Randomized dose-ranging study of a budesonide metered-dose inhaler by using co-suspension delivery technology in asthma

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ABSTRACT

Background: *This is the first study of the inhaled corticosteroid, budesonide, delivered by metered-dose inhaler (BD MDI) using innovative co-suspension delivery technology in adults with asthma.*

Objective: *To characterize the effects of BD delivered by MDI on lung function and safety.*

Methods: *Randomized, double-blind, 4-week cross-over, placebo-controlled, phase IIb study of adults (18–65 years of age) with mild-to-moderate persistent asthma. The subjects received twice-daily BD MDI 320 μg, 160 μg, and placebo MDI, and either BD MDI 80 μg or 40 μg. The primary endpoint was change from baseline in morning trough forced expiratory volume in 1 second (FEV_1) at the end of the treatment period (EOT). Secondary endpoints included change from baseline in morning and evening predose peak expiratory flow rate (PEFR), rescue medication use, and Asthma Control Questionnaire 5-question version (ACQ-5) score. Safety was also assessed.*

Results: *A total of 147 subjects were randomized. All doses of BD MDI improved morning trough FEV_1 at EOT, and morning and evening predose PEFR in the last treatment week versus placebo (all $p < 0.01$), with improvements in trough FEV_1 exceeding 100 mL for BD MDI 320 μg, and 160 μg only. Compared with placebo, all BD MDI doses reduced rescue medication use in the last week of treatment ($p < 0.01$) and improved ACQ-5 scores at EOT (all $p < 0.01$). All treatments were well tolerated.*

Conclusion: *Analysis of the data demonstrated greater efficacy improvements for the higher doses of BD MDI (320 μg and 160 μg), with similar adverse event profiles compared with the lower doses. Hence, BD MDI 320 μg and 160 μg warrant further evaluation in subjects with persistent asthma.*

Clinical trial NCT02105012, www.clinicaltrials.gov

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Current guidelines for asthma diagnosis and management recommend a stepwise approach when using inhaled corticosteroids (ICS), the cornerstone of asthma therapy, as the first-line controller treatment for persistent asthma (mild, moderate, and severe).[1] Regular ICS treatment controls the chronic airway inflammation associated with asthma[2,3]; improves symptoms, lung function, and quality of life; and reduces exacerbation frequency.[1,4,5]

Introduced in the 1980s,[6] the ICS budesonide has been widely prescribed for maintenance treatment of asthma. It is considered to have a favorable benefit-to-risk ratio due to its potent local anti-inflammatory action, combined with its limited systemic availability.[1,7–9] A number of studies confirm the safety and efficacy of budesonide in asthma when using a broad range of outcome measures.[7,10–13] For the treatment of asthma, budesonide is widely available in dry-powder inhaler (DPI) and nebulizer formulations. Device preference is an important consideration in selecting an inhaler,[4] and availability of budesonide as a pressurized metered-dose inhaler (MDI) would increase choice for patients with asthma. Short-acting bronchodilators, which are recommended as the first-line therapy for asthma,[1,4] are commonly delivered by using MDIs, and, thus, many patients

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who are prescribed an ICS are already familiar with a MDI device.

Co-suspension delivery technology is an innovative formulation platform that uses strong, nonspecific associations between drug crystals and micro-sized, spray-dried, phospholipid porous particles to provide uniform dose delivery of inhaled drugs or drug combinations from a MDI throughout the lungs.[14–17] To our knowledge, this study was the first to characterize the lung function benefits, dose-response effects, and safety of twice-daily budesonide delivered by an MDI (BD MDI) using co-suspension delivery technology in adults with mild-to-moderate persistent asthma.

METHODS

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, chronic-dosing, 4-week, 4-period, 5-treatment, incomplete block, cross-over, dose-ranging phase IIb study in adults with mild-to-moderate persistent asthma, conducted across 45 sites in the United States between May 13, 2014, and September 4, 2015. The study enrolled subjects who were receiving a low-to-medium dose of an ICS, or a combination treatment that contained low-dose ICS, for ≥4 weeks before screening (based on the ICS dose classification according to the 2012 Global Initiative for Asthma guidelines).

