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Effect of once-daily indacaterol maleate/mometasone furoate on exacerbation risk in adolescent and adult asthma: a double-blind randomised controlled trial

Richard W Beasley,[1] James F Donohue,[2] Rajendra Mehta,[3] Harold S Nelson,[4] Michelle Clay,[5] Allen Moton,[6] Han-Joo Kim,[6] Bettina M Hederer[7]

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For numbered affiliations see end of article.

Correspondence to
Dr Richard W Beasley;
Richard.Beasley@mrinz.ac.nz

ABSTRACT

Objective: To investigate the safety and efficacy of QMF149, a once-daily, fixed-dose combination of the long-acting β_2-agonist (LABA) indacaterol maleate and inhaled corticosteroid (ICS) mometasone furoate (MF) for the treatment of persistent asthma. The hypothesis was that QMF149 would not increase the risk of serious asthma exacerbations.

Setting: 174 research centres in nine countries.

Participants: 1519 adolescents and adults with persistent asthma who were treated or qualified for treatment with combination LABA/ICS were randomised, and 1508 were included in the intention-to-treat analysis.

Intervention: Patients were randomised to QMF149 (indacaterol maleate 500 µg/MF 400 µg) or MF (400 µg) once daily via Twisthaler inhalation device in a double-blind, parallel-group study for 6–21 months.

Primary and secondary outcome measures: The primary end point was time to first serious asthma exacerbation (resulting in hospitalisation, intubation or death). The key secondary end point was annual rate of exacerbations requiring systemic corticosteroids.

Results: Treatment with QMF149 resulted in no significant difference in time to first serious exacerbation compared to MF (2 (0.3%) vs 6 events (0.8%); difference −0.52 percentage point; 95% CI −1.25 to 0.21, p=0.160, HR=0.31; 95% CI 0.06 to 1.54, p=0.151). QMF149 significantly reduced the annual rate of exacerbations requiring systemic corticosteroids (rate ratio=0.71; 95% CI 0.55 to 0.90, p=0.005). Proportions of patients experiencing adverse events were similar across groups (74.0% in the QMF149 group and 73.4% in the MF group). Serious adverse events occurred in 4% and 5.8% of patients in the QMF149 and MF groups, respectively.

Conclusions: No significant difference was observed in the primary outcome of time to first serious asthma exacerbation in patients treated with QMF149 compared with patients treated with MF. Long-term treatment with QMF149 once daily had a favourable safety/efficacy profile in adolescent and adult patients with persistent asthma.

Strengths and limitations of this study

- This randomised controlled trial provides comprehensive data on the efficacy and safety of QMF149, a once-daily, fixed dose combination of the inhaled corticosteroid (ICS) mometasone furoate (MF) and the long-acting β_2-agonist (LABA) indacaterol for the treatment of asthma.
- QMF149 had a favourable efficacy/safety profile, reducing the rate of severe exacerbations requiring systemic corticosteroids by 29%, compared with MF therapy.
- Study findings may be generalised as the dose of indacaterol 500 µg/MF 400 µg delivered via the Twisthaler device is expected to be clinically comparable to the dose of indacaterol 150 µg/MF 160 µg delivered via the Breezhaler device, which will be the device used for QMF149 in phase III.
- The study was limited by the low rate of serious exacerbations, resulting in insufficient power to detect differences between treatment regimens.
- These findings are relevant to the issue of ICS/LABA safety in asthma.

Trial registration number: ClinicalTrials.gov; NCT00941798.

INTRODUCTION

Inhaled corticosteroids (ICS) are the cornerstone of therapy in persistent asthma in adolescents and adults. However, in patients with moderate-to-severe disease, the addition of a long-acting β_2-agonist (LABA) may be required to achieve asthma control.[1 2] This concomitant use should be prescribed in the form of a combination LABA/ICS single inhaler product, as the use of separate inhalers is likely to result in LABA monotherapy during

periods of ICS non-adherence.[3] This is important as LABA monotherapy may be associated with an increased risk of mortality in patients with unstable asthma.[4]

Combination LABA/ICS therapy also has the advantage of improving compliance with ICS therapy,[5 6] which has the potential to reduce the risk of death due to the dose-dependent relationship between ICS use and asthma mortality.[7] Existing twice-daily, fixed-dose combinations of LABA/ICS have demonstrated efficacy in randomised controlled trials.[8 9] To date there is no evidence to suggest an increase in risk of life-threatening attacks or death from asthma with combination LABA/ICS therapy.[10 11] However, in view of a potential risk due to LABA monotherapy, highlighted by the SMART study,[12] and by systematic reviews[4] including a meta-analysis conducted by the US Food and Drug Administration (FDA),[13] it has been proposed that studies should be conducted that specifically assess this risk with currently available and novel LABA/ICS products.[14]

QMF149 is a once-daily fixed-dose combination of the LABA indacaterol maleate and the ICS mometasone furoate (MF), which have both demonstrated 24 h duration of action as monotherapies.[15–18] QMF149 is under development for the treatment of asthma and chronic obstructive pulmonary disease. Increased dosing frequency has been found to affect medication compliance;[19] therefore, the convenience of once-daily QMF149 may help to improve treatment outcomes.

This phase II safety study was designed to investigate the impact of QMF149 compared with MF on serious outcomes of asthma-related death, intubation or hospitalisation[14] in adolescent and adult patients with asthma. As this composite outcome variable represents safety and efficacy, it has allowed an assessment of the safety/efficacy profile of QMF149 in adolescent and adult asthma. QMF149 and MF were delivered via the Twisthaler inhalation device, which is the current marketed device for MF (Asmanex Twisthaler inhalation powder (Merck Sharp & Dohme Corp; New Jersey, USA). However, as it has been demonstrated that the Breezhaler device, a single-dose dry powder inhaler, facilitates achievement of comparable clinical effect at lower doses of indacaterol and MF (150 µg/160 µg compared with 500 µg/400 µg via Twisthaler device[20–22]), the future development of QMF149 will be via the Breezhaler inhalation device.

METHODS

This was a randomised, double-blind, multicentre, parallel-group study conducted between July 2009 and May 2011. Investigators are listed in the online supplementary appendix section 1. All patients discontinued regular asthma maintenance therapy after giving informed consent and were switched to open-label MF 400 µg once daily for the run-in period (21–28 days).

Randomisation and masking

Eligible patients were randomised in a 1:1 ratio to receive once-daily QMF149 (indacaterol maleate 500 µg/MF 400 µg) or MF (400 µg) via Twisthaler inhalation device, in the evening. Randomisation numbers were generated using a procedure that ensured assignment was unbiased and concealed from patients and investigators: a patient randomisation list was produced by an interactive voice response system (IVRS; Oracle America Inc, Redwood City, California, USA) using a validated system that automated the random assignment of patient numbers to randomisation numbers. These randomisation numbers were linked to the different treatment groups, which in turn were linked to medication numbers. A separate medication randomisation list was produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to medication packs containing each of the study drugs. Randomisation was stratified by the presence or absence of the following demographic and baseline characteristics:

1. Patients who had an asthma-related hospitalisation within the 12 months prior to randomisation.
2. Patients who had experienced asthma worsening(s) that required either an emergency room visit with systemic corticosteroid, or two or more courses of systemic corticosteroids for asthma worsening during the 12 months prior to randomisation.
3. African American patients or patients of black African descent.

The study was completed per protocol when the first patient had been in the study for 21 months and/or the last patient for ≥6 months. The study was conducted according to the World Medical Association's Declaration of Helsinki and approvals from institutional review boards and/or ethics committees were obtained for each investigator site.

Patients

This study enrolled patients aged 12–70 years, with a documented diagnosis of persistent asthma for ≥6 months; a prebronchodilator forced expiratory volume in 1 s (FEV_1) ≥50% of predicted normal and a post-short-acting β_2-agonist (SABA) increase in FEV_1 of ≥12% (and ≥200 mL) at the screening visit (3–4 weeks prior to randomisation) or who had documented reversibility within the previous 12 months; who were treated or qualified for treatment with a LABA/ICS combination[15] and had used an ICS for ≥2 months prior to study start. No exacerbation history eligibility criteria were specified. Full inclusion and exclusion criteria are listed in the online supplementary appendix section 3.

Outcome measures

The primary end point was time to first serious asthma exacerbation (resulting in hospitalisation, intubation or death). Details of event adjudication and data monitoring

procedures are provided in the online supplementary appendix sections 4 and 5, respectively.

