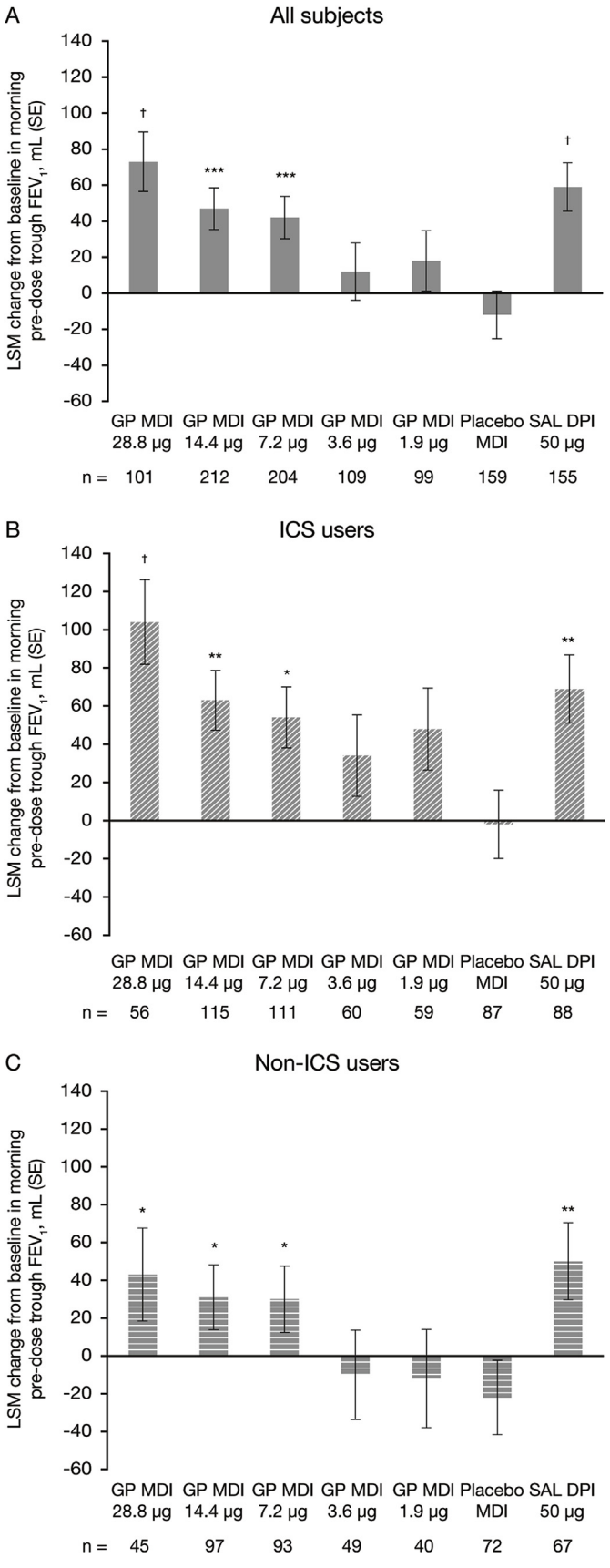

Fig. 4. Morning pre-dose trough FEV_1 on Day 15 in (A) all subjects, (B) ICS users, and (C) non-ICS users (mITT population). $^{*}p < .05$; $^{**}p < .01$; $^{***}p \leq .001$; $^{\dagger}p < .0001$ LSM difference versus placebo MDI. DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; GP, glycopyrronium; ICS, inhaled corticosteroid; LSM, least squares mean; mITT, modified intent-to-treat; MDI, metered dose inhaler; SAL, salmeterol; SE, standard error.

For the primary and secondary efficacy variables, analysis of the study population by ICS use at screening produced similar results as those observed for the overall population. In addition, qualitatively greater changes from baseline were observed for subjects who used ICS at screening compared with subjects who did not use ICS at screening for most endpoints. This is likely a reflection of the greater disease severity in the persistent asthma population (who were more likely to use an ICS) relative to the intermittent asthma population.

