Efficacy and safety of once-daily low-dose indacaterol/mometasone via Breezhaler® in symptomatic adult and adolescent patients with inadequately controlled asthma: Phase III randomised QUARTZ study findings

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Introduction

- Global initiative for asthma (GINA) 2019 recommends the addition of long-acting β_2-agonist (LABA) to inhaled corticosteroid (ICS) monotherapy as the maintenance controller therapy in patients with inadequately controlled asthma[1]
- The combination helps in achieving asthma control by reducing symptoms and improving lung function in these patients[1]
- Indacaterol acetate/mometasone furoate (IND/MF, a LABA/ICS combination) 150/80 μg once-daily (o.d.) delivered via Breezhaler®, a single-dose dry powder inhaler, is a fixed-dose combination (FDC) of IND (LABA) and MF (a low-dose ICS), and is under development for treatment of symptomatic adult and adolescent patients with inadequately controlled asthma
- Here, we present the results from QUARTZ study
- The objective of the study was to evaluate efficacy and safety of IND/MF (150/80 μg o.d.) delivered via Breezhaler® compared with MF 200 μg o.d. delivered via Twisthaler® in terms of lung function (trough forced expiratory volume in one second [FEV_1]) and asthma control (asthma control questionnaire [ACQ-7] score) in inadequately controlled asthma patients

Methods

Patients

Key inclusion criteria
- Men and women (adult and adolescent patients) aged ≥12 and ≤75 years
- Diagnosis of asthma for a period of ≥3 months prior to screening
- Patients who were taking low-dose ICS (with or without LABA) prior to the study visit for ≥1 month
- ACQ-7 ≥1.5 prior to randomisation
- Pre-bronchodilator FEV_1 ≥60% and <90% of the predicted normal value according to ATS/ERS criteria after withholding bronchodilators at the start and end of run-in period
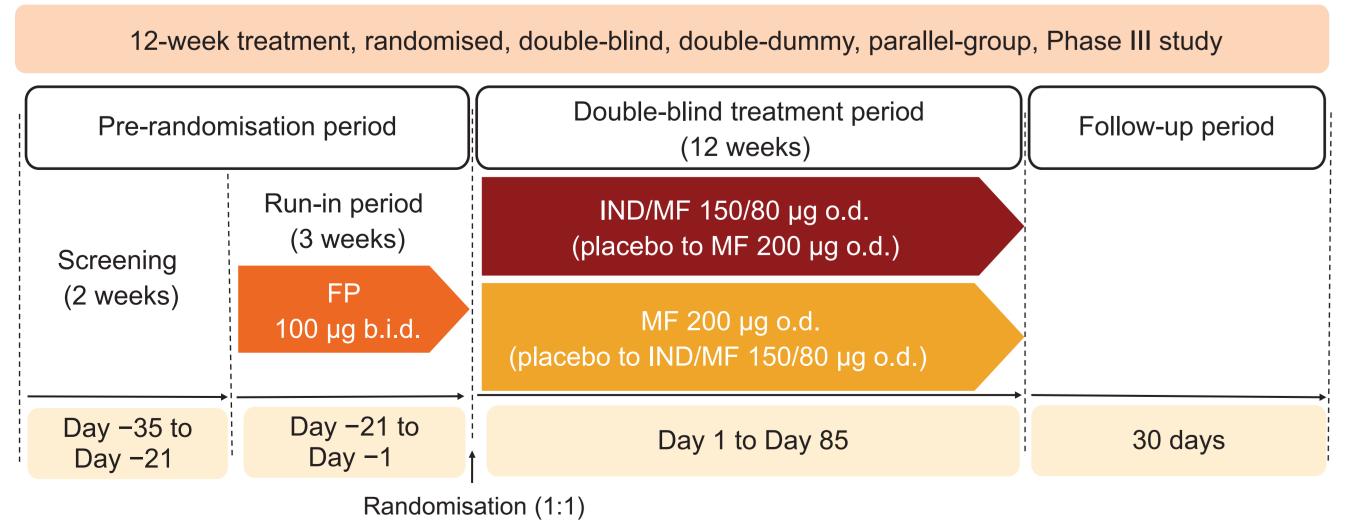
Key exclusion criteria
- Patients who had an asthma attack/exacerbation requiring systemic steroids or hospitalisation or emergency room visit within the past 6 weeks for adults (6 months for adolescents)
- Patients with history of a long QT syndrome, and a prolonged QTc interval
- History of chronic lung disease other than asthma