The key secondary end point was cumulative incidence of serious asthma exacerbations. Other secondary end points included time to first asthma exacerbation and rate of exacerbations requiring systemic corticosteroids, change from baseline in trough FEV_1, e-diary data (peak expiratory flow, rescue medication use, asthma scores), and asthma control, assessed by overall Asthma Control Questionnaire (ACQ-7) score.[20] Exploratory end points included impact on productivity and activity, as measured by the Work Productivity and Activity Impairment (WPAI-Asthma) questionnaire,[23] and Euro Quality of Life-5D Questionnaire (EQ-5D).[24] All adverse events (AEs) were recorded, including details of severity and relationship to the study drug. Compliance was assessed by counting remaining doses in each study device.

Data Monitoring Committee and interim analysis

An independent Data Monitoring Committee (DMC) was formed to monitor asthma-related events on behalf of study participants and investigators. The DMC planned to meet every 6 months to review safety data, with an additional event driven review to conduct interim analysis when 10 serious asthma exacerbation events had been accumulated and adjudicated.

One interim analysis was performed and a DMC meeting was held on 31 August 2010 where the DMC reviewed semiblinded safety data. Additional information can be found in the online supplementary appendix section 5.

Statistical analysis

Detailed statistical methods are provided in the online supplementary appendix section 6.

It was estimated that 20 serious asthma exacerbations were required to provide 80% power to detect a three-fold increase in HR at α=0.05 (one sided) using nQuery Advisor 7.0 (Statistical Solutions, Cork, Ireland). This was based on assumptions that the annual rate of serious asthma exacerbations would be 0.6% for MF[25] and between 1.8% and 2.4% for QMF149, following the FDA meta-analysis, which found asthma-related events in the range of 1.0–1.6% and estimated a risk difference of 2.80 per 1000 participants for patients receiving LABA treatment compared with non-LABA treatment.[13] The total of 750 patients per arm was chosen as the average of these two scenarios.

Time to the first serious exacerbation was analysed using a Cox proportional hazards regression model stratified by asthma-related hospitalisation in the last 12 months (no/yes), asthma worsening in the last 12 months (no/yes) and African-American patient (no/yes), including terms for treatment and region. The annualised rate of exacerbations was evaluated using a negative binomial regression model. Other secondary end points were analysed using a repeated measures analysis of covariance, based on longitudinal measurements, which assumed data were missing at random. No missing data imputation was performed. Analyses were performed using two sided 95% CI and p values.

Efficacy analyses were performed on the full analysis set (all randomised patients receiving at least one dose of randomised study medication, analysed according to randomised study medication). All safety parameters were summarised on the safety set (all patients receiving at least one dose of study medication, analysed according to treatment actually received).

RESULTS

Patients

A total of 1519 patients were randomised to receive treatment (QMF149=756; MF=763) (figure 1). The full analysis set comprised 1508 patients. The median duration of study treatment was 405 and 406 days in the QMF149 and MF treatment groups, respectively. Similar proportions of patients discontinued prematurely in both groups (QMF149=194 (25.7%) and MF=185 (24.2%)). The most common reason for early discontinuation of study treatment across both treatment groups was withdrawal of consent (9.6%). A higher proportion of patients in the QMF149 group withdrew due to AEs (5.7%) compared with the MF treatment group (3.0%), but a greater proportion of patients (2.2%) in the MF group withdrew due to unsatisfactory therapeutic effect of study treatment compared with the QMF149 treatment group (1.3%; figure 1).

Baseline demographics and clinical characteristics were well balanced across groups (table 1). The study population presented with a mean baseline (pre-SABA) FEV_1 of approximately 75% predicted and reversibility of approximately 22%. Similar proportions of patients were compliant with study medication at the final study visit (91% and 91.9% in the QMF149 and MF treatment groups, respectively).

Serious asthma exacerbations

In total, eight patients (two QMF149 and six MF) experienced a serious asthma exacerbation; none required intubation or resulted in death. There were too few events to estimate the time to first serious asthma exacerbation at most percentiles. The difference between QMF149 and MF did not reach statistical significance (HR=0.31; 95% CI 0.06 to 1.54, p=0.151 (table 2)). The difference in the cumulative incidence of serious asthma exacerbation between the QMF149 and MF treatment groups was −0.52 percentage point (95% CI −1.25 to 0.21, p=0.160).

Asthma exacerbations requiring systemic corticosteroids

More patients in the MF group had an asthma exacerbation requiring treatment with systemic corticosteroids compared with the QMF149 group (22.5% and 16.6%, respectively; difference 5.9 percentage points).

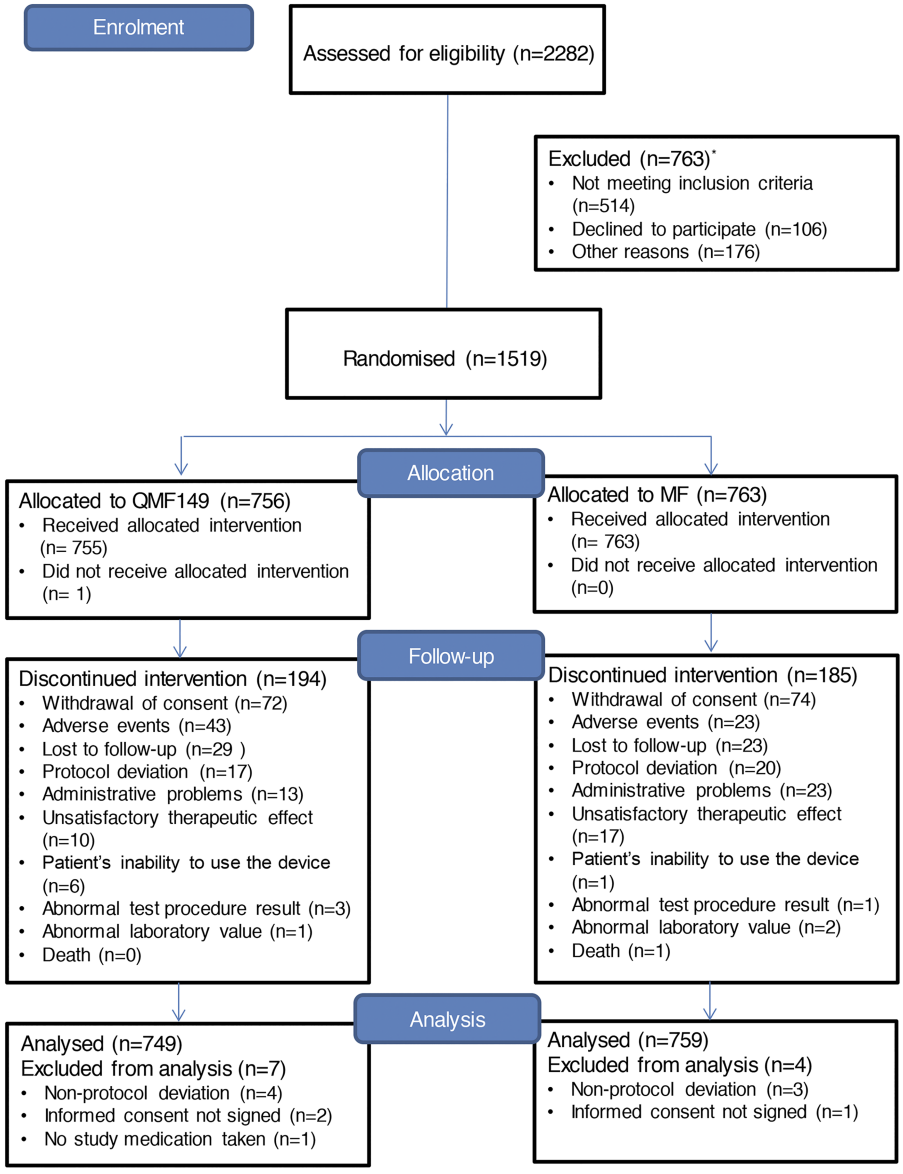

Figure 1 Patient flow through the study (CONSORT diagram). *Patients could be allocated to more than one group concerning reason for exclusion.

QMF149 significantly reduced the risk in the time to first exacerbation requiring systemic corticosteroids by 30% (HR=0.70; 95% CI 0.56 to 0.89, p=0.003; figure 2) and the annual rate of exacerbations requiring systemic corticosteroids by 29% (rate ratio=0.71; 95% CI 0.55 to 0.90, p=0.005) compared with MF.

Lung function

Trough FEV_1 significantly improved during treatment with QMF149 compared with MF at all study visits (table 3). Improvements at week 4 were maintained over 68 weeks with treatment differences ranging from 0.10 L (95% CI 0.05 to 0.15) to 0.14 L (0.11 to 0.18; p≤0.001 at all visits). Compared with MF, QMF149 also resulted in significantly (p≤0.001) greater improvements in forced vital capacity (FVC) at each visit (day 1, weeks 4–68).

