Mometasone furoate delivered via Breezhaler® and Twisthaler® in patients with asthma

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Introduction

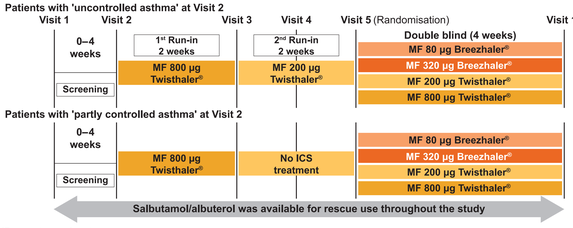
- Mometasone furoate (MF) delivered with Asmanex® Twisthaler® is approved in the United States for the treatment of asthma in adults and children ≥4 years and in over 60 countries worldwide for adults and adolescents ≥12 years
- MF delivered with the Breezhaler® inhalation device is in development for the treatment of asthma in fixed-dose combinations with bronchodilators
- Based on a human pharmacokinetic study[1] and *in vitro* pharmaceutical performance testing, MF Breezhaler® doses of 80 and 320 µg once daily (o.d.) were identified as corresponding to MF Twisthaler® doses of 200 and 800 µg o.d., respectively and are expected to elicit similar lung function effects in patients with asthma at the corresponding doses
- The primary objective of this study was to show non-inferiority in terms of trough forced expiratory volume in one second (FEV_1) on Day 29 of the low (80 µg) and high (320 µg) doses of MF delivered via the Breezhaler® o.d., compared with the corresponding low (200 µg) and high (800 µg [400 µg x 2 inhalations]) doses of MF delivered via the Twisthaler® o.d. (prespecified non-inferiority margin: 90 mL)
- Since sensitivity to ICS is variable, individual patients' ICS sensitivity (as measured by FEV_1 decline on ICS weaning; see footnote to **Table 2**) was used to build a robust analysis model for the study data
- A secondary objective was to evaluate the efficacy of MF 80 µg and 320 µg delivered via Breezhaler®, and MF 200 µg and 800 µg delivered via Twisthaler® in terms of Asthma Control Questionnaire (ACQ-5)

Methods

Study design

- Randomised, double-blind, double-dummy, four-week, parallel-group study of 739 adolescents and adults with asthma (ClinicalTrials.gov number: NCT01555151; **Figure 1**)

Figure 1. Study design



MF: mometasone furoate

Patients

Key inclusion criteria

- Patients with persistent asthma on ICS treatment up to the maximum dose per day on a stable regimen for at least four weeks before screening
- Asthma control 'partly controlled'/'uncontrolled' at screening[2]
- Pre-bronchodilator FEV_1 of ≤80% of predicted normal value at screening
- Reversibility of bronchoconstriction to short-acting β_2-agonist
- Patients with ICS sensitivity (see footnote to **Table 2**)

Key exclusion criteria

- Patients who were current smokers or have a smoking history of >10 pack years
- Patients diagnosed with COPD
- Patients with any chronic conditions affecting the respiratory tract or chronic lung diseases, which in the opinion of the investigator may interfere with the study evaluation or optimal participation in the study

Endpoints

- The primary endpoint, trough FEV_1, was defined as the average of the 23 h 10 min and 23 h 45 min post-dose values on Day 29
- A secondary endpoint was ACQ-5, measured after one, two, three and four weeks of treatment

Statistical analysis

- The primary endpoint was analysed using a mixed model on the full analysis set. The model contained treatment, level of asthma control (partly controlled/uncontrolled) and gender as fixed effects with the baseline FEV_1 measurement and age as covariates. The model also included region as fixed effects with centre nested within region as a random effect
  - ICS sensitivity was added to the pre-specified analysis as a covariate in a post-hoc analysis, because it was shown to be a strong predictor of response and was also imbalanced between treatment groups
- The change in ACQ-5 from baseline at each visit was analysed using a similar mixed model as specified for the primary analysis

Results

Patients

- 739 patients were randomised; 702 patients (95.0%) completed the study
- Patients' baseline characteristics were balanced between the four treatment groups (**Tables 1** and **2**) apart from ICS sensitivity