Study design

- The QUARTZ study was a Phase III, multicentre, randomised, double-blind, double-dummy and parallel-group study that included a 12-week treatment period (Clinical trials identifier: NCT02892344; **Figure 1**)

Figure1. QUARTZ study design

Rescue medication available
IND/MF was administered via Breezhaler® and MF via Twisthaler®
MF 200 μg o.d. via Twisthaler® is equivalent to MF 80 μg o.d. via Breezhaler®
b.i.d., twice daily; FP, fluticasone propionate; IND/MF, indacaterol acetate/mometasone furoate; MF, mometasone furoate; o.d., once-daily

Endpoints for evaluation of the efficacy of IND/MF (150/80 μg o.d.; [low-dose ICS]) versus MF 200 μg o.d. over 12 weeks of treatment

Primary endpoint
- Superiority of IND/MF (150/80 μg o.d.) to MF 200 μg o.d. in terms of trough FEV_1 after 12 weeks of treatment

Key secondary endpoint
- Superiority of IND/MF (150/80 μg o.d.) over MF 200 μg o.d. in terms of ACQ-7 score treatment difference after 12 weeks of treatment

Other secondary endpoints
- Proportion of patients with improvement in ACQ-7 score of at least 0.5 units (responder analysis)
- Morning and evening peak expiratory flow (PEF)
- Mean total daily symptom score, rescue medication use and nighttime awakenings (recorded via electronic diary)
- Asthma-related quality of life (asthma quality of life questionnaire [AQLQ] total score)
- Rate of moderate-to-severe exacerbations

Safety
- Safety assessments included adverse events, vital signs, ECG, laboratory analysis, serious asthma outcomes, other serious or clinically significant adverse events and deaths