An interactive Web response system was used to randomize subjects to one of eight treatment sequences, which included four of the five treatments. All treatment sequences included twice-daily BD MDI 320 μg, BD MDI 160 μg, and placebo MDI. Four treatment sequences included twice-daily BD MDI 80 μg. The other four included twice-daily BD MDI 40 μg. The five study treatments (four doses of BD MDI and placebo MDI) were identical in all aspects and impossible to differentiate. Each treatment period lasted 28 ± 2 days. The subjects were permitted to use sponsor-provided rescue albuterol sulfate 90 μg (Ventolin hydrofluoroalkane GlaxoSmithKline, Research Triangle Park, NC) as required during screening, washout, and treatment periods. During screening (15–28 days) and washout periods (14–21 days), the subjects received twice-daily sponsor-provided budesonide 180 μg dry powder inhaler (BUD DPI) (Pulmicort Flexhaler AstraZeneca, Wilmington, DE), which corresponded to a 160-μg dose delivered from the mouthpiece.

This study was conducted in accordance with Good Clinical Practice Guidelines, including the International Council on Harmonisation, the U.S. Code of Federal Regulations, and the Declaration of Helsinki. The protocol and the informed consent form were approved by Schulman Associates Institutional Review Board, Inc. (201401722). The subjects provided written informed consent before screening.

Study Population

Eligible subjects were 18–65 years of age with persistent asthma diagnosed ≥6 months before the start of the screening period, based on the National Heart, Lung, and Blood Institute's Guidelines for the Diagnosis and Management of Asthma.[1] In addition, a prealbuterol forced expiratory volume in 1 second (FEV_1) of 60–90% (inclusive) of predicted normal value was required during screening and randomization (day 1 of treatment period 1; calculated by using the Third National Health and Nutrition Examination Survey reference equations). This was expanded in October 2014 from <85% to ≤90% to evaluate a broader spectrum of subjects with mild asthma.

On day 1 of treatment period 1, the baseline predose FEV_1 value (the average of the −60-minute and −30-minute predose FEV_1) for each subject had to be within 20% of his or her prebronchodilator FEV_1 value at screening (baseline FEV_1 stability criteria). In addition, the subjects had to maintain this baseline FEV_1 stability on day 1 of each remaining treatment period to be eligible to receive the next treatment. The subjects were also required to demonstrate reversibility to a bronchodilator during screening, as assessed by an increase in FEV_1 of ≥12% and ≥200 mL over the prealbuterol FEV_1 within 30–60 minutes after inhalation of four puffs of albuterol. The subjects were required to have used albuterol on ≥2 of the last 7 days before randomization and to have an Asthma Control Questionnaire 5-question version (ACQ-5) total score of ≥1.5.

Subjects were excluded if they had worsening asthma (which involved an emergency department visit, hospitalization, or oral and/or parenteral corticosteroid use within 6 weeks of screening); life-threatening asthma (a history of a significant episode[s] that required intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or an asthma-related syncopal episode[s] within 12 months of screening); intermittent, seasonal, and/or exercise-induced asthma alone; or any other concurrent conditions (including other respiratory diseases) deemed to potentially put the subject at risk and/or confound interpretation of results. Moreover, subjects with cardiac conditions (*e.g.,* a history of myocardial infarction), abnormal electrocardiogram or liver function tests, or hypersensitivity to a study medication component were excluded. In addition, subjects were excluded if they developed a respiratory tract infection within 6 weeks before or during screening, had received chronic treatment with antibiotics or oral and/or systemic corticosteroids, had received depot or intra-articular corticosteroids 3 months before screening, or had initiated or

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discontinued ICS 30 days before screening. Current smokers or subjects with a ≥10 pack-year history were also excluded.

Endpoints and Assessments

The primary efficacy endpoint was a change from baseline in morning predose trough FEV_1 at the end of the treatment period (EOT). Secondary endpoints were a change from baseline in the mean morning and evening predose peak expiratory flow rate (PEFR) and a change from baseline in the mean number of puffs of rescue albuterol over the last week of the treatment period (both recorded in the subject's eDiary), and change from baseline in the ACQ-5 score at EOT. Safety assessments, including electrocardiograms, vital-sign measurements, clinical laboratory tests, monitoring for paradoxical bronchospasm, physical examinations, and monitoring of adverse events (AE) were conducted throughout.

Statistical Analyses

Efficacy analyses were performed on the modified intent-to-treat (mITT) population, defined as subjects who received study treatment and had posttreatment efficacy data from two or more treatment periods. Safety analyses were based on the safety population (all the subjects who were randomized and received one or more doses of the study treatment). The primary endpoint was analyzed by using a repeated-measures mixed model with fixed effects for treatment, baseline FEV_1, and treatment period; subject was included as a random effect. The model-based least squares mean (LSM), standard error, and corresponding two-sided 95% confidence intervals (CI) were calculated for each treatment and pairwise treatment difference. Type I error was controlled at the two-sided 0.05 level for the primary endpoint by using a sequential gatekeeping approach. Secondary endpoints were analyzed by using similar repeated-measures mixed models as for the primary endpoint.