Longer-term studies are necessary to more thoroughly evaluate the impact of ICS use on long-term asthma control following treatment with GP MDI. Real-world studies indicate that persistence with ICS treatment in adults with asthma reduces the risk of exacerbation [32], although this is as yet unexplored in subjects undergoing chronic treatment with GP MDI in asthma.

Overall, the treatments were well tolerated and there was no evidence of a dose-related effect of GP MDI on the pattern or type of AEs observed in this study. The incidence of TEAEs was similar across all treatment groups, ranging from 9.3% (during treatment with GP MDI 3.6 µg) to 18.9% (during treatment with GP MDI 7.2 µg). The incidence of dry mouth, a common symptom associated with the use of anticholinergic medications, was low (≤8%) and similar between the highest doses of GP MDI dose and placebo MDI, and also comparable with the incidence reported in a meta-analysis of clinical trials with tiotropium in patients with COPD [33].

Although this study investigated the effects of GP MDI as an add-on to ICS therapy, as well as in subjects who were not using ICS, its impact as an add-on to an ICS/LABA regimen was not evaluated, and this is a noted limitation. The evidence base for tiotropium shows sustained bronchodilation [9,10] and also reduced risk of severe exacerbations in subjects with poorly controlled asthma as add-on therapy to ICS/LABA [10].

The co-suspension delivery technology used to formulate GP MDI in this study can also be used to formulate dual and triple FDCs [25,26]. Delivery of dual and triple FDCs via an MDI, one of the most commonly prescribed types of bronchodilator device [34], may be beneficial as many patients are already familiar with this device type. In this regard, a retrospective study of patients with asthma who were prescribed an ICS/LABA FDC (fluticasone/SAL) delivered using either an MDI or a DPI found that patients using the MDI were more likely to achieve asthma control over the year-long evaluation period compared with those using the DPI [35].

Currently, there is clear unmet clinical need in asthma, given that a substantial proportion of patients remain symptomatic despite receiving treatment with an ICS/LABA combination and as-needed use of a SABA [36]. This study is one of the first to investigate the efficacy and safety of GP MDI as a maintenance therapy in asthma, and the results suggest that GP MDI could be a valuable therapeutic addition to current asthma treatment regimens, warranting further investigation in a Phase III clinical setting. Studies of longer duration in a broader population (including subjects with more severe asthma who are symptomatic despite treatment with an ICS/LABA) need to be conducted, and should include assessments of the effects of GP MDI on lung function and asthma exacerbations.

5. Declaration of interest

Edward Kerwin has performed consulting for Amphastar, AstraZeneca, Mylan, Pearl – a member of the AstraZeneca Group, Sunovion, and Theravance Biopharma. He has served on advisory

Table 3
Summary of TEAEs (safety population, all subjects).

	GP MDI					Placebo MDI	SAL DPI 50 μg
	28.8 μg (n = 112)	14.4 μg (n = 230)	7.2 μg (n = 228)	3.6 μg (n = 118)	1.9 μg (n = 107)	(n = 174)	(n = 167)
Subjects with at least one TEAE, n (%)	18 (16.1)	40 (17.4)	43 (18.9)	11 (9.3)	18 (16.8)	32 (18.4)	27 (16.2)
Subjects with TEAEs related[a] to study treatment, n (%)	11 (9.8)	21 (9.1)	20 (8.8)	6 (5.1)	11 (10.3)	16 (9.2)	10 (6.0)
Subjects with serious TEAEs, n (%)	0	0	0	0	0	1 (0.6)	0
Subjects with serious TEAEs related[a] to study treatment, n (%)	0	0	0	0	0	0	0
Subjects with TEAEs leading to premature discontinuation, n (%)	2 (1.8)	3 (1.3)	0	0	0	0	0
Deaths – all causes during treatment period, n (%)	0	0	0	0	0	0	0
TEAEs occurring in ≥2% of subjects with any one treatment, n (%) (preferred term)							
Dry mouth	9 (8.0)	15 (6.5)	16 (7.0)	8 (6.8)	8 (7.5)	13 (7.5)	9 (5.4)
Asthma	3 (2.7)	1 (0.4)	3 (1.3)	0	0	1 (0.6)	1 (0.6)