Statistical analysis
- All efficacy analyses were performed using the full analysis set (FAS) population
  - FAS included all randomised patients who received at least one dose of study treatment
- All safety analyses were performed using the safety set
  - Safety set consisted of all patients who received at least one dose of study treatment
- Trough FEV_1 and ACQ-7 scores were analysed using mixed model for repeated measure (MMRM) model
- ACQ-7 responder analysis was analysed using a logistic regression model
- Percentage of nights with no nighttime awakenings was analysed using linear mixed model
- Rate of moderate-to-severe exacerbations was analysed using a generalised linear model assuming the negative binomial distribution
- All other efficacy assessments were evaluated using analysis of covariance (ANCOVA) model
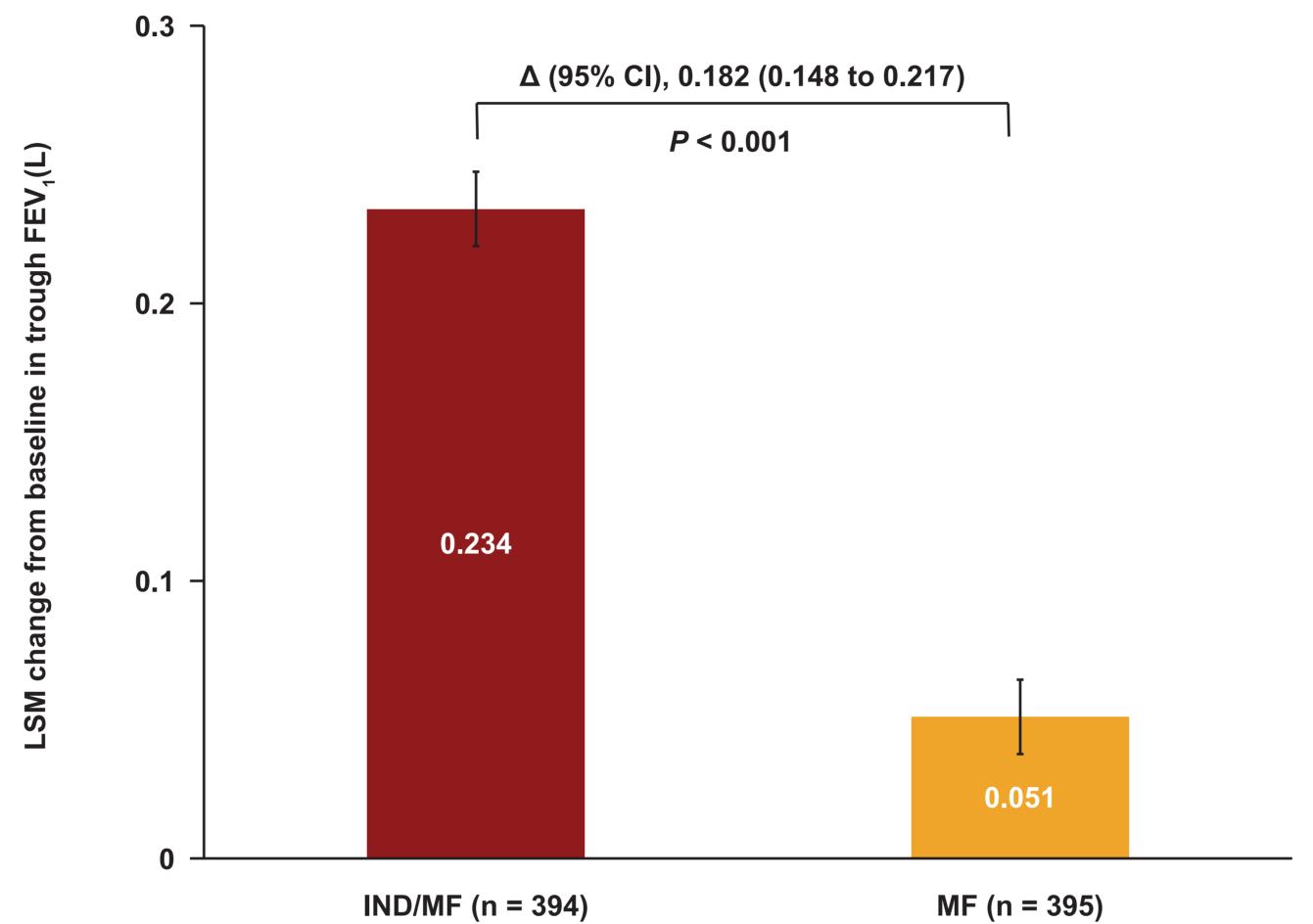
Results

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

Characteristic	IND/MF 150/80 μg o.d. (N = 398)	MF 200 μg o.d. (N = 404)	Total (N = 802)
Age, years	46.1 ± 16.26	45.1 ± 16.27	45.6 ± 16.26
Adolescents, n (%)	31 (7.8)	33 (8.2)	64 (8.0)
Adults, n (%)	367 (92.2)	371 (91.8)	738 (92.0)
Men, n (%)	151 (37.9)	163 (40.3)	314 (39.2)
Duration of asthma, years	14.4 ± 13.18	13.6 ± 12.48	14.0 ± 12.83
Baseline ACQ-7 score	2.24 ± 0.40	2.30 ± 0.39	2.27 ± 0.39
Prior asthma treatment, n (%)			
Low-dose ICS	177 (44.5)	167 (41.3)	344 (42.9)
Medium- to high-dose ICS	1 (0.3)	0	1 (0.1)
Low-dose ICS/LABA	217 (54.5)	232 (57.4)	449 (56.0)
Medium- to high-dose ICS/LABA	3 (0.8)	0	3 (0.4)
Missing	0	5 (1.2)	5 (0.6)
FEV_1 pre-bronchodilator (L)	2.24 ± 0.64	2.22 ± 0.58	2.23 ± 0.61
FEV_1 pre-bronchodilator (% predicted)	73.3 ± 7.57	72.2 ± 7.63	72.7± 7.61
FEV_1 reversibility (% increase)	20.6 ± 11.66	20.7 ± 11.94	20.7 ± 11.79