In the *post hoc* analysis, noninferiority between BD MDI and BUD DPI was performed by evaluating the within-treatment LSM change in morning predose trough FEV_1 value from baseline to EOT for each BD MDI dose. Because the subjects were treated with BUD DPI for 14–28 days (15–28−day screening period and 14–21−day washout period), the baseline predose trough FEV_1 value approximated the effect of BUD DPI after 28 days of treatment. Similarly, because the subjects were switched to BD MDI at the start of the treatment period, the predose trough FEV_1 value at EOT approximated the effect of a BD MDI dose after 28 days of treatment. A noninferiority margin of 50 mL was used. With 150 randomized subjects and a dropout rate of 20%, the study was estimated to have 90% power to demonstrate a difference from placebo MDI of 120 mL for BD MDI 320 μg or 160 μg, and 80% power to demonstrate a difference from a placebo MDI of 140 mL for BD MDI 80 μg or 40 μg for the primary endpoint. The within-subject standard deviation was estimated as 285 mL.

RESULTS

Study Populations

Of 147 subjects who were randomized and received treatment, 115 subjects (78.2%) received one or more doses of the study treatment drug during each treatment period, and 97 subjects (66.0%) completed all four treatment periods, with an additional 19 subjects (12.9%) completing three of four treatment periods (Fig. 1). Thirty-three subjects (22.4%) were discontinued from the study. Reasons for discontinuations are shown in Fig. 1. A total of 121 subjects (82.3%) were included in the mITT population; 26 subjects were excluded: did not receive treatment in two or more treatment periods ($n = 20$), took prohibited medicines ($n = 6$), had a baseline ACQ-5 score of <1.5 ($n = 2$), or did not meet reversibility criteria ($n = 1$) (subjects may have been excluded for multiple reasons). Baseline demographics and clinical characteristics for the mITT population are shown in Table 1.

Efficacy Outcomes

Primary Endpoint. The change from baseline in morning predose trough FEV_1 at EOT was greater than in placebo for all BD MDI doses (LSM differences range, 83–115 mL; all $p < 0.01$) (Fig. 2*A*). For BD MDI 320 μg and 160 μg, the LSM differences in the change from baseline versus placebo were >100 mL (114 and 115 mL, BD MDI 320 g and 160 g, respectively).

Post Hoc *Comparison of Morning Predose Trough FEV_1.* A noninferiority comparison of BD MDI versus BUD DPI at EOT was approximated in a *post hoc* analysis of the within-treatment LSM change from baseline at EOT for each BD MDI dose (at baseline, the subjects had completed ~28 days' treatment with BUD DPI). The morning predose trough FEV_1 values at EOT with BD MDI 320 μg and 160 μg were unchanged from baseline (−2 and −1 mL, respectively), with lower bounds of the associated 95% CIs within the 50 mL noninferiority margin versus BUD DPI (Fig. 2*B*). BD MDI 80 μg and 40 μg exhibited negative changes from baseline (−34 and −31 mL, respectively) with 95% CI lower bounds that did not fall within the noninferiority margin. Placebo MDI showed the greatest negative change from baseline, of −116 mL (95% CI lower bound of −150 mL).

Secondary Endpoints. Treatment with all BD MDI doses resulted in significant increases in the change from baseline in morning and evening predose PEFR