The adjusted mean treatment difference (QMF149–MF) for changes from baseline in morning and evening peak expiratory flow were statistically significant in favour of QMF149 (adjusted mean difference 0.44 L/s (95% CI 0.36 to 0.52) and 0.42 L/s (0.34 to 0.50), respectively, both p≤0.001).

Asthma symptoms, rescue medication use and asthma control

The percentage of days with no asthma symptoms was significantly increased during treatment with QMF149 compared with MF (table 3). Adjusted mean treatment differences during the morning, daytime and night-time were 3.9% (95% CI 1.5 to 6.3), 7.7% (95% CI 4.5 to 10.9) and 6.3% of days (95% CI 3.4 to 9.2), respectively. QMF149 also significantly increased the percentage of days with no rescue medication use during daytime, night-time and 24-h periods compared with MF. Adjusted mean treatment differences ranged from 9.8%

Table 1 Baseline demographic and clinical characteristics

	QMF149 (n=749)	MF (n=759)	Total (N=1508)
Age (years)	42.4 (14.75)	42.3 (14.58)	42.3 (14.66)
Age group (years)			
<18	31 (4.1%)	35 (4.6%)	66 (4.4%)
18–64	675 (90.1%)	682 (89.9%)	1357 (90.0%)
≥65	43 (5.7%)	42 (5.5%)	85 (5.6%)
Sex			
Male	313 (41.8%)	310 (40.8%)	623 (41.3%)
Female	436 (58.2%)	449 (59.2%)	885 (58.7%)
Race			
Caucasian	460 (61.4%)	474 (62.5%)	934 (61.9%)
Asian	142 (19.0%)	143 (18.8%)	285 (18.9%)
Black	58 (7.7%)	53 (7.0%)	111 (7.4%)
Other	89 (11.9%)	89 (11.7%)	178 (11.8%)
BMI (kg/m^2)	27.4 (6.33)	27.5 (6.37)	27.5 (6.35)
Smoking history			
Never smoked	631 (84.2)	635 (83.7)	1266 (84.0)
Ex-smoker	117 (15.6)	123 (16.2)	240 (15.9)
FEV_1 before inhalation of SABA (L)	2.29 (0.773)	2.30 (0.755)	2.29 (0.764)
FEV_1 before inhalation of SABA (% of predicted FEV_1)	75.1 (15.86)	75.5 (15.28)	75.3 (15.56)
FEV_1 reversibility (%)	21.6 (13.46)	21.8 (13.61)	21.7 (13.53)
Mean ACQ-7 score at baseline	1.7	1.7	1.7

Data are mean (SD) or n (%). Reversibility is the percentage increase of FEV_1 after inhalation of SABA compared with FEV_1 before inhalation of SABA.
ACQ-7, Asthma Control Questionnaire; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; MF, mometasone furoate; SABA, short-acting β_2-agonist.

(95% CI 6.8 to 12.8) to 11.3% of days (8.1 to 14.4; all p<0.001).

Asthma control, as assessed by ACQ-7 score, was significantly improved with QMF149 compared with MF by week 4 and thereafter at each subsequent visit throughout the treatment period (table 3). Adjusted mean treatment differences between QMF149 and MF ranged from −0.13 (−0.20 to −0.06) to −0.23 (−0.33 to −0.13; all p<0.001), with an overall adjusted mean difference of −0.19 (−0.25 to −0.14; p<0.001) in favour of QMF149. The overall changes from baseline were −0.49 for QMF149 and −0.29 for MF.

Improvements from baseline in EQ-5D were similar in the QMF149 and MF treatment groups. For WPAI-asthma, change from baseline in the percentage of activity

Table 2 Time to first serious exacerbation — summary statistical and Cox regression analysis

	QMF149 (n=749)	MF (n=759)
Patients with serious asthma exacerbation	2 (0.3%)	6 (0.8%)
Difference in cumulative incidences % (95% CI)	−0.52 (−1.25 to 0.21)	
		p=0.160
Follow-up time, median months (range)	13.3 (0–19.6)	13.4 (0–20.3)
Event-free rates % (95% CI)		
6 months	99.7 (98.8 to 99.9)	99.7 (98.9 to 99.9)
12 months	99.7 (98.8 to 99.9)	99.3 (98.2 to 99.7)
18 months	99.7 (98.8 to 99.9)	99.0 (97.6 to 99.5)
21 months	–	–
Cox regression analysis		
HR QMF149/MF (95% CI)	0.31 (0.06 to 1.54)	
		p=0.151

Data are n (%) unless otherwise specified. Patients who did not experience a serious asthma exacerbation were censored at their last follow-up date. Follow-up time=time from randomisation until the first serious asthma exacerbation or censoring. Event-free time rates were calculated by the Kaplan Meier method. The Cox regression model included the terms for treatment and region, stratified by history of asthma related hospitalisation in the past 12 months (yes/no), history of asthma worsening in the past 12 months (yes/no) and African-American patient (yes/no). A HR <1 favours QMF149.
CI, confidence interval; MF, mometasone furoate; MR, mometasone.

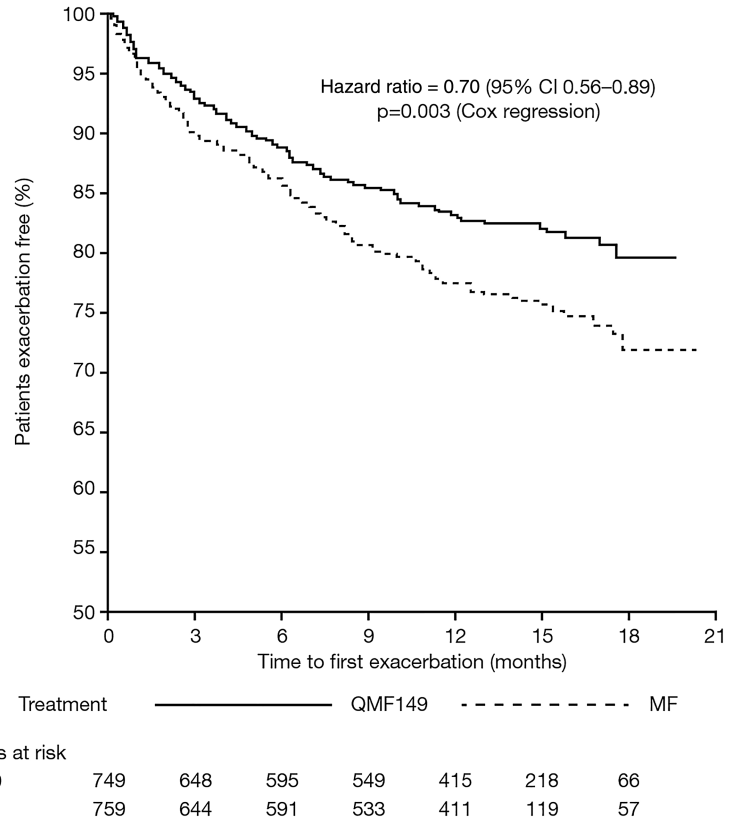

Figure 2 Kaplan–Meier plot of time to first asthma exacerbation requiring treatment with systemic corticosteroids.

impairment during work caused by asthma was statistically significantly reduced (improved) in the QMF149 treatment group compared with the MF treatment group overall (−1.5 (−2.7 to −0.2); p=0.022), at week 12 (−1.8 (−3.5 to −0.2); p=0.032) and at the final clinic visit (−2.2 (−4.2 to −0.3); p=0.026).

Table 3 Changes from baseline in trough FEV_1 and ACQ-7 average score by visit, and asthma symptoms summarised throughout the treatment period