DPI, dry powder inhaler; GP, glycopyrronium; MDI, metered dose inhaler; SAL, salmeterol; TEAE, treatment-emergent adverse event.
[a] Related was defined as possibly, probably, or definitely related to study medication in the opinion of the investigator.

boards for Amphastar, AstraZeneca, Mylan, Novartis, Pearl – a member of the AstraZeneca Group, Sunovion, and Theravance Biopharma, and has conducted multicenter clinical research trials for 40 pharmaceutical companies.

Andrew Wachtel has served on advisory boards for Pearl – a member of the AstraZeneca Group and GlaxoSmithKline. He has served on speaker's panels for Boehringer Ingelheim, GlaxoSmithKline, and Forest, and has conducted more than 40 multicenter clinical research trials.

Lawrence Sher has served on advisory boards for Optinose, Regeneron, and Sanofi-Aventis. He currently sits on speaker bureaus for GlaxoSmithKline, Regeneron, and Sanofi-Aventis, and has conducted more than 200 multicenter clinical research trials in 19 years of clinical research experience.

Jack Nyberg, Patrick Darken, Elizabeth A. Duncan, and Paul Dorinsky are employees of Pearl – a member of the AstraZeneca Group.

Shahid Siddiqui is an employee of AstraZeneca.

Colin Reisner is an employee of AstraZeneca and Pearl – a member of the AstraZeneca Group.

Funding

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Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, data interpretation and writing of the report. All authors had full access to all the data in the study and the corresponding author had the final responsibility for the decision to submit for publication. No restrictions were placed on authors regarding the statements made in the manuscript.

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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.rmed.2018.04.013.

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SUPPLEMENTARY MATERIAL

	GP MDI					Placebo MDI	SAL DPI 50 «g	All subjects
	28.8 «g (n = 107)	**14.4 «g (n = 213)**	**7.2 «g (n = 211)**	**3.6 «g (n = 110)**	**1.9 «g (n = 100)**	**(n = 162)**	**(n = 157)**	**(n = 222)**
Mean age, years (SD)	46.4 (14.1)	46.1 (13.9)	46.4 (13.9)	44.5 (13.7)	47.8 (14.1)	46.5 (13.6)	46.0 (14.2)	46.0 (13.8)
Male gender, n (%)	43 (40.2)	75 (35.2)	75 (35.5)	39 (35.5)	31 (31.0)	57 (35.2)	55 (35.0)	80 (36.0)
Smoking status, n (%)								
Current	0	0	0	0	0	0	0	0
Former	16 (15.0)	45 (21.1)	45 (21.3)	27 (24.5)	20 (20.0)	37 (22.8)	34 (21.7)	47 (21.2)
Never	91 (85.0)	168 (78.9)	166 (78.7)	83 (75.5)	80 (80.0)	125 (77.2)	123 (78.3)	175 (78.8)
Use of ICS at baseline[a], n (%)	58 (54.2)	115 (54.0)	115 (54.5)	60 (54.5)	59 (59.0)	88 (54.3)	88 (56.1)	122 (55.0)
ACQ-5 summary score[b], mean (SD)	1.4 (0.8)	1.4 (0.8)	1.4 (0.8)	1.3 (0.7)	1.4 (0.8)	1.4 (0.8)	1.4 (0.7)	1.4 (0.8)
Mean duration of asthma, years (SD)	28.9 (16.8)	27.2 (16.3)	27.5 (16.1)	25.5 (16.4)	28.4 (16.5)	27.2 (16.6)	26.9 (14.9)	27.3 (16.1)
Asthma severity, n (%)								
Intermittent	17 (15.9)	42 (19.7)	43 (20.4)	24 (21.8)	20 (20.0)	29 (17.9)	32 (20.4)	43 (19.4)
Mild persistent	52 (48.6)	94 (44.1)	90 (42.7)	47 (42.7)	40 (40.0)	77 (47.5)	64 (40.8)	99 (44.6)
Moderate persistent	38 (35.5)	77 (36.2)	78 (37.0)	39 (35.5)	40 (40.0)	56 (34.6)	61 (38.9)	80 (36.0)