Data presented as mean ± standard deviation, unless otherwise specified.
ACQ-7, asthma control questionnaire; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; IND/MF, indacaterol acetate/mometasone furoate; LABA, long-acting β_2-agonist; MF, mometasone furoate; o.d., once-daily
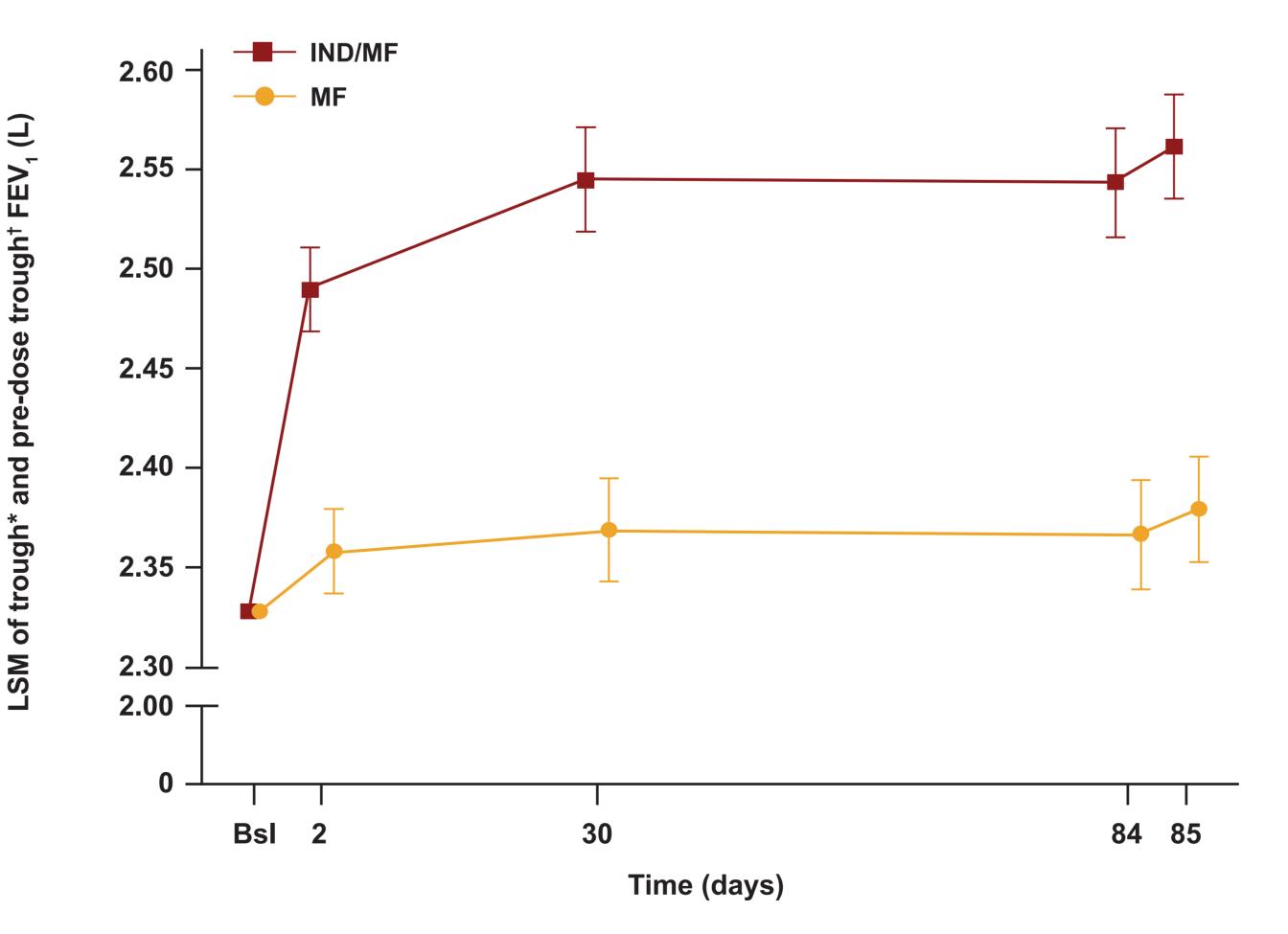
Primary endpoint: Trough FEV₁ at 12 weeks

Figure 2. IND/MF showed statistically significant improvement in trough FEV_1 compared with MF after 12 weeks of treatment