	QMF149			MF			Treatment difference: QMF149–MF		
Variable	**n (%)**	**LS mean**	**SE**	**n (%)**	**LS mean**	**SE**	**LS mean**	**SE**	**95% CI**
Change from baseline in trough FEV_1 by visit (L)									
Overall	727 (100)	0.07	0.023	746 (100)	−0.05	0.023	0.12***	0.014	(0.09 to 0.15)
Week 4	709 (97.5)	0.09	0.023	728 (97.6)	−0.04	0.023	0.13***	0.014	(0.10 to 0.16)
Week 12	681 (93.7)	0.08	0.024	693 (92.9)	−0.02	0.024	0.11***	0.016	(0.08 to 0.14)
Week 26	643 (88.4)	0.08	0.024	658 (88.2)	−0.04	0.024	0.12***	0.017	(0.08 to 0.15)
Week 52	431 (59.3)	0.07	0.025	443 (59.4)	−0.07	0.025	0.14***	0.018	(0.11 to 0.18)
Week 68	176 (24.2)	0.06	0.028	171 (22.9)	−0.05	0.028	0.10***	0.026	(0.05 to 0.15)
Final visit	674 (92.7)	0.06	0.025	699 (93.7)	−0.07	0.024	0.12***	0.018	(0.09 to 0.16)
Change from baseline in ACQ-7 score by visit									
Overall	728 (100)	−0.49	0.049	745 (100)	−0.29	0.049	−0.19***	0.028	(−0.25 to −0.14)
Week 4	709 (97.4)	−0.35	0.049	734 (98.5)	−0.15	0.049	−0.20***	0.031	(−0.26 to −0.14)
Week 12	679 (93.3)	−0.45	0.050	697 (93.6)	−0.24	0.050	−0.21***	0.034	(−0.28 to −0.15)
Week 26	648 (89.0)	−0.50	0.051	660 (88.6)	−0.38	0.051	−0.13***	0.035	(−0.20 to −0.06)
Week 52	432 (59.3)	−0.52	0.052	447 (60.0)	−0.35	0.052	−0.17***	0.038	(−0.24 to −0.10)
Week 68	178 (24.5)	−0.55	0.056	173 (23.2)	−0.32	0.057	−0.23***	0.050	(−0.33 to −0.13)
Final visit	675 (92.7)	−0.55	0.052	687 (92.2)	−0.32	0.052	−0.22***	0.040	(−0.30 to −0.14)
Percentage of days with no asthma symptoms during									
Morning	730	22.3	2.17	746	18.4	2.17	3.9***	1.20	(1.5 to 6.3)
Daytime	731	27.1	2.96	749	19.5	2.95	7.7***	1.63	(4.5 to 10.9)
Night-time	730	23.6	2.69	746	17.3	2.68	6.3***	1.49	(3.4 to 9.2)

***p≤0.001. The ACQ-7 score ranges from 0=good control of asthma to 6=very poor control of asthma.
ACQ-7, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 s; LS, least squares; MF, mometasone furoate; SE, standard error.

Safety

The median number of days of exposure was 405 days in the QMF149 group and 406 days in the MF group. Serious AE (SAEs) occurred in 4.0% of patients in the QMF149 group and 5.8% of patients in the MF group. Asthma (defined as asthma worsening and/or asthma exacerbation) was the most frequent SAE, reported by two patients in the QMF group (0.3%) and nine patients in the MF group (1.2%) (see online supplementary table S1 and appendix section 7). The other most frequently reported SAEs were pneumonia (none with QMF149 and 4 (0.5%) with MF; confirmed by either radiographic evidence or investigator examination) and appendicitis (2 (0.3%) in each group). Seven patients (0.9%) in both treatment groups discontinued treatment because of an SAE. There was one death (in the MF group) due to multiorgan failure following surgery that was not treatment or asthma related.

The overall incidence of AEs was similar in both treatment groups: 554 QMF149 patients (74%) and 557 MF patients (73.4%) (see online supplementary table S2 and appendix section 7). Treatment-related AEs (TRAEs) (as per investigator assessment) were reported in 269 (35.9%) and 81 (10.7%) patients in the QMF149 and MF groups, respectively. The most frequently occurring AEs (in >1% patients in either group) were asthma and cough (see online supplementary table S3).

Overall, asthma was reported as an AE in 275 (36%) patients in the MF group and 196 (26%) patients in the QMF149 group, and as a TRAE in 21 (3%) and 13 (2%) patients in the two groups, respectively. Cough was reported overall as an AE in 266 (36%) patients in the QMF149 group and in 64 (8%) patients in the MF group, and as a TRAE in 238 (32%) and 32 (4%) patients in the two groups, respectively.

DISCUSSION

This phase II study has shown a favourable safety/efficacy profile for once-daily QMF149 in the treatment of adolescents and adults with persistent asthma. Compared with MF, treatment with QMF149 demonstrated a trend towards reducing the risk of serious asthma exacerbations, and a significant reduction of 29% in the annual rate of asthma exacerbations requiring systemic corticosteroids. QMF149 also resulted in significant improvements in lung function, asthma symptoms and asthma control.

In this study, the HR for the risk of serious exacerbations was numerically in favour of QMF149 but was not significant (0.31; 95% CI 0.06 to 1.54, p=0.151). Based on the Wolfe *et al*[25] study and event rates in the FDA LABA safety meta-analysis,[13] it was predicted that the sample size of 1500 patients would result in 20 serious asthma exacerbations during this study, thereby providing 80% power to detect a threefold increase in HR with QMF149. The numbers of serious asthma exacerbations were lower than predicted in the QMF149 treatment group with a corresponding reduction in power and wider CI. However, the low event rate may be seen as indirect evidence that both treatments are effective in the prevention of serious asthma events.

These findings are consistent with those from previous studies of currently prescribed LABA/ICS products.[10 11] To date, there has been no evidence that fixed-dose combinations of salmeterol/fluticasone propionate[11] or formoterol/budesonide,[10] both of which require twice-daily administration, are associated with an increased risk of serious asthma exacerbations leading to hospital admission, intubation or death, compared with ICS therapy. However, the interpretation relating to mortality is limited to some extent by the low statistical power of the available studies for this outcome.

The primary outcome variable was time to first serious asthma exacerbation resulting in hospital admission, intubation or mortality, based on that mandated by the FDA in a series of related randomised controlled trials of LABA/ICS products currently used in the treatment of asthma.[14] The use of this outcome variable recognises that it is difficult to assess mortality alone as a primary outcome variable in clinical trials of asthma, largely owing to its rarity, even in patients with moderate-to-severe disease. This is well illustrated by an independent analysis of a salmeterol database, in which there were no deaths or intubations among more than 22 000 subjects in the 63 studies of salmeterol/fluticasone propionate.[11] The outcome's rationale is also based on the observation that an increased risk in hospital admission tracks with mortality risk in studies of LABA therapy and, as a result, hospital admissions can be considered an acceptable surrogate for risk of mortality.[11]

A further clinically important outcome was the time to first asthma exacerbation requiring treatment with systemic corticosteroids. There was a clear difference between treatment groups for this end point with 17% of QMF149 patients experiencing exacerbations requiring systemic corticosteroids compared with 23% receiving MF. Overall, there was a 30% reduction in risk in the time to first exacerbation requiring treatment with systemic corticosteroids in patients receiving QMF149 compared with MF. Similarly, asthma reported as an AE (defined as asthma worsening and/or asthma exacerbation) occurred more frequently in the MF treatment group (36%) compared with the QMF149 treatment group (26%).

Lung function, assessed as change from baseline in trough FEV_1, showed statistically significant treatment differences in favour of QMF149, ranging between 0.10 L and 0.14 L throughout the study period. These differences between two active treatments are within the range considered to be clinically relevant for treatments compared with placebo.[26 27] This demonstrated persistence of efficacy during the treatment period, with no evidence of bronchodilator tolerance.

Other secondary efficacy variables such as symptom-free days (morning, daytime and night-time) and rescue

medication use showed statistically significant treatment differences in favour of QMF149 throughout the study. Such improvements over MF are consistent with those demonstrated with other LABA/ICS combination therapies compared with ICS used as monotherapy.[8 9]

Improvements in asthma control as measured with the ACQ-7 were consistently statistically significantly higher with QMF149 compared with MF. QMF149 achieved an overall improvement of −0.49 from baseline, which is considered clinically relevant.[28] Clinically relevant improvements were not demonstrated in the MF treatment group.

QMF149 is comprised of two molecules with established efficacy and safety profiles. The indacaterol maleate dose, selected from dose ranging studies in asthma, results in rapid onset bronchodilation that is maintained for at least 24 h.[15 21] Once-daily dosing is established as an effective regimen for MF.[22 29] The use of a once-daily evening dose of 400 µg was based on a clinical trial programme, which demonstrated that 400 µg is near the top of the therapeutic dose-response curve in persistent asthma,[22] that once-daily was as efficacious as twice-daily dosing[29] and that evening may be superior to morning dosing.[30] The choice of MF as the ICS component was also based on its favourable efficacy/safety profile.[31] Thus, indacaterol maleate and MF have established efficacy when used once daily in the evening. It is possible that once-daily dosing of LABA/ICS products may lead to improved compliance[19] and, thereby, efficacy compared with twice-daily regimens; however, this issue requires further study.

While the assessment of safety was based primarily on serious asthma exacerbations and exacerbations requiring systemic corticosteroids, the trial was of sufficient duration to assess the overall safety profile of QMF149, and AEs were recorded rigorously throughout the study. In general, the incidence of AEs was similar across the treatment groups with the exception of asthma and cough. The higher incidence of cough in the QMF149 treatment group was likely due to the use of the maleate salt of indacaterol in this study. A study comparing the maleate with the acetate salt of indacaterol showed that indacaterol acetate is associated with a lower incidence of cough with no impact on the efficacy, safety, or tolerability of treatment (Novartis data on file, 2012). Future studies of QMF149 will use indacaterol acetate rather than indacaterol maleate.