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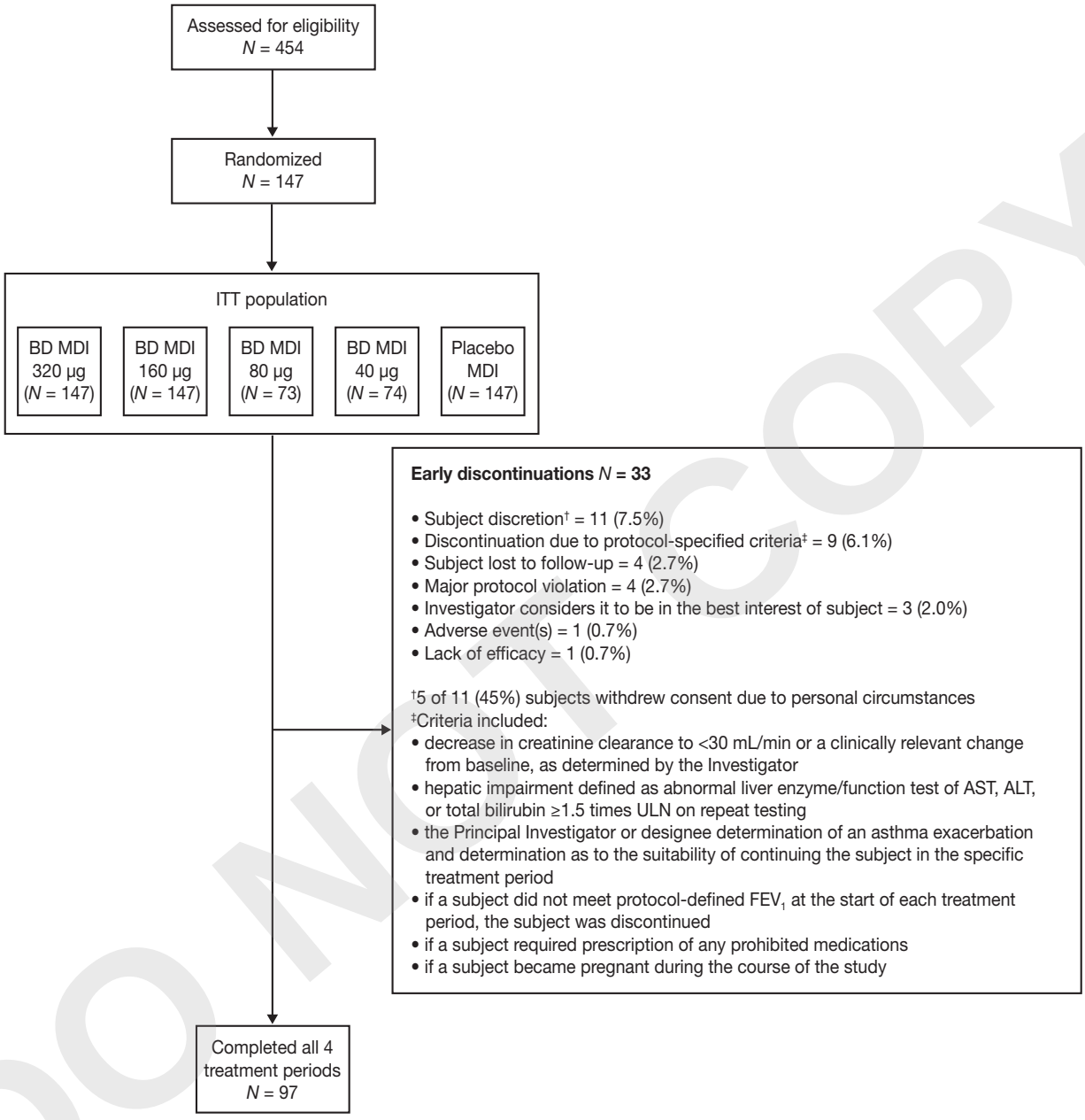

Figure 1. *Subject disposition. The number of subjects who completed all four treatment periods and the number of subjects who were discontinued from the study early does not total the number of subjects randomized because the subjects could have been discontinued from a treatment period but still undergo further treatment periods until the end of the study and, therefore, were not classified as being discontinued from the study early. AST = aspartate aminotransferase; ALT = alanine aminotransferase; BD MDI = budesonide metered dose inhaler; FEV_1 = forced expiratory volume in 1 second; ULN = upper limit of normal.*

versus placebo over the last week of the treatment period (Fig. 3). LSM differences versus placebo ranged from 19.9 to 24.3 L/min and 18.4 to 30.9 L/min for morning and evening predose PEFR (eDiary), respectively (all $p < 0.01$). Rescue albuterol use was reduced with all BD MDI doses over the last week of the treatment period versus placebo (LSM differences range, −0.7 to −0.9 puffs/day; all $p < 0.01$) (Table 2). Moreover, ACQ-5 scores improved at EOT for all BD MDI doses versus placebo (LSM differences range, −0.3 to −0.5; all $p < 0.01$) (Table 2).