Mean baseline FEV_1, mL (SD)	2298 (636)	2270 (587)	2266 (575)	2334 (543)	2203 (567)	2247 (599)	2241 (552)	2280 (592)
Mean pre-bronchodilator FEV_1,	[n = 106/57][f]	[n = 212/114][f]	[n = 210/114][f]	[n = 109/59][f]	[n = 100/59][f]	[n = 162/87][f]	[n = 156/88][f]	[n = 221/121][f]
% predicted, Visit 1/Visit 2	73.3/72.0	73.4/71.8	73.3/71.7	74.5/72.3	72.9/71.6	73.4/72.4	72.2/71.0	73.4/71.8
Reversibility to salbutamol								
Reversible[c], n (%)	107 (100.0)	213 (100.0)	211 (100.0)	110 (100.0)	100 (100.0)	162 (100.0)	157 (100.0)	222 (100.0)
Mean reversibility[d], % (SD)	22.3 (9.3)	21.5 (9.2)	21.3 (9.1)	20.1 (8.2)	21.8 (9.4)	21.2 (9.0)	21.7 (9.1)	21.5 (9.1)
Mean number of puffs of rescue		[n = 211][f]	[n = 210][f]			[n = 161][f]		
medication per day at baseline (SD)[e]	1.65 (2.21)	1.81 (2.55)	1.68 (2.25)	1.75 (2.23)	1.87 (2.59)	1.81 (2.46)	1.73 (2.35)	1.83 (2.53)

Supplementary Table 1

Subject demographics and clinical characteristics according to treatment group (mITT population).

[a]At baseline was defined as ongoing at the time of the first dose of study medication.

[b]The ACQ-5 score is the mean of all five questions (range 0 to 6).

[c]Reversible was defined as improvement in FEV_1 post-salbutamol versus pre-salbutamol of ≥12% and ≥200 mL at screening.

[d]Reversibility was defined as 100 x (post-salbutamol FEV_1 - pre-salbutamol FEV_1)/pre-salbutamol FEV_1 (for whichever screening visit had pre-dose and post-dose values that yielded the highest reversibility value).

[e]Subjects for whom data on change in rescue medication use were available (as shown in Table A.4).

[f]N values for group sizes are reported where different from those of the overall mITT population.

ACQ-5, Asthma Control Questionnaire-5; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; GP, glycopyrronium; ICS, inhaled corticosteroid; MDI, metered dose inhaler; mITT, modified intent-to-treat; SAL, salmeterol; SD, standard deviation.