In addition, based on systemic exposure comparisons for indacaterol[32 33] and MF,[34] QMF149 will be delivered via the Breezhaler device in future development, rather than the Twisthaler device marketed for MF. QMF149 delivered via the Breezhaler device is currently being evaluated as a fixed-dose combination, where a dose of indacaterol acetate 150 µg/MF 160 µg is comparable to indacaterol maleate 500 µg/MF 400 µg delivered via the Twisthaler device. Thus, since QMF149 150 µg/160 µg via the Breezhaler device with the acetate salt is expected to be clinically comparable to QMF149 500 µg/400 µg with the maleate salt via the Twisthaler device, the current study provides important data to support the safety and efficacy profile of the final product.

In conclusion, this study has shown a favourable safety/efficacy profile of QMF149 in the treatment of persistent asthma. Improvements in lung function, symptom control and rescue medication use, and reductions in risk in time to first exacerbation requiring systemic corticosteroids, and in the annual rate of asthma exacerbations requiring systemic corticosteroids, were all significantly in favour of treatment with QMF149. QMF149 treatment was also associated with a numerical, but not significant, reduction in the risk of serious asthma exacerbations. QMF149 may be a useful treatment option in adolescents and adults with asthma who qualify for treatment with a LABA/ICS combination.

Author affiliations
[1]Medical Research Institute of New Zealand, Wellington, New Zealand
[2]Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA
[3]Dr Mehta's Allergy & Asthma Care and Research Center, Indore, Madhya Pradesh, India
[4]National Jewish Health, Denver, Colorado, USA
[5]Novartis Horsham Research Centre, Horsham, West Sussex, UK
[6]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA
[7]Novartis Pharmaceuticals Corporation, Basel, Switzerland

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Contributors RM was a principal investigator directly involved in the recruitment and care of the participants, and in data collection. MC, BMH and AM (current and ex-employees of the funding source) contributed to study design and conduct, data analysis and interpretation. H-JK (ex-employee of the funding source) contributed to study design, performed the statistical analysis and contributed to data interpretation. RWB was involved in the interpretation of statistical analyses. JFD and HSN both served on the Adjudication Committee for the current study. RWB took primary responsibility for writing the manuscript. All authors had access to the study data, were involved in interpretation and/or presentation of the data for this report, reviewed and revised the initial draft and subsequent versions of the manuscript, had final responsibility for the decision to submit for publication and approved the version submitted.

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Competing interests RWB received funding support from Novartis to present the study findings at the European Respiratory Society 2012 Annual Scientific Meeting. He has been a member of the GlaxoSmithKline (NZ) Advisory Board; consulted for Cytos Biotechnology and Pharmaxis; received research grants from AstraZeneca, Cephalon, Chiesi, Genentech, GlaxoSmithKline and Novartis; and received payment for lectures or support to attend meetings from Boehringer Ingelheim, GlaxoSmithKline, Novartis, Nycomed and Otsuka Pharmaceuticals. JFD served on the Adjudication Committee for the current study and has served on data monitoring safety boards for other Novartis clinical studies as well as for PneumoRx, Otsuka and Teva. He has received payment from Novartis for consultancy and expert testimony, and also served as a consultant for Almirall, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Forest, Merck, Pfizer, Sunovian, Pearl, Mylan and Gilead. RM was a principal investigator for the current study. HSN has consulted for Merck, Pearl Therapeutics and Circassia and has received research grants from NIH, Circassia and the Immune Tolerance Network. He served on the Adjudication Committee for the current study. BMH is an employee of

Novartis Pharmaceuticals Corporation. MC, AM and H-JK are ex-employees of Novartis Pharmaceuticals Corporation.

Ethics approval Ethics committees for each investigator site.

Provenance and peer review Not commissioned; externally peer reviewed.

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Effect of once-daily indacaterol maleate/mometasone furoate on exacerbation risk in adult asthma

Richard W Beasley, James F Donohue, Rajendra Mehta, Harold S Nelson, Michelle Clay, Allen Moton, Han-Joo Kim, Bettina M Hederer

Supplementary Appendix

Contents

SECTION 1
Study investigators

Brazil: Dr Adalberto S. Rubin, Dr Adelmir S. Machado, Dr Alex G. Macedo, Dr Carlos A. Pereira, Dr Emilio Pizzichini, Dr Fabio F. Castro, Dr Guilherme F. Garcia, Dr Jussara Fiterman, Dr Marina A. Lima, Dr Ricardo A. Corrêa.

Columbia: Dr Alvaro Urbina, Dr Carlos Matiz, Dr Carlos Tirado, Dr Diego Sereviche, Dr Elizabeth García, Dr Guido Cardona, Dr Juan G. Arcinegas, Dr Mirna Atencia, Dr Ricardo Aristizabal, Dr Ruben Contreras.

Czech Republic: Dr Blanka Novakova, Dr Dana Krtickova, Dr Eva Ohnutkova, Dr Iveta Nemcova, Dr Jana Teturova, Dr Jiri Hlavaty, Dr Jirina Vankova, Dr Hana Paukova, Dr Milan Kasl, Dr Luba Strouhova, Dr Marie Mattauchova, Dr Miroslav Klima, Dr Ondrej Rybnicek, Dr Petr Kucera, Dr Petr Panzner, Prof. Petr Zatloukal, Dr Tomas Rohovsky, Prof. Vladmir Vondra, Dr Yassin Shaker, Dr Yvona Hanzalkova.

Hungary: Dr Beatrix Balint, Dr Csaba Bocskei, Dr Eva Valyon, Dr Istvan Varkonyi, Dr Katain Gomori, Dr Marta Czompo, Dr Valeria Csajbok, Dr Zsuzsanna Mark, Dr Zsuzsanna Szalai.

India: Dr Anthony Mesquita, Dr Mohammed Samiuddin, Dr Pramod Niphadkar, Dr Rajendra Mehta, Dr Ramesh C. Sahoo, Dr Ravindra Sarniak, Dr Santhalingam Balamurugan, Dr Srikanth Krishnamurthy, Dr Srinivasan Nagarajan, Dr Vivek Gupta.

Korea: Dr Byoungwhui Choi, Prof. Inseon Choi, Prof. Sangheon Cho, Prof. Youngjoo Cho, Prof. Yousook Cho.

Peru: Dr Alberto Matsuno, Dr Andres Piñeiro, Dr Jorge Rey de Castro, Dr Jose Portugal, Dr Jorge De Los Rios, Dr Jose Torres, Dr Marco Camere, Dr Miguel Tsukayama, Dr Oscar Gayoso, Dr Socorro Castro.

Slovakia: Dr Anna Valentova, Dr Boris Hruskovic, Dr Dagmar Klcova, Dr Daniela Hasicova, Dr Iveta Hajdenova, Dr Jana Kiselova, Dr Katarina Papsova, Dr Lucia Kovacikova, Dr Maria Dzupinova, Dr Martin Dzurilla, Dr Miriam Michalickova, Dr Peter Ciznar, Dr Roman Benedik, Dr Yveta Kubikova.

USA: Dr Adam Wanner, Dr Adina Knight, Dr Aditi Satti, Dr Allen F. Kossoy, Dr Amit I. Patel, Dr Amy Darter, Dr Andrew J. Pedinoff, Dr Andrew C. Engler, Dr Anjuli S. Nayak, Dr Bobby Q. Lanier, Dr Brad Goodman, Dr Bruce Charous, Dr Bruce A. Decotiis, Dr Carlos J. Piniella, Dr Chao I. Lin, Dr Charles P. Andrews, Dr Christopher John, Dr Clifton Baylor, Dr Craig LaForce, Dr Dareen Siri, Dr David S. Pearlman, Dr David L. Schneider, Dr David Laman, Dr Dean A. Atkinson, Dr Deren Sinkowitz, Dr Donatella B. Graffino, Dr Edward E. Lisberg, Dr Edward Kent, Dr Emory H. Robinette, Dr Erik Van Ginkel, Dr Frank C. Hampel Jr., Dr Garrison Ayars, Dr Gary N. Gross, Dr Gary D. Berman, Dr George Zieg, Dr Grant C. Olson, Dr Harold Kaiser, Dr Henry D. Covelli, Dr Holly C. Brown, Dr Hugh H. Windom, Dr Ita Tripathy, Dr James D. Wolfe, Dr James N. Moy, Dr James L. Pearle, Dr John J. Condemi, Dr John Parrinello, Dr John Zwetchkenbaum, Dr John A. Winder, Dr John T. Given, Dr Jonathan Corren, Dr Jonathan Matz, Dr Jordan Fink, Dr Jose A. Bardelas, Dr Jose Mandujano, Dr Joseph Diaz, Dr Joshua S. Jacobs, Dr Judith White, Dr Karl V. Sitz, Dr Laura Somerville, Dr Lawrence Landwehr, Dr Lee Clore, Dr Leon S. Greos, Dr Leonard J. Dunn, Dr Linda B. Ford, Dr Lon D. Lynn, Dr Majed Koleilat, Dr Manav Singla, Dr Marc Goldstein, Dr Mark Woods, Dr Martha Tarpay, Dr Mercedes B.