Data are presented as LSM ± SE. Error bars represent SE values
Δ, LSM treatment difference; CI, confidence interval; FEV_1, forced expiratory volume in 1 second;
IND/MF, indacaterol/ mometasone furoate 150/80 μg o.d.; LSM, least squares mean; MF, mometasone furoate 200 μg o.d.; o.d., once-daily; SE, standard error

Figure 3. Trough and pre-dose trough FEV_1 was consistently higher with IND/MF at all time-points compared with MF over 12 weeks
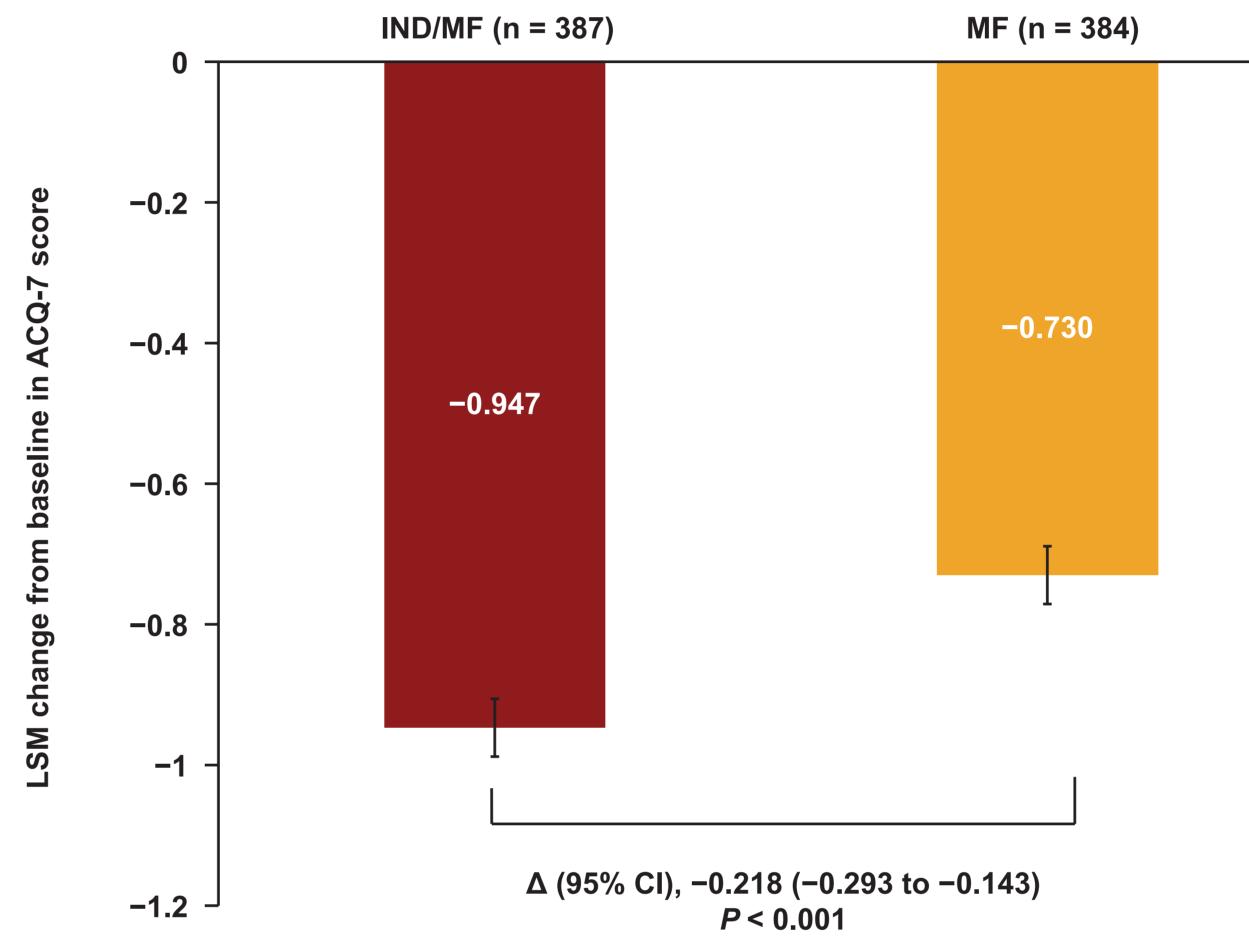