Safety Outcomes

In the safety population ($n = 147$), the lowest frequency of treatment-emergent AEs (TEAEs) by subject was reported with the BD MDI 40 µg treatment (9.5%) and the highest with placebo MDI (20.5%). The only

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Table 1 **Baseline demographics and clinical characteristics (mITT population)**

	BD MDI Dose				Placebo MDI (n = 118)	All subjects (n = 121)
	320 μg (n = 112)	160 μg (n = 118)	80 μg (n = 57)	40 μg (n = 58)		
Age, mean ± SD, y	45.9 ± 11.1	46.3 ± 11.0	46.8 ± 10.3	45.5 ± 11.9	46.0 ± 11.0	46.2 ± 11.0
Men, no. (%)	36 (32.1)	36 (30.5)	15 (26.3)	21 (36.2)	38 (32.2)	38 (31.4)
White, no. (%)	81 (72.3)	83 (70.3)	39 (68.4)	43 (74.1)	85 (72.0)	86 (71.1)
BMI, mean ± SD, kg/m^2	32.3 ± 8.0	32.1 ± 7.8	31.7 ± 7.3	32.0 ± 7.9	32.1 ± 7.9	32.1 ± 7.8
Smoking status, no. (%)						
Former smoker	27 (24.1)	31 (26.3)	14 (24.6)	17 (29.3)	30 (25.4)	31 (25.6)
Lifelong non-smoker	85 (75.9)	87 (73.7)	43 (75.4)	41 (70.7)	88 (74.6)	90 (74.4)
Pack-years smoked, mean ± SD, no.*	4.2 ± 2.6	4.2 ± 2.7	4.3 ± 2.5	4.1 ± 3.0	4.3 ± 2.7	4.2 ± 2.7
ACQ-5 summary score, mean ± SD#	2.3 ± 0.7	2.3 ± 0.7	2.3 ± 0.7	2.3 ± 0.7	2.3 ± 0.7	2.4 ± 0.7
Duration of asthma, mean ± SD, y	28.9 ± 13.8	29.2 ± 13.8	29.7 ± 13.0	29.1 ± 14.5	28.7 ± 13.7	29.0 ± 13.8
FEV_1, mean ± SD, L§	2.279 ± 0.554	2.252 ± 0.547	2.176 ± 0.552	2.361 ± 0.551	2.284 ± 0.554	2.268 ± 0.557
FEV_1, mean ± SD, % predicted§	72.3 ± 7.5	72.5 ± 7.8	71.9 ± 7.9	72.4 ± 7.3	72.6 ± 7.7	72.5 ± 7.8
PEFR, mean ± SD, L/min§	392.9 ± 91.5	390.2 ± 89.4	382.8 ± 83.4	399.3 ± 98.2	393.6 ± 89.9	391.9 ± 89.5
Rescue medication use, mean ± SD, puffs/day¶	2.5 ± 2.1	2.5 ± 2.1	2.9 ± 2.2	2.3 ± 1.8	2.6 ± 2.1	2.6 ± 2.1

mITT = Modified intent to treat; BD MDI = budesonide metered dose inhaler; SD = standard deviation; BMI = body mass index; ACQ-5 = Asthma Control Questionnaire five-question version; FEV_1 = forced expiratory volume in 1 s; PEFR = peak expiratory flow rate.

** No. of pack-years smoked = (no. of cigarettes per day/20) × no. of years smoked; excluded non-smokers.*

 # The ACQ-5 summary score is the mean of all 5 questions and has a possible range of 0 to 6.

§ Baseline is defined as the mean of the predose values on day 1 across all treatment periods.

¶ n = 111, n = 115, n = 56, n = 56, n = 114, n = 121.

TEAEs reported by ≥2% of subjects were upper respiratory tract infection, nasopharyngitis, and asthma (Table 3). Three subjects were discontinued from the study due to TEAEs with onset during a treatment period: due to an asthma exacerbation, dyspnea, and bronchitis (all mild and possibly treatment related; placebo MDI), a severe asthma exacerbation (not related; placebo MDI), and increased blood triglycerides and γ-glutamyltransferase (both moderate and not related; BD MDI 160 μg). Four severe TEAEs were reported, all considered not treatment related. Two subjects withdrew from the study due to an asthma exacerbation, one during treatment with placebo MDI and one during a washout period (21 days after the last dose of the BD MDI 80 μg treatment). Colitis and vomiting occurred in one subject treated with BD MDI 80 μg and 160 μg, respectively. No deaths occurred.