Table 1. Baseline demographics and clinical characteristics (randomised set)

	MF 80 µg Breezhaler® n = 188	MF 200 µg Twisthaler® n = 181	MF 320 µg Breezhaler® n = 184	MF 800 µg Twisthaler® n = 186	Total N = 739
Age, years, median (range)	47 (12–75)	49 (12–75)	48 (12–81)	48 (12–82)	48 (12–82)
Age, years, n (%)					
12–<18	22 (11.7)	18 (9.9)	16 (8.7)	17 (9.1)	73 (9.9)
18 –<65	148 (78.7)	148 (81.8)	146 (79.3)	153 (82.3)	595 (80.5)
≥65	18 (9.6)	15 (8.3)	22 (12.0)	16 (8.6)	71 (9.6)
Gender, n (%)					
Female	98 (52.1)	94 (51.9)	113 (61.4)	97 (52.2)	402 (54.4)
BMI (kg/m²)	26.4 ± 5.49	26.4 ± 4.86	26.7 ± 5.41	26.4 ± 5.08	26.5 ± 5.21
Asthma control, n (%)*					
Partly controlled	71 (37.8)	71 (39.2)	66 (35.9)	65 (34.9)	273 (36.9)
Uncontrolled	117 (62.2)	110 (60.8)	118 (64.1)	121 (65.1)	466 (63.1)
Duration of asthma, years	16.0 ± 13.09	16.0 ± 12.88	14.0 ±11.17	15.1 ± 12.60	15.3 ± 12.46
Smoking history, n (%)					
Never smoked	156 (83.0)	147 (81.2)	158 (85.9)	155 (83.3)	616 (83.4)
Ex-smoker	32 (17.0)	34 (18.8)	26 (14.1)	31 (16.7)	123 (16.6)

Data presented as mean ± SD, unless otherwise specified. MF: mometasone furoate; BMI: body mass index. *Level of asthma control was based on Global Initiative for Asthma (GINA) 2010[2]

Table 2. Lung function, baseline ACQ-5 (randomised set), and ICS sensitivity (full analysis set)

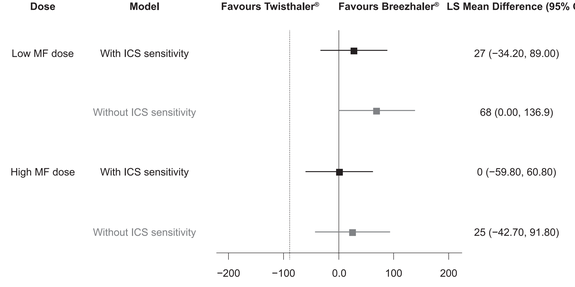
	MF 80 µg Breezhaler® n = 188	MF 200 µg Twisthaler® n = 181	MF 320 µg Breezhaler® n = 184	MF 800 µg Twisthaler® n = 186	Total N = 739
FEV_1 pre-bronchodilator (L)	1.93 ± 0.628	1.94 ± 0.602	1.87 ± 0.550	1.94 ± 0.571	1.92 ± 0.588
FEV_1 pre-bronchodilator, % predicted	61.3 ± 11.64	62.7 ± 11.07	62.9 ± 11.28	61.9 ± 10.47	62.2 ± 11.12
FEV_1 reversibility, %	26.4 ± 13.07	26.7 ± 14.69	27.7 ± 17.76	25.9 ± 12.84	26.7 ± 14.70
Baseline ACQ-5	2.4 ± 1.03	2.2 ± 0.90	2.5 ± 0.94	2.5 ± 0.92	2.4 ± 0.96
	n = 186	n = 180	n = 183	n = 186	N = 735
ICS sensitivity* (%)	18.4 ± 12.39	14.8 ± 11.16	17.8 ± 11.60	16.4 ± 12.34	16.9 ± 11.95