Samson, Dr Michael J. Noonan, Dr Miguel E. Trevino, Dr Nancy K. Ostrom, Dr Nicole Hanania, Dr Paul E. Shapero, Dr Paula J. Lane, Dr Phillip E. Korenblat, Dr Pinkus Goldberg, Dr Rauno Joks, Dr Richard E. Mills, Dr Robert Anolik, Dr Robert Cartwright, Dr Robert Lapidus, Dr Robert Ziering, Dr Roger Menendez, Dr S. David Miller, Dr Sally Wenzel, Dr Samir Arora, Dr Santiago D. Reyes, Dr Sherwin A. Gillman, Dr Stephen A. Tilles, Dr Steve M. Meltzer, Dr Susan Louise Andrew, Dr Talaat Alshuqairat, Dr Thomas D. Casale, Dr Tracy A. Bridges, Dr Usha Chandrahasa, Dr Vadim Leyenson, Dr Vivek Awasty, Dr Warren Pleskow.

SECTION 2
Randomisation and blinding procedures

At the screening visit, the investigator or his/her designee called the Interactive Voice Response System (IVRS) to dispense the screening/run-in medication (mometasone furoate [MF] 400 µg open label). At the randomisation visit (Day 1 of treatment) the investigator or designee called IVRS after confirming that the patient fulfilled all the inclusion/exclusion criteria. The IVRS assigned a randomisation number to the patient (not communicated to the caller), which was used to assign the patient to a treatment group and specify a unique medication number (communicated to the site) for the first package of study drug to be dispensed to the patient.

The randomisation numbers were generated using the following procedure to ensure that treatment assignment was unbiased and concealed from patients and investigator staff: a patient randomisation list was produced by the IVRS provider using a validated system that automated the random assignment of patient numbers to randomisation numbers. These randomisation numbers were linked to the different treatment groups, which in turn were linked to medication numbers. A separate medication randomisation list was produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to medication packs containing each of the study drugs.

Randomisation was stratified by the presence or absence of the following demographic and baseline characteristics:

1. Patients who had an asthma-related hospitalisation within the 12 months prior to randomisation.
2. Patients who had experienced asthma worsening(s) during the 12 months prior to randomisation that required one of the following courses of action:
   - An emergency room visit requiring systemic corticosteroid treatment (not resulting in hospitalisation).
   - Two or more courses of systemic corticosteroids for asthma worsening.
3. African American patients or patients of black African descent.

Patients, investigator staff, persons performing the assessments, and data analysts remained blind to the identity of the treatment from the time of randomisation until database lock, using the following methods:

- Randomisation data were kept strictly confidential until the time of un-blinding and were not accessible by anyone else involved in the study with the following exceptions: the bioanalyst was un-blinded to enable identification of samples from the QMF149 arm of the study for indacaterol analysis. An external independent statistician and an independent programmer produced semi-blinded (ie, treatments labelled as A, B) interim analysis results for review by the external independent data monitoring committee (DMC).
- The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, schedule of administration, and appearance. Un-blinding only occurred in the case of patient emergencies, at the time of the interim analysis (semi-blinded manner with treatment labelled as A or B), and at the conclusion of the study.

SECTION 3
Patient inclusion and exclusion criteria

Inclusion criteria

1. Patients must have given written informed consent before any study-related activity was performed, including any adjustments to asthma medication prior to Visit 2 (screening). Patients below the legal age of consent were required to have the Informed Consent Form signed by their parent/guardian; adolescents should also have signed an assent form.
2. Male or female, adult or adolescent patients aged ≥12 years (or ≥18 years depending upon regulatory and/or International Review Board/Independent Ethics Committee/Research Ethics Board approval and/or country participation), and ≤70 years.
3. Patients with a documented diagnosis of persistent asthma (according to Global Initiative for Asthma [GINA] guidelines) for a period of at least 6 months prior to Visit 1 and who were currently treated with or qualified for treatment (according to asthma treatment guidelines) with both an inhaled corticosteroid (ICS) and a long-acting β_2-agonist (LABA). Patients must have used an ICS as part of their asthma regimen for at least 2 months prior to Visit 1.
4. Patients who demonstrated an increase in forced expiratory volume in 1 s (FEV_1) of ≥12% or ≥200 mL within 30 min after administration of a short-acting β_2-agonist (SABA) as per site protocol. Alternatively, patients may have had documented evidence of reversibility within the last 12 months.
5. Patients with an FEV_1 ≥50% of predicted normal at Visit 2. This criterion for FEV_1 was to have been demonstrated after all restricted medications had been withheld for appropriate intervals (washout period of at least 6 h for a SABA and a minimum of 24 h for a LABA).

Exclusion criteria

1. Pregnant or nursing (lactating) women.
2. Women of child-bearing potential unless post-menopausal or using acceptable contraception.
3. Patients who smoked or inhaled tobacco products within the 3-month period prior to Visit 2 (screening), or who had a smoking history of greater than 10 pack-years (defined as the number of packs of 20 cigarettes smoked per day multiplied by number of years the patient smoked).
4. Patients with a previous diagnosis of chronic obstructive pulmonary disease (COPD).
5. Patients who had experienced an asthma attack/exacerbation requiring hospitalisation within 1 month prior to Visit 3.
6. Patients who had an emergency room visit for an asthma attack/asthma exacerbation within 1 month prior to Visit 3.
7. Patients who had experienced a respiratory tract infection or asthma worsening within 1 month prior to Visit 3. Patients could be re-screened after 4 weeks once their respiratory tract infection had resolved.
8. Patients who had ever required ventilator support for respiratory failure secondary to asthma.
9. Patients with evidence upon visual inspection of clinically significant oropharyngeal candidiasis at baseline or earlier, with or without treatment. Patients could be re-screened once their candidiasis had been treated and resolved.
10. Patients with any chronic conditions affecting the respiratory tract (eg, chronic sinusitis) or chronic lung diseases, which in the opinion of the investigator might interfere with the study evaluation or optimal participation in the study.

11. Patients who had Type 1 diabetes or uncontrolled (in the judgment of the investigator) Type 2 diabetes.
12. Patients who, either in the judgment of the investigator or the responsible Novartis personnel, had a clinically relevant laboratory abnormality or a clinically significant condition such as (but not limited to) unstable ischaemic heart disease, arrhythmia (excluding chronic atrial fibrillation), uncontrolled hypertension, uncontrolled hypo- and hyperthyroidism, hypokalaemia, hyperadrenergic state, or an ophthalmologic disorder that might have compromised patient safety or compliance, interfered with evaluation, or precluded completion of the study.
13. Any patient who had active cancer or a history of cancer with less than 5 years disease-free survival time (whether or not there is evidence of local recurrence or metastases). Localised basal cell carcinoma (without metastases) of the skin was acceptable. Patients with a history of cancer and 5 years or more disease-free survival time could be included in the study by agreement with Novartis personnel on a case-by-case basis.
14. Patients with a history of long QT syndrome or whose QTc interval (Fridericia) measured at Visit 2 (screening) or Visit 3 (randomisation) was prolonged: >450 ms as assessed by the central electrocardiogram (ECG) interpretation (Visit 2) or investigator's interpretation of the pre-dose ECGs (Visit 3). Patients who failed the screening ECG were not to be re-screened.
15. Patients with a history of myocardial infarction within the previous 12 months, uncontrolled or unstable angina pectoris or arrhythmia (excluding chronic atrial fibrillation), known history of congestive heart failure (New York Heart Association [NYHA] Class II to IV) or known left ventricular ejection fraction <45%, implanted cardiac pacemaker or defibrillator.
16. Patients with a history of hypersensitivity to any of the study drugs or to similar drugs within the class including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof.
17. Patients who did not maintain regular day/night, waking/sleeping cycles (eg, night shift workers).
18. Patients who had received live attenuated vaccinations within 30 days prior to screening visit or during the run-in period. Inactivated influenza vaccination, pneumococcal vaccination, or any other inactivated vaccine was acceptable provided it was not administered within 48 h prior to study visit.
19. Patients who were using prohibited medications or patients who could adhere to medication washouts. The following medications must not have been used prior to Visit 2 for at least the minimum washout period specified below:
    - Long-acting anti-cholinergic agent tiotropium (bromide): 7 days.
    - Short acting anti-cholinergics: 8 h.
    - Fixed combinations of β_2-agonists and ICS (other than as prescribed in the study): 24 h.
    - LABAs: 24 h.
    - SABAs (other than those prescribed in the study): 6 h.
    - ICS (other than those prescribed in the study): 12 h.
    - Theophylline and other xanthines: 7 days.
    - Omalizumab treatment within 4 months prior to Visit 2.
    - Parenteral or oral corticosteroids: 4 weeks.
20. Maintenance immunotherapy (desensitisation) for allergies was allowed if the maintenance dose had been administered for at least 3 months prior to Visit 2 and was expected to remain unchanged throughout the course of the study.
21. Other excluded medications:
    - Non-potassium sparing diuretics (unless used in combination with potassium conserving drugs) or with a potassium supplement for which

