Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials

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Summary

Background To date, no studies have assessed the efficacy of single-inhaler triple therapy in asthma. Here we report on two studies that compared the single-inhaler extrafine combination of beclometasone dipropionate (BDP; inhaled corticosteroid), formoterol fumarate (FF; long-acting β_2 agonist), and glycopyrronium (G; long-acting muscarinic antagonist) with the combination of BDP with FF.

Methods Two parallel-group, double-blind, randomised, active-controlled, phase 3 trials (Triple in Asthma With Uncontrolled Patients on Medium Strength of ICS + LABA [TRIMARAN] and Triple in Asthma High Strength Versus ICS/LABA HS and Tiotropium [TRIGGER]) recruited patients from 171 sites across 16 countries (TRIMARAN), and from 221 sites across 17 countries (TRIGGER). The sites were a mixture of secondary and tertiary care centres and specialised investigation units. Eligible patients were adults (aged 18–75 years) with uncontrolled asthma, a history of one or more exacerbations in the previous year, and previously treated with inhaled corticosteroid (TRIMARAN: medium dose; TRIGGER: high dose) plus a long-acting β_2 agonist. Enrolled patients were initially treated with BDP/FF (TRIMARAN: 100 µg BDP and 6 µg FF; TRIGGER: 200 µg BDP and 6 µg FF) for 2 weeks, then randomly assigned to treatment using an interactive response technology system with a balanced block randomisation scheme stratified by country. Patients, investigators, site staff, and sponsor staff were masked to BDP/FF/G and BDP/FF assignment. In TRIMARAN, patients were randomly assigned (1:1) to 52 weeks of BDP/FF/G (100 µg BDP, 6 µg FF, and 10 µg G) or BDP/FF (100 µg BDP and 6 µg FF), two inhalations twice daily. In TRIGGER, patients were randomly assigned (2:2:1) to 52 weeks of BDP/FF/G (200 µg BDP, 6 µg FF, and 10 µg G) or BDP/FF (200 BDP and 6 µg FF), both two inhalations twice daily, or open-label BDP/FF (200 µg BDP and 6 µg FF) two inhalations twice daily plus tiotropium 2·5 µg two inhalations once daily. Coprimary endpoints for both trials (BDP/FF/G *vs* BDP/FF) were pre-dose forced expiratory volume in 1 s (FEV_1) at week 26 and rate of moderate and severe exacerbations over 52 weeks. Safety was assessed in all patients who received at least one dose of study treatment. These trials were registered with ClinicalTrials.gov, NCT02676076 (TRIMARAN), NCT02676089 (TRIGGER).

Findings Between Feb 17, 2016, and May 17, 2018, 1155 patients in TRIMARAN were given BDP/FF/G (n=579) or BDP/FF (n=576). Between April 6, 2016, and May 28, 2018, 1437 patients in TRIGGER were given BDP/FF/G (n=573), BDP/FF (n=576), or BDP/FF plus tiotropium (n=288). Compared with the BDP/FF group, week 26 predose FEV_1 improved in the BDP/FF/G group by 57 mL (95% CI 15–99; p=0·0080) in TRIMARAN and by 73 mL (26–120; p=0·0025) in TRIGGER, with reductions in the rate of moderate and severe exacerbations of 15% (rate ratio 0·85, 95% CI 0·73–0·99; p=0·033) in TRIMARAN and 12% (0·88, 0·75–1·03; p=0·11) in TRIGGER. Four patients had treatment-related serious adverse events, one in TRIMARAN in the BDP/FF/G group and three in TRIGGER—one in the BDP/FF/G and two in the BDP/FF group. Three patients in the BDP/FF/G group in TRIMARAN and two patients in TRIGGER—one in the BDP/FF/G group and one in the BDP/FF group—had adverse events leading to death. None of the deaths were considered as related to treatment.

Interpretation In uncontrolled asthma, addition of a long-acting muscarinic antagonist to inhaled corticosteroid plus long-acting β_2-agonist therapy improves lung function and reduces exacerbations.