*Trough FEV_1 is defined as average of the two FEV_1 measurements at 23 hr 15 min and 23 hr 45 min post-evening dose on Day 2 and Day 85
†Pre-dose trough FEV_1 is defined as average of the two FEV_1 measurements at 45 min and 15 min pre-evening dose on Day 30 and Day 84
Data are presented as LSM ± 95% CI. Error bars represent 95% CI
Bsl, baseline; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; IND/MF, indacaterol/ mometasone furoate 150/80 μg o.d.; LSM, least squares mean; MF, mometasone furoate 200 μg o.d.; o.d., once-daily

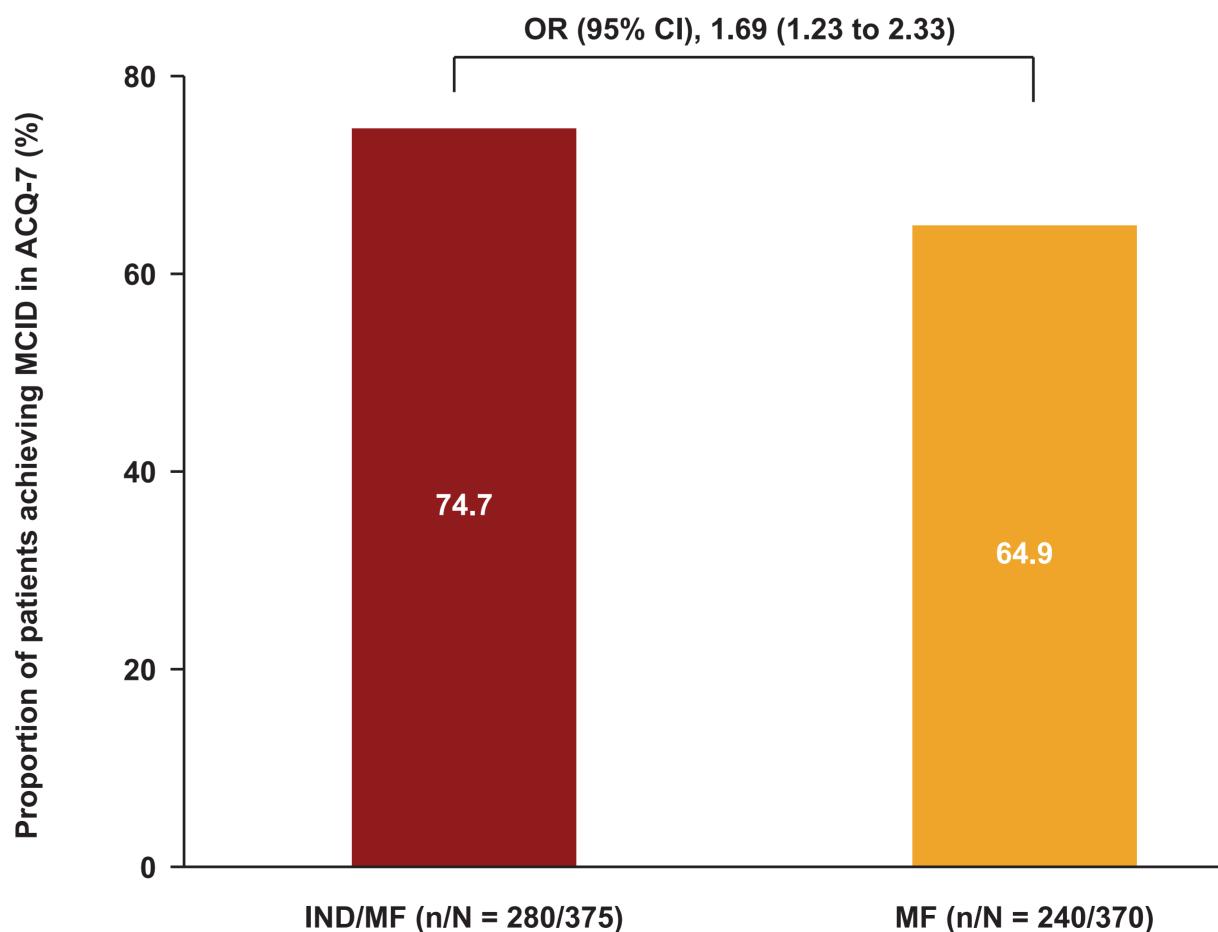## Key secondary endpoint: ACQ-7 at Week 12