	GP MDI					Placebo MDI	SAL DPI 50 µg
	28.8 µg	**14.4 µg**	**7.2 µg**	**3.6 µg**	**1.9 µg**		
All subjects	(n = 101)	(n = 212)	(n = 202)	(n = 109)	(n = 99)	(n = 158)	(n = 155)
LSM change from baseline (SE)	191 (17)	167 (13)	146 (13)	147 (17)	113 (17)	38 (14)	190 (15)
LSM difference vs placebo MDI (SE)	153† (18)	129† (15)	108† (15)	109† (18)	75† (19)	NA	152† (16)
95% CI	117, 189	100, 158	79, 137	74, 144	38, 111	NA	120, 184
ICS users	(n = 56)	(n = 115)	(n = 110)	(n = 60)	(n = 59)	(n = 86)	(n = 88)
LSM change from baseline (SE)	211 (23)	179 (18)	163 (18)	174 (22)	132 (22)	57 (19)	192 (19)
LSM difference vs placebo MDI (SE)	154† (25)	122† (20)	106† (20)	117† (24)	75** (24)	NA	135† (21)
95% CI	105, 202	83, 161	67, 146	70, 164	28, 123	NA	93, 177
Non-ICS users	(n = 45)	(n = 97)	(n = 92)	(n = 49)	(n = 40)	(n = 72)	(n = 67)
LSM change from baseline (SE)	172 (25)	156 (19)	129 (20)	120 (25)	93 (27)	19 (21)	189 (22)
LSM difference vs placebo MDI (SE)	153† (27)	136† (22)	110† (22)	101† (26)	74** (28)	NA	169† (24)
95% CI	99, 206	94, 178	67, 153	49, 152	19, 130	NA	122, 216

Supplementary Table 2

FEV_1 $AUC_{0–3}$ on Day 15, mL (mITT population).

**p < .01; ***p ≤ .001; †p ≤ .0001 versus placebo MDI.

CI, confidence interval; DPI, dry powder inhaler; GP, glycopyrronium; ICS, inhaled corticosteroid; LSM, least squares mean; MDI, metered dose inhaler; mITT, modified intent-to-treat; NA, not applicable; SAL, salmeterol; SE, standard error.

	GP MDI					Placebo MDI	SAL DPI 50 «g
	28.8 «g	**14.4 «g**	**7.2 «g**	**3.6 «g**	**1.9 «g**		
Pre-dose PEFR, L/min							
All subjects	(n = 106)	(n = 210)	(n = 210)	(n = 109)	(n = 100)	(n = 159)	(n = 156)
LSM change from baseline (SE)	3.26 (4.64)	−4.37 (3.76)	−3.15 (3.76)	−0.08 (4.59)	−11.96 (4.77)	−-20.28 (4.06)	0.22 (4.11)
LSM difference vs placebo MDI (SE)	23.54† (4.74)	15.90† (3.84)	17.13† (3.86)	20.19† (4.67)	8.32 (4.88)	NA	20.49† (4.22)
95% CI	14.24, 32.83	8.36, 23.45	9.56, 24.70	11.02, 29.36	−1.26, 17.90	NA	12.21, 28.77
ICS users	(n = 58)	(n = 114)	(n = 115)	(n = 60)	(n = 59)	(n = 87)	(n = 88)
LSM change from baseline (SE)	8.50 (6.23)	−0.36 (5.07)	5.04 (5.06)	0.20 (6.15)	−7.27 (6.18)	−16.20 (5.46)	0.81 (5.45)
LSM difference vs placebo MDI (SE)	24.70† (6.38)	15.84** (5.19)	21.24† (5.19)	16.4** (6.29)	8.93 (6.32)	NA	17.01** (5.62)
95% CI	12.17, 37.22	5.65, 26.04	11.04, 31.44	4.05, 28.76	−3.48, 21.34	NA	5.98, 28.04
Non-ICS users	(n = 48)	(n = 96)	(n = 95)	(n = 49)	(n = 41)	(n = 72)	(n = 68)
LSM change from baseline (SE)	−1.97 (6.86)	−8.39 (5.56)	−11.33 (5.58)	−0.37 (6.81)	−16.64 (7.27)	−24.35 (6.02)	−0.38 (6.14)
LSM difference vs placebo MDI (SE)	22.38** (6.98)	15.96** (5.68)	13.02* (5.70)	23.98*** (6.91)	7.71 (7.44)	NA	23.98† (6.29)
95% CI	8.67, 36.09	4.82, 27.11	1.83, 24.21	10.41, 37.55	−6.89, 22.31	NA	11.63, 36.32