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Introduction

Goals of asthma management are to achieve symptom control and avoid future risks, especially risks of exacerbations.[1] Asthma is characterised by the presence of chronic airway inflammation; hence inhaled corticosteroids are the mainstay of therapy.[1] Many patients are able to achieve good disease control, especially from an inhaled corticosteroid plus long-acting β_2 agonist

Research in context

Evidence before this study

We searched PubMed for articles published from database inception until April 4, 2019, using the search term "drug therapy, combination" [MeSH terms] OR triple AND asthma AND trial NOT theophylline NOT montelukast, with no restrictions. Of the 1068 hits, eight articles presented data from clinical trials that assessed the efficacy of triple therapy comprising an inhaled corticosteroid plus a long-acting β_2 agonist plus a long-acting muscarinic antagonist. Of these articles, six reported data in adults (the other two reported data in children or adolescents), of which one article was a short-term (4-week) study, one reported pooled safety data, and one reported subgroup analyses of studies presented in another manuscript. The remaining three articles reported data from studies in which the long-acting muscarinic antagonist tiotropium was added as a free combination to any inhaled corticosteroid and long-acting β_2 agonist. The first of these articles presented data from two 48-week studies, in which the addition of tiotropium to high-dose inhaled corticosteroid plus a long-acting β_2 agonist delayed the time to first asthma exacerbation and reduced the overall risk of these events, with improvements in lung function. The second article focused on the long-term (52-week) safety profile of the addition of tiotropium to inhaled corticosteroid plus a long-acting β_2 agonist, which was similar to inhaled corticosteroid plus a long-acting β_2 agonist alone. In the third article, the addition of tiotropium improved airflow and reduced airway wall thickness after 48 weeks. All three studies assessed the effect of tiotropium plus inhaled corticosteroid plus long-acting β_2-agonist therapy in patients with spirometrically assessed persistent airflow limitation (ie, ratio of forced expiratory volume in 1 s to forced vital capacity <0·7).

Added value of this study

TRIMARAN and TRIGGER are the first studies to assess the efficacy and safety of single-inhaler triple therapy compared with inhaled corticosteroid plus a long-acting β_2 agonist in adults with asthma. Additionally, these are the first long-term studies undertaken in patients who had no requirement to show persistent airflow limitation after short-acting β_2 agonist use.

Implications of all the available evidence

The combination of a long-acting muscarinic antagonist with an inhaled corticosteroid plus long-acting β_2-agonist therapy in adults with uncontrolled asthma results in improved lung function. In large, long-term studies, triple therapy has a positive effect on severe exacerbations.

combination.[2] However, until recently, few options were available for patients who could not achieve controlled asthma with such combinations.

The addition of the long-acting muscarinic antagonist tiotropium to inhaled corticosteroid plus long-acting β_2-agonist therapy has been shown to improve lung function and, in longer studies (48-week duration), reduce the risk of exacerbations in patients with asthma, although in a subgroup of patients with persistent airflow limitation.[3–5] However, the addition of tiotropium requires patients to use two different inhalers of different design with different instructions for use, and often with different dosing regimens. Such a combination is not only inconvenient for patients and health-care providers who instruct on correct inhaler use, but can negatively affect treatment adherence and persistence.[6–9] A single-inhaler triple therapy consisting of an extrafine formulation (ie, with mass median aerodynamic diameter <2 μm) of the inhaled corticosteroid beclometasone dipropionate, the long-acting β_2 agonist formoterol fumarate, and the long-acting muscarinic antagonist glycopyrronium (known as BDP/FF/G from hereon) delivered via a pressurised metered-dose inhaler is in development for patients with asthma. Such extrafine formulations result in improved deposition in the small airways,[10] which is potentially important given that patients with asthma with substantial dysfunction of the small airways tend to have worse asthma control and quality of life and are at increased exacerbation risk.[11]

See Online for appendix

In this Article, we report the results of two phase 3, 52-week studies (Triple in Asthma With Uncontrolled Patients on Medium Strength of ICS + LABA [TRIMARAN] and Triple in Asthma High Strength Versus ICS/LABA HS and Tiotropium [TRIGGER]) comparing the efficacy and safety of medium-strength (TRIMARAN) and high-strength (TRIGGER) BDP/FF/G with that of the medium-strength (TRIMARAN) and high-strength (TRIGGER) beclometasone dipropionate plus formoterol fumarate (BDP/FF) in patients with asthma that is poorly controlled on medium-dose (TRIMARAN) or high-dose (TRIGGER) inhaled corticosteroid plus long-acting β_2 agonist therapy. These are the first studies to assess single-inhaler triple therapy in a broad asthma population not restricted to those with persistent airflow limitation.

Methods

Study design and participants

TRIMARAN and TRIGGER were both randomised, parallel-group, double-blind, active-controlled phase 3 studies. The main difference between the studies was the inhaled corticosteroid dose received before and during the study, with patients in TRIMARAN receiving a medium dose and patients in TRIGGER receiving a high dose.

Patients were recruited for TRIMARAN from 171 sites across 16 countries, and for TRIGGER patients were recruited from 221 sites across 17 countries (countries listed in the appendix [p 2]). The sites were a mixture of secondary and tertiary care centres and specialised investigation units, and 126 sites participated in both studies.