DISCUSSION

To our knowledge, this study was the first to characterize the lung function benefits and dose-response effects of BD MDI formulated using innovative co-suspension delivery technology in adults with persistent asthma. Treatment with all the BD MDI doses resulted in significant improvements in the change from baseline in morning trough FEV_1 versus placebo. There was a ~25% greater benefit in trough FEV_1 with higher doses (BD MDI 320 μg and 160 μg) versus placebo than with the lower doses of BD MDI (80 μg and 40 μg), and differences from placebo exceeded 100 mL only with BD MDI 320 μg and 160 μg. These findings were considered clinically relevant for this study design in which all the subjects received BUD DPI 180 μg (which corresponded to 160 μg delivered from the mouthpiece) twice daily during the screening and washout periods, and had relatively small baseline

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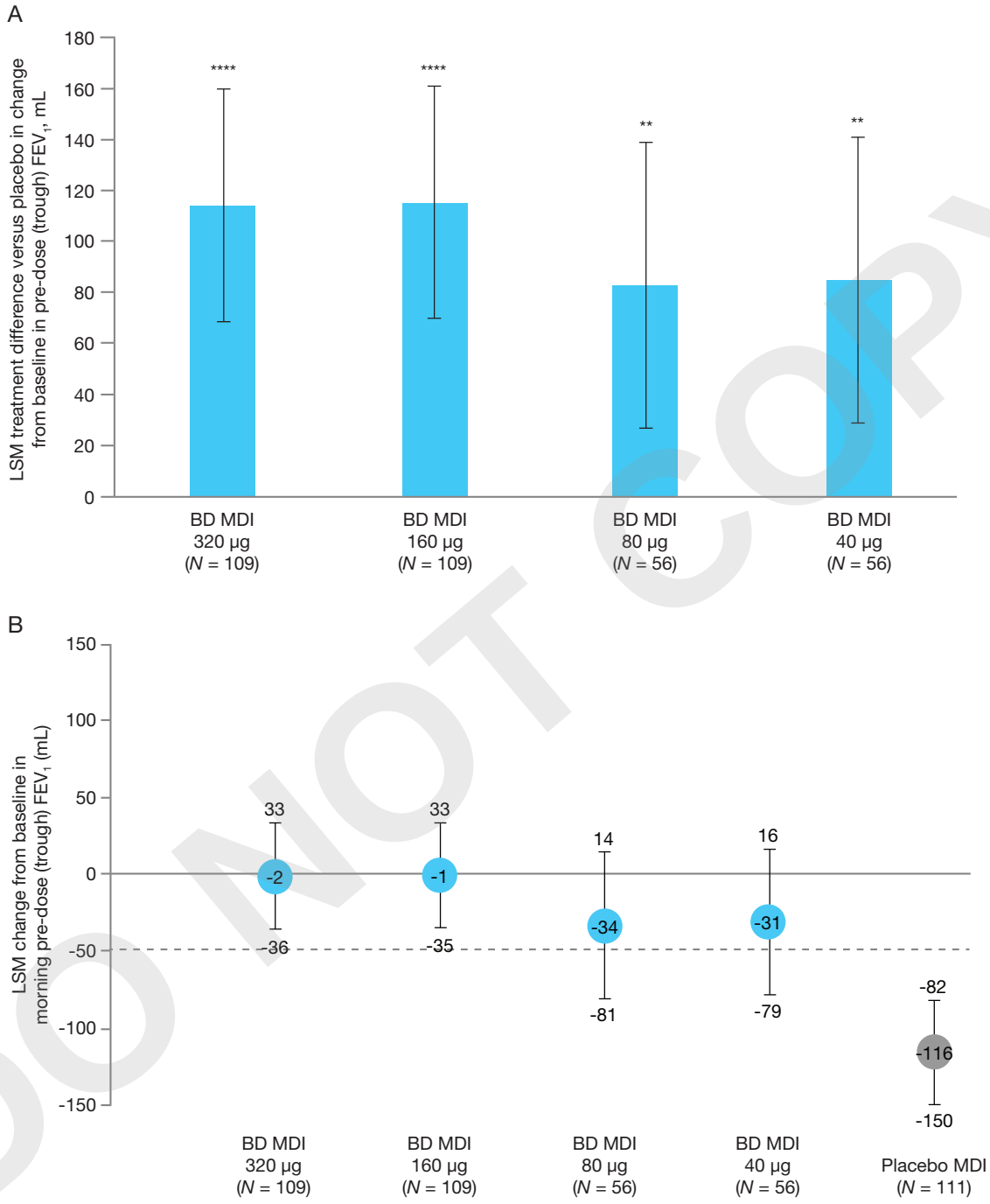