Post-dose PEFR, L/min							
All subjects	(n = 106)	(n = 211)	(n = 210)	(n = 109)	(n = 100)	(n = 159)	(n = 156)
LSM change from baseline (SE)	9.14 (4.32)	−0.76 (3.61)	0.53 (3.61)	4.09 (4.28)	−7.13 (4.43)	−21.49 (3.85)	5.78 (3.89)
LSM difference vs placebo MDI (SE)	30.62† (4.14)	20.73† (3.36)	22.02† (3.37)	25.58† (4.09)	14.35*** (4.27)	NA	27.26† (3.69)
95% CI	22.49, 38.76	14.14, 27.32	15.40, 28.63	17.56, 33.60	5.97, 22.74	NA	20.02, 34.50
ICS users	(n = 58)	(n = 115)	(n = 115)	(n = 60)	(n = 59)	(n = 87)	(n = 88)
LSM change from baseline (SE)	15.70 (5.81)	2.21 (4.85)	8.42 (4.85)	7.25 (5.74)	−3.36 (5.76)	−16.36 (5.18)	8.66 (5.16)
LSM difference vs placebo MDI (SE)	32.06† (5.58)	18.57† (4.53)	24.78† (4.54)	23.61† (5.51)	13.00* (5.53)	NA	25.02† (4.91)
95% CI	21.11, 43.01	9.68, 27.45	15.87, 33.68	12.80, 34.42	2.14, 23.86)	NA	15.39, 34.65
Non-ICS users	(n = 48)	(n = 96)	(n = 95)	(n = 49)	(n = 41)	(n = 72)	(n = 68)
LSM change from baseline (SE)	2.57 (6.40)	−3.73 (5.34)	−7.36 (5.35)	0.92 (6.35)	−10.91 (6.73)	−26.62 (5.70)	2.89 (5.80)
LSM difference vs placebo MDI (SE)	29.19† (6.11)	22.89† (4.96)	19.25† (4.98)	27.54† (6.04)	15.71* (6.51)	NA	29.51† (5.50)
95% CI	17.21, 41.17	13.15, 32.63	9.48, 29.02	15.68, 39.40	2.94, 28.48	NA	18.72, 40.30

Supplementary Table 3

Daily pre- and post-dose PEFR over 14 days (mITT population).

$^{*}p < .05$; $^{**}p < .01$; $^{***}p \leq .001$; $^{\dagger}p \leq .0001$ versus placebo MDI.

CI, confidence interval; DPI, dry powder inhaler; GP, glycopyrronium; ICS, inhaled corticosteroid; LSM, least squares mean; MDI, metered dose inhaler; mITT, modified intent-to-treat; NA, not applicable; PEFR, peak expiratory flow rate; SAL, salmeterol; SE, standard error.