there was adequate documentation of the subject's use taken together with a diuretic.
- Non-selective systemic β-blocking agents.
- Drugs with potential to significantly prolong the QT interval; cardiac antiarrhythmics Class Ia (eg, disopyramide, procainamide, quinidine); cardiac antiarrhythmics Class III (eg, amiodarone, dofetilide, ibutilide, sotalol); the antihistamines astemizole and mizolastin; macrolides and antipsychotics (eg, haloperidol, thioridazine).
- Tricyclic antidepressants (and similar compounds like tetracyclic antidepressants) and monoamino-oxidase inhibitors.
- Strong inhibitors of cytochrome P4503A4 (eg, ketoconazole).

22. Patients who had used other investigational drugs at the time of enrolment, or within 30 days or five half-lives prior to Visit 2, whichever was longer.

23. Patients who were unable to use a dry powder inhaler device, metered dose inhaler or perform spirometry measurements.

24. Patients who had a known history of non-compliance to medication or who were unable or unwilling to use Electronic Peak Flow with e-diary device.

25. Patients were not to be randomised into this study more than once.

26. No person directly associated with the administration of the study could participate as a study subject. No family member of the investigational study staff could participate in this study.

SECTION 4
Adjudication procedure

In this study, serious asthma exacerbations were defined as asthma exacerbations resulting in hospitalisation, intubation, or death. Serious asthma exacerbations were collected as a study endpoint and recorded on the asthma exacerbation electronic case report form (eCRF).

All hospitalisations, intubations, and deaths were assessed by an independent adjudication committee to determine asthma relatedness. Investigators were informed if the investigator assessment differed from the final assessment of the adjudication committee. The primary analysis was based on asthma-related events as defined by the adjudication committee.

Serious Exacerbation Adjudication Committee

Dr James Kemp, MD
University of California School of Medicine
San Diego, CA
USA

Dr James Donohue, MD
University of North Carolina
Chapel Hill, NC
USA

Dr Harold Nelson, MD
National Jewish Health
Denver, CO
USA

SECTION 5
Data Monitoring Committee and interim analysis

An independent DMC was formed to monitor asthma-related events on behalf of study participants and investigators. A DMC charter and a separate DMC Report Analysis Plan (RAP) document for analysis were written.

Initially the DMC planned to meet every 6 months to review safety data with an additional event driven review. The threshold for the latter was to conduct interim analysis when 10 serious asthma exacerbation events had been accumulated and adjudicated.

In fact, only one interim analysis was performed and a DMC meeting was held on 31 August 2010 where the DMC reviewed semi-blinded safety data. By the original charter, a subsequent DMC meeting would be scheduled on or about 28 February 2011. However, given the close proximity of the meeting to the last patient last visit date of 6 May 2011 and the database lock date that was planned to be 25 May 2011 at the time, the DMC unanimously agreed to cancel the DMC meeting.

Data Monitoring Committee

William Busse, MD (Chair)
Department of Medicine
University of Wisconsin Medical School
Madison, WI
USA

Paul O'Byrne, MD
Firestone Institute for Respiratory Health
St. Joseph's Hospital and McMaster University
Hamilton, ON
Canada

Neil Schluger, MD
Division of Pulmonary, Allergy, and Critical Care Medicine
Columbia University Medical Center
New York, NY 10032
USA

Scott Emerson
Department of Biostatistics
University of Washington
Seattle, WA
USA

SECTION 6
Statistical methods

Primary endpoint
The time to the first serious asthma exacerbation was analysed using a Cox proportional hazards regression model stratified by asthma-related hospitalisation in the last 12 months (no/yes), asthma worsening in the last 12 months (no/yes), and African American patient (no/yes), including terms for treatment and region. Region was defined as USA, Asia, Europe, or Latin America. The null-hypothesis was formulated to a hazard ratio of QMF149 relative to MF being equal or greater than one at α=0.05 (one-sided). In this manuscript, the two-sided 95% confidence interval (CI) of the estimated hazard ratio (QMF149/MF) and its two-sided p-value were provided.

The time to the first serious asthma exacerbation was also displayed for each treatment group with a Kaplan-Meier curve. Patients who did not experience a serious asthma exacerbation were censored at their last follow-up date.

Cumulative incidence of serious asthma exacerbation
Treatment groups were compared using the CI approach (based on the normal approximation). Cumulative incidence was defined as the number of patients with serious asthma exacerbation divided by total number of patients for each treatment group. The null-hypothesis could be rejected if the upper bound of the one-sided 95% CI for QMF149–MF was less than 1% (percentage-point difference). In this manuscript, the two-sided 95% CI of the percentage-point difference in cumulative incidence and its two-sided p-value were provided.

Asthma exacerbations requiring treatment with systemic corticosteroids
The percentage of patients having the event was summarised. Additionally, the event rate, defined by total number of events divided by total follow-up days, was summarised by treatment group.

A negative binomial regression model included (log-transformed) exposure in years as an offset variable, treatment, region, asthma-related hospitalisation in the last 12 months (no/yes), asthma worsening in the last 12 months (no/yes), and Black/African American patient (no/yes) as fixed effect factors. Rate ratio of QMF149 relative to MF and its associated two-sided 95% CI were obtained from the model. In addition, a Cox regression analysis for time to first asthma exacerbation requiring treatment with systemic corticosteroids, similar to the primary analysis, was performed (presenting the two-sided p-value and 95% CI).

Time to event was defined as the number of days from start of treatment up to the exacerbation start date (not up to the start date of systemic corticosteroids, if different). Kaplan-Meier estimates were plotted.

Spirometry measurements: FEV_1 and forced vital capacity (FVC)
Any spirometry measurement taken up to 6 h after rescue medication was set to missing and not imputed. Change from baseline in trough FEV_1 measured at 15 min before dosing was analysed using a repeated measures analysis of covariance (ANCOVA) model. Data from Visits 5, 7, 9, 12, 14, 16 (ie, weeks 4, 12, 26, 52, 68, and final visit) were included. The ANCOVA model included treatment, visit, treatment-by-visit interaction, region, asthma-related hospitalisation in the last 12 months (no/yes), asthma worsening in the last 12 months (no/yes), and African American patient (no/yes) as fixed effect factors and baseline FEV_1 as covariate. Estimates of adjusted treatment effect overall and for each visit were displayed with their associated 95% CIs. Similar analyses were repeated for FVC.

Morning peak expiratory flow (PEF) and evening trough PEF as recorded on the e-diary

The average morning (AM) and evening (PM) PEF was calculated for each patient by month (defined by intervals of 30 days) and over the entire post-baseline period. Change from baseline was also analysed separately for AM and PM data. The baseline value was defined as the average over the last 14 days prior to start of treatment. A repeated measures ANCOVA included treatment, month, treatment-by-month interaction, region, asthma-related hospitalisation in the last 12 months (no/yes), asthma worsening in the last 12 months (no/yes), and African American patient (no/yes) as fixed effect factors and baseline PEF as a covariate. Due to non-convergence of the repeated ANCOVA model after a database lock, the compound symmetry was used to model within-patient correlation. For PEF averaged over the entire post baseline period, the ANCOVA model did not include month and treatment-by-month interaction.

Asthma symptoms as recorded on the e-diary

Asthma symptoms were analysed on a monthly basis and also over the entire post baseline period according to the same rules described for PEF. The following variables were calculated for each patient and period:

- Percentage of days with no morning asthma symptoms.
- Percentage of days with no daytime asthma symptoms (ie, days with a daytime asthma symptom score=0).
- Percentage of nights with no night-time asthma symptoms (ie, nights with a night-time asthma symptom score=0).
- Average daytime asthma symptom score (score range is from 0 to 4) over the entire post baseline period.
- Average night-time asthma symptom score (score range is from 0 to 4) over the entire post baseline period.
- Average total asthma symptom score (defined as the daily sum of morning, daytime, and night-time asthma symptom scores, the range is from 0 to 9) over the entire post baseline period.