Figure 2. *(A) LSM treatment difference versus placebo in the change from baseline in morning predose trough FEV_1 at the end of treatment (primary endpoint; mITT population); (B) LSM change from baseline in morning predose trough FEV_1 at the end of treatment (post hoc analysis; mITT population). Error bars represent two-sided 95% confidence interval. Baseline was defined as the mean among treatment periods of the mean evaluable 60- and 30-minute predose values on day 1. The end of the treatment period was day 29 or day 15 if the day 29 value was missing or not evaluable. LSM = least squares mean; FEV_1 = forced expiratory volume in 1 second; mITT = modified intent to treat; BD MDI = budesonide metered dose inhaler. **$p < 0.01$; ****$p < 0.0001$ versus placebo MDI ($N = 111$).*

lung function impairments (mean baseline percentage predicted FEV_1 value, 72.5%).[1] Secondary endpoints supported the results for the primary endpoint. All BD MDI doses were well tolerated, without dose-related trends in the pattern or frequency of AEs. The only AEs reported in ≥2% of the subjects were nasopharyngitis, upper respiratory tract infection, and asthma. AEs reported here were reflective of those reported for BUD DPI, a marketed BD product with an established safety profile.[18]

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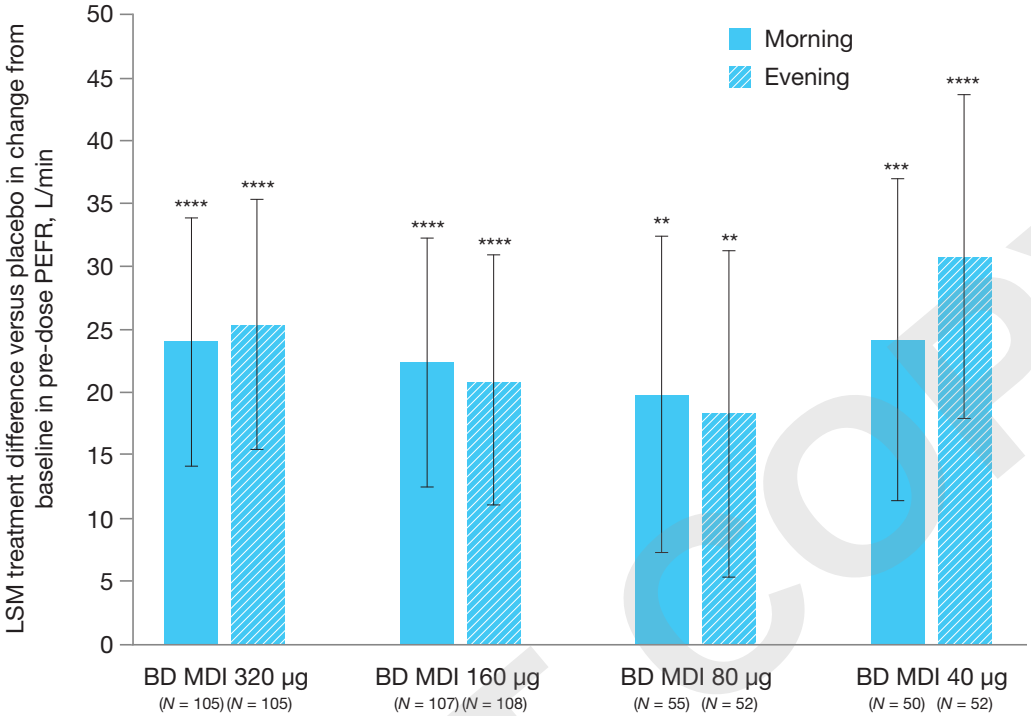

Figure 3. *LSM treatment difference versus placebo in the change from baseline in the morning and evening predose PEFR (eDiary) over the last week of the treatment period (mITT population). Error bars represent two-sided 95% confidence interval. Baseline is defined as the mean over the 7 days preceding day 1 of treatment period 1. Last week of the treatment period is the last 7 days of the treatment period. LSM = least squares mean; PEFR = peak expiratory flow rate; mITT = modified intent to treat; BD MDI = budesonide metered dose inhaler. **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$ versus placebo MDI (N = 107 [morning], N = 110 [evening]).*

Table 2 **LSM treatment difference in change from baseline in rescue albuterol use and ACQ-5 score (mITT population)**