Data presented as mean ± SD. *ICS sensitivity determination: At Visit 2 patients defined as either 'uncontrolled' or 'partly controlled' received MF 800 µg delivered via Twisthaler® every evening for two weeks. At the end of this period, ICS treatment was either reduced or stopped for the second run-in period, based on the level of asthma control at Visit 2. Patients whose asthma at Visit 2 had been considered 'uncontrolled' changed from MF 800 µg to MF 200 µg delivered via Twisthaler every evening. Patients who were considered 'partly controlled' stopped ICS treatment. After the second run-in period, ICS sensitivity was evaluated. Patients were considered 'ICS sensitive' if the absolute FEV_1 value at Visit 5 (pre-dose, –50 min) was decreased by ≥5% compared with the value at Visit 3 and at least one item of ACQ-5 at Visit 5 was worsened (by ≥ 1 point) compared with the value at Visit 3. The percent difference in FEV_1 between these two visits was defined as "degree of ICS sensitivity".

Lung function

- The least square (LS) mean difference in trough FEV_1 between the low MF dose delivered via Breezhaler® and the low MF dose delivered via Twisthaler® was 27 mL (95% CI, –34 to 89); for the high MF dose delivered via Breezhaler® and the high MF dose delivered via Twisthaler® the difference was 0 mL (95% CI, –60 to 61; **Figure 2**) after 4 weeks of treatment or Day 29
- When ICS sensitivity was added as covariate, FEV_1 ratio differences between delivery systems tended to decrease (**Figure 2**)

Figure 2. No difference in lung function between low and high doses of MF via the Breezhaler® and Twisthaler®

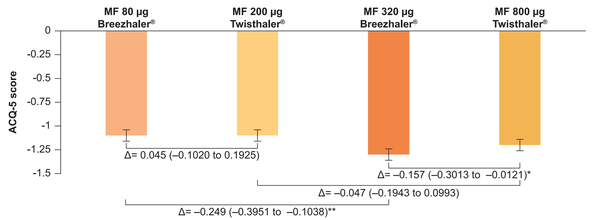


Forest plot of least square (LS) mean ± CI for Breezhaler® compared with Twisthaler® for trough FEV_1 (mL) at Week 4 (full analysis set), using models with and without ICS sensitivity as a covariate. The pre-specified non-inferiority margin was –90 mL (shown by dotted line).

Asthma control

- All treatment arms provided clinically relevant improvements in ACQ-5 after 4 weeks of treatment compared with baseline (**Figure 3**)

Figure 3. Change from baseline in ACQ-5 and between-treatment comparisons for the corresponding low and high doses of MF via Breezhaler® and Twisthaler®



Change from baseline in ACQ-5 (LS means ± SE) and between-treatment differences (LS means, 95% CI) *$P < 0.05$; **$P < 0.001$.

Safety

- All treatments showed a similar safety profile with a similar low incidence of adverse events across treatment groups. No new safety signals were detected for MF (**Table 3**)

Table 3. Common treatment-emergent adverse events, (at least 2% in either treatment group; safety set)

	MF 80 µg Breezhaler® n = 186	MF 200 µg Twisthaler® n = 180	MF 320 µg Breezhaler® n = 183	MF 800 µg Twisthaler® n = 186
Preferred term	n (%)	n (%)	n (%)	n (%)
Number of subjects with any AE	33 (17.7)	41 (22.8)	37 (20.2)	33 (17.7)
Headache	6 (3.2)	5 (2.8)	5 (2.7)	0
Blood cortisol decreased	4 (2.2)	3 (1.7)	5 (2.7)	6 (3.2)
Nasopharyngitis	3 (1.6)	7 (3.9)	6 (3.3)	2 (1.1)
Oropharyngeal pain	0	4 (2.2)	1 (0.5)	0

MF: mometasone furoate; AE: adverse event

Conclusions

- Mometasone furoate via Breezhaler® delivers comparable lung function efficacy and is formally non-inferior to mometasone furoate via Twisthaler®, at corresponding low and high MF doses (80 µg and 320 µg delivered with Breezhaler® and 200 µg and 800 µg delivered with Twisthaler®)
- The pattern and frequency of local and systemic adverse events was comparable between all treatment groups

References

1. Vaidya S et al. Eur Resp J 2012;40: P382
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2010. Available from www.gina.org

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