Changes from baseline were analysed in a similar fashion to PEF using the respective baseline values for each variable. Due to non-convergence of the repeated ANCOVA model after a database lock, the compound symmetry matrix was used to model within-patient correlation. Moreover, the repeated ANCOVA model excluded data from Month 20 due to non-convergence and only Months 1 to 19 were included in the model. ANCOVA as well as descriptive analyses were performed.

Rescue medication use as recorded on the e-diary

The use of rescue medication was analysed on a monthly basis and also over the entire post baseline period according to the same rules as for PEF. The following variables were calculated for each patient and period:

- Percentage of days with no rescue medication use (ie, during both daytime and night-time).
- Percentage of days with no rescue medication use during 12-h daytime.
- Percentage of nights with no rescue medication use during 12-h night-time.
- Average daytime number of puffs of rescue medication over the entire post baseline period.
- Average night-time number of puffs of rescue medication over the entire post baseline period.
- Average total daily number of puffs of rescue medication (defined as the daily sum of daytime and night-time number of puffs of rescue medication) over the entire post baseline period.

Changes from baseline were analysed similar to PEF using the respective baseline values for each variable. Due to non-convergence of the repeated ANCOVA model after a database lock, the compound symmetry matrix was used to model within-patient correlation. ANCOVA as well as descriptive analyses were performed.

SECTION 7
Adverse events

Table S1. Serious adverse events, including asthma exacerbations, by primary system organ class and preferred term (six or more patients in any class, safety set)

	QMF149 n=749 n (%)	MF n=759 n (%)
Patients with any SAE(s)	30 (4.0)	44 (5.8)
Cardiac disorders	2 (0.3)	5 (0.7)
Angina unstable	1 (0.1)	0 (0)
Coronary artery disease	1 (0.1)	0 (0)
Myocardial ischaemia	1 (0.1)	0 (0)
Supraventricular tachycardia	1 (0.1)	1 (0.1)
Angina pectoris	0 (0.0)	1 (0.1)
Atrial fibrillation	0 (0.0)	1 (0.1)
Cardiac arrest	0 (0.0)	1 (0.1)
Palpitations	0 (0.0)	1 (0.1)
Stress cardiomyopathy	0 (0.0)	1 (0.1)
Gastrointestinal disorders	4 (0.5)	3 (0.4)
Nausea	2 (0.3)	0 (0.0)
Vomiting	2 (0.3)	0 (0.0)
Abdominal hernia obstructive	1 (0.1)	0 (0.0)
Abdominal pain	1 (0.1)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)
Haemorrhoids	0 (0.0)	1 (0.1)
Inguinal hernia	0 (0.0)	2 (0.3)
General disorders and administration site conditions	2 (0.3)	6 (0.8)
Chest pain	1 (0.1)	2 (0.3)
Pyrexia	1 (0.1)	0 (0.0)
Cyst	0 (0.0)	1 (0.1)
Multi-organ failure	0 (0.0)	1 (0.1)
Non-cardiac chest pain	0 (0.0)	2 (0.3)
Infections and infestations	5 (0.7)	9 (1.2)
Appendicitis	2 (0.3)	2 (0.3)
Cellulitis	1 (0.1)	0 (0.0)
Gastroenteritis	1 (0.1)	0 (0.0)
Malaria	1 (0.1)	0 (0.0)
Abscess intestinal	0 (0.0)	1 (0.1)
Diverticulitis	0 (0.0)	2 (0.3)
External ear cellulitis	0 (0.0)	1 (0.1)
Pneumococcal sepsis	0 (0.0)	1 (0.1)
Pneumonia	0 (0.0)	4 (0.5)
Septic shock	0 (0.0)	1 (0.1)
Injury, poisoning, and procedural complications	3 (0.4)	4 (0.5)
Concussion	1 (0.1)	0 (0.0)
Pneumothorax traumatic	1 (0.1)	0 (0.0)
Rib fracture	1 (0.1)	0 (0.0)
Road traffic accident	1 (0.1)	0 (0.0)
Spinal compression fracture	1 (0.1)	0 (0.0)
Spinal fracture	1 (0.1)	0 (0.0)
Foot fracture	0 (0.0)	1 (0.1)
Lower limb fracture	0 (0.0)	1 (0.1)

Meniscus lesion	0 (0.0)	1 (0.1)
Tendon rupture	0 (0.0)	1 (0.1)
Neoplasms benign, malignant, and unspecified	4 (0.5)	4 (0.5)
Colon cancer	1 (0.1)	0 (0.0)
Malignant melanoma	1 (0.1)	0 (0.0)
Prostate cancer	1 (0.1)	0 (0.0)
Thyroid cancer	1 (0.1)	1 (0.1)
Bladder cancer	0 (0.0)	1 (0.1)
Meningioma	0 (0.0)	1 (0.1)
Osteochondroma	0 (0.0)	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	3 (0.4)	10 (1.3)
Asthma	2 (0.3)	9 (1.2)
Sinus polyp	1 (0.1)	0 (0.0)
Cough	0 (0.0)	1 (0.1)
Dyspnoea	0 (0.0)	2 (0.3)

MF, mometasone furoate; SAE, serious adverse event.

Table S2. Frequency of adverse events (≥2.0% in any treatment group)

	QMF149 n=749 n (%)	MF n=759 n (%)
Patients with any AE(s)	554 (74.0)	557 (73.4)
Cough	266 (35.5)	64 (8.4)
Asthma	196 (26.2)	275 (36.2)
Nasopharyngitis	112 (15.0)	106 (14.0)
Upper respiratory tract infection	83 (11.1)	96 (12.6)
Sinusitis	55 (7.3)	52 (6.9)
Bronchitis	39 (5.2)	58 (7.6)
Pharyngitis	29 (3.9)	27 (3.6)
Rhinitis allergic	29 (3.9)	25 (3.3)
Viral upper respiratory tract infection	29 (3.9)	36 (4.7)
Headache	26 (3.5)	30 (4.0)
Influenza	26 (3.5)	27 (3.6)
Oropharyngeal pain	24 (3.2)	18 (2.4)
Rhinitis	21 (2.8)	14 (1.8)
Acute sinusitis	16 (2.1)	8 (1.1)
Back pain	16 (2.1)	11 (1.4)
Upper respiratory tract infection, bacterial	15 (2.0)	21 (2.8)
Respiratory tract infection	13 (1.7)	15 (2.0)
Viral infection	10 (1.3)	24 (3.2)

AE, adverse event; MF, mometasone furoate.

Table S3. Most frequent occurring treatment-related adverse events (≥1% in any treatment group) by body system class

Body system class	AE	QMF149 (N=749) n (%)	MF (N=759) n (%)
	Patients with any TRAE*	269 (35.9)	81 (10.7)
Respiratory, thoracic and mediastinal disorders	Total	249 (33.2)	53 (7.0)
	Cough	238 (31.8)	32 (4.2)
	Asthma	13 (1.7)	21 (2.8)
	Dysphonia	3 (0.4)	1 (0.1)
	Dyspnea	3 (0.4)	0 (0.0)
	Oropharyngeal pain	3 (0.4)	0 (0.0)
	Rhinitis allergic	2 (0.3)	0 (0.0)
	Throat irritation	2 (0.3)	0 (0.0)
	Dry throat	1 (0.1)	2 (0.3)
	Pharyngeal oedema	1 (0.1)	1 (0.1)
	Productive cough	1 (0.1)	1 (0.1)
	Respiratory tract irritation	1 (0.1)	0 (0.0)
	Rhonchi	1 (0.1)	0 (0.0)
	Throat tightness	1 (0.1)	0 (0.0)
	Asthmatic crisis	0 (0.0)	1 (0.1)
	Wheezing	0 (0.0)	1 (0.1)
Infections and infestations	Total	13 (1.7)	13 (1.7)
	Oral candidiasis	6 (0.8)	3 (0.4)
	Oesophageal candidiasis	2 (0.3)	0 (0.0)
	Bronchitis	1 (0.1)	2 (0.3)
	Candidiasis	1 (0.1)	4 (0.5)
	Oral fungal infection	1 (0.1)	1 (0.1)
	Upper respiratory tract infection	1 (0.1)	2 (0.3)
	Viral upper respiratory tract infection	1 (0.1)	0 (0.0)
	Urinary tract infection	0 (0.0)	1 (0.1)
General disorders and administration site conditions	Total	8 (1.1)	2 (0.3)
	Product taste abnormal	6 (0.8)	0 (0.0)
	Chest discomfort	1 (0.1)	1 (0.1)
	Malaise	1 (0.1)	0 (0.0)
	Fatigue	0 (0.0)	1 (0.1)

*The total number (%) of TRAEs reported in the study

A patient with multiple occurrences of an AE was counted only once in the AE category. A patient with multiple AE within a primary system organ class was counted only once in the total row.

AE, adverse event; TRAE, treatment-related adverse event