Patients were eligible if they were aged 18–75 years, with a documented history of asthma for at least 1 year before screening and that was diagnosed before age 40 years, prebronchodilator forced expiratory volume in 1 s (FEV_1) of less than 80% predicted normal value, and a change in FEV_1 of more than 12% and over 200 mL at 10–15 min after inhaling salbutamol 400 µg. Further inclusion criteria were uncontrolled asthma (Asthma Control Questionnaire-7 [ACQ-7] ≥1·5); at least one exacerbation requiring treatment with systemic corticosteroids or an emergency department visit or inpatient admission to hospital in the previous 12 months; and that the patient was receiving a stable dose of an inhaled corticosteroid plus a long-acting β_2 agonist for at least 4 weeks before study entry (TRIMARAN medium dose and TRIGGER high dose of inhaled corticosteroid; dose equivalents are in the appendix [p 2]). Key exclusion criteria were a history of near fatal asthma or previous admission to an intensive care unit for asthma that might place the patient at risk; a severe exacerbation in the 4 weeks before study entry or during the run-in period; any other substantial lung disease that could interfere with study assessments; current smokers or former smokers with 10 or more pack-years of exposure or who stopped smoking 1 year or less before screening; current treatment with monoclonal antibodies or other biological drugs; clinically significant cardiovascular conditions or laboratory abnormalities; or unstable concurrent disease that could affect efficacy or safety. Full inclusion and exclusion criteria and non-permitted asthma medications are listed in the appendix (pp 2–5).

The studies were approved by the ethics committee or institutional review board at each site and were undertaken in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice (ICH/CPMP/135/95). There were no substantial protocol amendments that affected any patients who were randomly assigned to treatment. The two protocols had one substantial amendment to the inclusion criteria: to clarify that any long-acting β_2 agonist was permitted as previous medication, providing it was taken at an approved daily dose that was clinically comparable to formoterol 24 µg, salmeterol 100 µg, or vilanterol 25 µg. All patients provided written informed consent before any study-related procedures.

Randomisation and masking

After a run-in period of treatment with BDP/FF, eligible patients were randomly assigned to treatment. In TRIMARAN, patients were randomly assigned (1:1) to either BDP/FF or extrafine BDP/FF/G. In TRIGGER, patients were randomly assigned (2:2:1) to BDP/FF, extrafine BDP/FF/G, or open-label BDP/FF plus tiotropium. Randomisation was done according to a randomisation list generated by the interactive response technology provider, stratified by country. Patients, investigators, site staff, and sponsor personnel were masked to BDP/FF/G and BDP/FF assignment for the duration of the studies, with all patients using pressurised metered-dose inhalers. In TRIGGER, the BDP/FF plus tiotropium group was open-label.

Procedures

Patients who met the eligibility criteria at screening had their asthma maintenance therapy switched to extrafine BDP/FF at 100 µg of BDP and 6 µg of FF in TRIMARAN and 200 µg of BDP and 6 µg of FF in TRIGGER, at two inhalations twice daily via pressurised metered-dose inhaler for a 2-week open-label run-in period. At the end of the run-in period, patients were randomly assigned to treatment. In TRIMARAN, patients either continued on BDP/FF at the same dose as the run-in period, at two inhalations twice daily, or received extrafine BDP/FF/G at 100 µg of BDP, 6 µg of FF, and 10 µg of G, two inhalations twice daily via pressurised metered-dose inhaler. In TRIGGER, patients either continued on BDP/FF at the same dose as the run-in period with two inhalations twice daily via a pressurised metered-dose inhaler; or received extrafine BDP/FF/G at 200 µg of BDP, 6 µg of FF, and 10 µg of G with two inhalations twice daily; or open-label BDP/FF at 200 µg of BDP and 6 µg of FF at two inhalations twice daily via a pressurised metered-dose inhaler plus tiotropium 2·5 µg at two inhalations once daily via a soft mist inhaler (Respimat, Boehringer Ingelheim, Ingelheim am Rhein, Germany). Over the 52-week treatment period, patients attended visits at weeks 4, 12, 26, 40, and 52. Salbutamol via pressurised metered-dose inhaler was permitted as rescue medication, but not within 6 h before any visit.

At each visit during the treatment period, data were collected for spirometry (predose and 15 min, 30 min, 1 h, 2 h, and 3 h after dose, with centralised spirometry) and ACQ-7. Asthma exacerbations were captured throughout the study. Each day, before treatment in the morning and evening, patients recorded their peak expiratory flow (PEF), asthma symptoms (on a scale of 0 to 3, where 0 was no symptoms), and study treatment and rescue medication use in an electronic diary.