	BD MDI Dose			
	320 µg	**160 µg**	**80 µg**	**40 µg**
Change from baseline in no. of puffs of albuterol over the last week of the treatment period				
No. of subjects	111	115	56	56
LSM difference vs placebo MDI (95% CI)#	−0.75 (−1.14 to −0.36)**	−0.87 (−1.26 to −0.49)***	−0.92 (−1.42 to −0.42)**	−0.70 (−1.20 to −0.21)*
Change from baseline in ACQ-5 score at the end of the treatment period				
No. of subjects	109	114	57	57
LSM difference vs placebo MDI (95% CI)§	−0.48 (−0.64 to −0.31)***	−0.47 (−0.63 to −0.31)***	−0.42 (−0.62 to −0.21)***	−0.31 (−0.51 to −0.10)*

LSM = Least squares mean; ACQ-5 = Asthma Control Questionnaire five-question version; mITT = modified intent to treat; BD MDI = budesonide metered dose inhaler; CI = confidence interval.
* $p < 0.01$; ** $p < 0.001$; *** $p < 0.0001$.
 # Placebo MDI: n = 114.
§ Placebo MDI: n = 115.

In this study, budesonide was administered *via* a pressurized MDI using the innovative co-suspension delivery technology. Although widely prescribed, portable, and relatively inexpensive,[19] pressurized MDIs have been challenging to formulate, especially as combination treatments.[20] Co-suspension delivery technology has helped overcome formulation difficulties associated with hydrofluoroalkane propellants to enable uniform delivery of single, dual, and triple combination treatments from a single inhaler device.[14–16] Co-suspension delivery technology can deliver consistent dosing, despite common patient-handling errors, such

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Table 3 **Incidence of TEAEs (safety population)***

	BD MDI Dose				Placebo MDI
	320 μg (*n* = 124)	160 μg (*n* = 132)	80 μg (*n* = 64)	40 μg (*n* = 63)	(*n* = 127)
At least 1 TEAE, no. (%)	22 (17.7)	25 (18.9)	11 (17.2)	6 (9.5)	26 (20.5)
TEAEs related to study treatment#	3 (2.4)	3 (2.3)	0	0	4 (3.1)
Serious TEAEs	0	0	1 (1.6)	0	0
Serious TEAEs related to study treatment#	0	0	0	0	0
TEAEs that led to early discontinuation of the study drug	0	1 (0.8)	0	0	2 (1.6)
Deaths§	0	0	0	0	0
TEAEs reported by ≥2% of subjects in any treatment group, no. (%)					
Nasopharyngitis	4 (3.2)	1 (0.8)	0	1 (1.6)	1 (0.8)
Upper respiratory tract infection	3 (2.4)	5 (3.8)	1 (1.6)	1 (1.6)	4 (3.1)
Worsening asthma	0	1 (0.8)	0	0	7 (5.5)

TEAE = Treatment-emergent adverse event; BD MDI = budesonide metered dose inhaler.
** Excluding TEAEs with onset during the washout periods.*
 # Related indicates "possibly," "probably," or "definitely" related to study treatment as judged by the site investigator.
§ Including events that occurred within 14 days after the final dose of study medication.

as inadequate shaking or long delays between shaking and actuation.[14]

These findings support co-suspension delivery technology as an important delivery platform for patients with airway diseases, which enable use of a common device type, such as a pressurized MDI, for both rescue medication and maintenance therapy. This is important because inhaler type may influence asthma outcomes in real-world settings.[21,22] For example, when the same agents (fluticasone-salmeterol fixed-dose combination) were delivered by pressurized MDI compared with DPI in a real-world setting, the pressurized MDI was associated with better asthma control.[23] A potential study limitation was the relatively short treatment duration (4 weeks). Nonetheless, there are studies that show that ICS treatment effects on lung function generally plateau within 4 weeks, which potentially mitigates this concern.[18,24]

CONCLUSION

In subjects with persistent asthma, all the doses of BD MDI formulated using innovative co-suspension delivery technology resulted in significant improvements versus placebo in morning predose trough FEV_1 at EOT. However, only the 320 μg and 160 μg doses resulted in clinically meaningful LSM differences from placebo, of ≥100 mL.[25] Overall, all the doses of BD MDI were well tolerated, without dose-related trends with regard to TEAEs. Moreover, TEAEs observed across all BD MDI groups were similar to those reported for placebo.[26] Taken together, analysis of these data indicated that BD MDI 320 μg and 160 μg warrant further investigation in subjects with asthma.

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