Figure 4. At Week 12, IND/MF treatment showed statistically significant improvements in asthma control from baseline

Data are presented as LSM ± SE. Error bars represent SE values
ACQ-7, asthma control questionnaire; CI, confidence interval; IND/MF, indacaterol/ mometasone furoate 150/80 μg o.d.;
LSM, least squares mean; MF, mometasone furoate 200 μg o.d.; o.d., once-daily; SE, standard error

ACQ-7 responder analysis

Figure 5. Higher proportion of patients achieved improvement of at least 0.5 units (MCID) in ACQ-7 score with IND/MF compared with MF after 12 weeks

n, The number of patients with an improvement of ≥0.5 units, i.e. a decrease of ≥0.5 units in ACQ-7 from baseline;
N, The number of patients with data at the respective visit.
Data are presented as LSM ± SE. Error bars represent SE values
ACQ-7, asthma control questionnaire; CI, confidence interval; IND/MF, indacaterol/ mometasone furoate 150/80 μg o.d.;
MF, mometasone furoate 200 μg o.d.; o.d., once-daily; OR, odds ratio; SE, standard error; MCID, minimal clinically important difference

Table 2. Other secondary endpoints assessed over 12 weeks of treatment

Secondary endpoint	IND/MF 150/80 μg o.d. vs MF 200 μg o.d. Treatment difference (95% CI)
Mean morning PEF, L/min	27.2 (22.1 to 32.4)
Mean evening PEF, L/min	26.1 (21.0 to 31.2)
Rescue medication use	−0.26 (−0.37 to −0.14)
Quality of life (AQLQ total score)	0.149 (0.064 to 0.234)
Mean total daily symptom score	−0.15 (−0.26 to −0.05)
Percentage of nights with no nighttime awakenings	4.8 (1.8 to 7.7)
Rate of moderate-to-severe exacerbations	RR: 0.25 (0.12 to 0.52)

AQLQ, asthma quality of life questionnaire; CI, confidence interval; IND/MF, indacaterol/ mometasone furoate 150/80 μg o.d.;
LSM, least squares mean; MF, mometasone furoate 200 μg o.d.; o.d., once-daily; PEF, peak expiratory volume; RR, rate ratio

Safety

- The overall incidence of adverse events (AEs) was lower in patients treated with IND/MF 150/80 μg o.d. (32.3%) compared with the MF (38.3%)
- One serious asthma outcome (asthma-related hospitalisation) was reported in the MF group and none in IND/MF group
- Overall, the incidence of serious AEs was low and comparable between the treatment groups (1.3% in the IND/MF group and 1.8% in the MF group)
- No death was reported in any treatment group throughout the study

Conclusions

- To our knowledge, this is the first study to compare a low-dose ICS/LABA FDC o.d. to low-dose ICS monotherapy in adult and adolescent patients with inadequately controlled asthma
- IND/MF 150/80 μg o.d. significantly improved trough FEV_1 and asthma control versus MF 200 μg o.d. in adult and adolescent patients with inadequately controlled asthma
- This study provided evidence for benefits across a range of lung function and symptomatic endpoints including: morning and evening PEF, AQLQ total score, mean daily total symptom score, rescue medication use, nighttime awakenings and rate of moderate-to-severe exacerbations
- Safety profile was comparable between the two treatment groups
- Overall, results support the use of IND/MF 150/80 μg o.d. as a potential treatment in adult and adolescent patients with asthma, inadequately controlled on low-dose ICS (+/- controller)
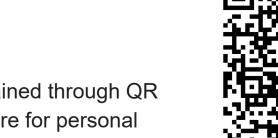
References
1. Global strategy for asthma management and prevention, Global Initiative for Asthma (GINA) 2019. Available from: http://www.ginasthma.org/

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