	GP MDI					Placebo MDI	SAL DPI 50 µg
	28.8 µg	**14.4 µg**	**7.2 µg**	**3.6 µg**	**1.9 µg**		
All subjects	(n = 107)	(n = 211)	(n = 210)	(n = 110)	(n = 100)	(n = 161)	(n = 157)
LSM change from baseline (SE)	–0.43 (0.12)	–0.27 (0.10)	–0.28 (0.10)	–0.36 (0.12)	–0.29 (0.13)	–0.13 (0.11)	–0.57 (0.11)
LSM difference vs placebo MDI (SE)	–0.30* (0.13)	–0.13 (0.10)	–0.15 (0.10)	–0.23 (0.12)	–0.15 (0.13)	NA	–0.44† (0.11)
95% CI	−0.54, −0.05	−0.33, 0.06	−0.35, 0.05	−0.47, 0.01	−0.41, 0.10	NA	−0.65, −0.22
ICS users	(n = 58)	(n = 115)	(n = 115)	(n = 60)	(n = 59)	(n = 88)	(n = 88)
LSM change from baseline (SE)	–0.36 (0.16)	–0.24 (0.13)	–0.31 (0.13)	–0.38 (0.16)	–0.27 (0.16)	–0.09 (0.14)	–0.64 (0.14)
LSM difference vs placebo MDI (SE)	–0.28 (0.17)	–0.15 (0.14)	–0.22 (0.14)	–0.29 (0.17)	–0.18 (0.17)	NA	–0.55*** (0.15)
95% CI	−0.61, 0.06	−0.42, 0.11	−0.49, 0.05	−0.62, 0.03	−0.51, 0.14	NA	−0.84, −0.26
Non-ICS users	(n = 49)	(n = 96)	(n = 95)	(n = 50)	(n = 41)	(n = 73)	(n = 69)
LSM change from baseline (SE)	–0.50 (0.18)	–0.29 (0.15)	–0.25 (0.15)	–0.34 (0.18)	–0.30 (0.19)	–0.18 (0.16)	–0.50 (0.16)
LSM difference vs placebo MDI (SE)	–0.32 (0.18)	–0.11 (0.15)	–0.07 (0.15)	–0.16 (0.18)	–0.12 (0.20)	NA	–0.32 (0.17)
95% CI	−0.68, 0.04	−0.41, 0.18	−0.37, 0.22	−0.52, 0.19	−0.51, 0.26	NA	−0.64, 0.01

Supplementary Table 4

Daily rescue medication use over 14 days (mITT population).

*p < .05; ***p ≤ .001; †p < .0001 versus placebo MDI.

CI, confidence interval; DPI, dry powder inhaler; GP, glycopyrronium; ICS, inhaled corticosteroid; LSM, least squares mean; MDI, metered dose inhaler; mITT, modified intent-to-treat; NA, not applicable; SAL, salmeterol; SE, standard error.

	GP MDI					Placebo MDI	SAL DPI 50 µg
	28.8 µg	**14.4 µg**	**7.2 µg**	**3.6 µg**	**1.9 µg**		
All subjects	(n = 106)	(n = 215)	(n = 211)	(n = 110)	(n = 101)	(n = 160)	(n = 158)
Baseline							
Mean	1.36	1.39	1.38	1.26	1.42	1.42	1.39
SD	0.73	0.78	0.77	0.71	0.83	0.79	0.73
Change from baseline, LSM	–0.17	–0.17	–0.11	–0.10	–0.21	–0.06	–0.30
SE	0.06	0.05	0.05	0.06	0.06	0.05	0.05
LSM difference vs placebo MDI	–0.11	–0.12*	–0.06	–0.04	–0.15*	NA	–0.25†
SE	0.07	0.05	0.05	0.06	0.07	NA	0.06
95% CI	–0.24, 0.02	–0.22, –0.01	–0.16, 0.05	–0.17, 0.08	–0.28, –0.02	NA	–0.36, –0.14

Supplementary Table 5

Asthma Control Questionnaire-5 score on Day 15 (mITT population).

*p < .05; †p < .0001 versus placebo MDI.

The ACQ-5 score is the mean of all five questions (range 0 to 6).

ACQ-5, Asthma Control Questionnaire-5; CI, confidence interval; DPI, dry powder inhaler; GP, glycopyrronium; ICS, inhaled corticosteroid; LSM, least squares mean; MDI, metered dose inhaler; NA, not applicable; mITT, modified intent-to-treat; SAL, salmeterol; SD, standard deviation; SE, standard error.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6-7
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8-10
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	8
Participants	4a	Eligibility criteria for participants	10-11
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13-14
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	14-15
	13b	For each group, losses and exclusions after randomisation, together with reasons	14-15
Recruitment	14a	Dates defining the periods of recruitment and follow-up	14
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	17, 39-40
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	14
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	18-26
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	18-26
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	26-27
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	30
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	29-30
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	29-30
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	31

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

NA, not applicable.