Treatment-emergent adverse events (defined as events starting on or after first intake of randomly assigned study medication) were captured by the investigators throughout the study, along with severity and association with study medication.

Outcomes

The coprimary endpoints for both studies were morning predose FEV_1 at week 26 and the rate of moderate and severe exacerbations over 52 weeks in each study. The key secondary objectives were change from baseline in peak FEV_1 at week 26 and average morning PEF over the first 26 weeks in each study, and the rate of severe exacerbations using data pooled from the two studies.

Other secondary endpoints were change from baseline in peak and predose FEV_1 at all other visits; FEV_1 area under the curve from 0 to 3 h after dose ($AUC_{0–3h}$) at all clinical visits; FEV_1 response (change from baseline in predose FEV_1 ≥100 mL) at weeks 26 and 52; change from baseline in ACQ-7 at all visits and ACQ-7 response (decrease from baseline score of at least 0·5 units) at weeks 26 and 52; change from baseline in average morning and evening PEF over each between-visit period and over 52 weeks, and average evening PEF over the first 26 weeks of treatment; time to first moderate exacerbation and first moderate or severe exacerbation; rate of moderate exacerbations; and rescue medication use, days without rescue medication, daily asthma symptoms, asthma symptom-free days, and asthma control days (ie, days with a total asthma symptoms score of 0 and no rescue medication use) over each between-visit period and over the first 26 weeks and 52 weeks of treatment. Data were pooled from the two studies to compare BDP/FF/G with BDP/FF for the time to first moderate, severe, and moderate or severe exacerbation, and the rate of moderate exacerbations and combined moderate and severe exacerbations. Severe exacerbations were prespecified to be analysed only in the pooled population because we anticipated that the occurrence of these events would be relatively low.

A severe asthma exacerbation was defined as worsening of asthma that required treatment with systemic corticosteroids for at least 3 days (with any associated emergency department visit or admission to hospital documented). Moderate exacerbations were defined in accordance with the American Thoracic Society and European Respiratory Society joint statement[12] as meeting one or more of the following criteria: nocturnal awakenings due to asthma requiring a short-acting β_2 agonist for 2 consecutive nights or an increase of 0·75 or more from baseline in daily symptom score on 2 consecutive days; increase from baseline in use of short-acting β_2 agonist on 2 consecutive days (minimum increase 4 puffs per day); 20% or more decrease in PEF from baseline on at least 2 consecutive mornings or evenings, or 20% or more decrease in FEV_1 from baseline; or a visit to an emergency department or a study site for asthma treatment not requiring systemic corticosteroids.

Safety was assessed throughout the study. Major adverse cardiovascular events were adjudicated by an independent committee, comprising three cardiologists.

Statistical analysis

To show superiority of BDP/FF/G over BDP/FF in terms of the coprimary and key secondary endpoints in both studies, 574 patients needed to be randomly assigned to each treatment group. Since patients were randomly assigned in a ratio of 2:2:1 in TRIGGER, 287 patients were needed for the BDP/FF plus tiotropium group. As such, a total of 1148 patients in TRIMARAN and 1435 in TRIGGER would be needed. Our sample size calculation assumed an approximate 13% drop-out rate at week 12, 16·5% at week 26, and 20% at week 52. Considering a two-sided significance level of 0·05, these numbers of patients would result in an approximately 99% power to detect a mean difference of 90 mL in favour of BDP/FF/G over BDP/FF in change from baseline in predose FEV_1 at week 26, assuming an SD of 311 mL; approximately 93% power to detect a rate ratio (RR) of 0·80 between BDP/FF/G and BDP/FF using a negative binomial model and assuming an annualised rate of 2·70 moderate and severe exacerbations per patient in the BDP/FF group and an overdispersion parameter of the negative binomial distribution of 0·56; approximately 99% power to detect a mean difference of 100 mL in favour of BDP/FF/G over BDP/FF in peak FEV_1 change from baseline at week 26, assuming an SD of 338 mL; at least 99% power to detect a mean difference of 20 L/min in favour of BDP/FF/G over BDP/FF in morning PEF change from baseline over the 26-week treatment period, assuming an SD of 45 L/min; and approximately 86% power to detect an RR of 0·80 between BDP/FF/G and BDP/FF in the pooled analysis, using a negative binomial model and assuming an annualised rate of 0·60 severe exacerbations per patient in the BDP/FF group and an overdispersion parameter of the negative binomial distribution of 0·56.

To account for multiplicity, we did the comparisons between BDP/FF/G and BDP/FF in terms of coprimary and key secondary efficacy endpoints according to the following prespecified hierarchical testing procedure: (1) predose FEV_1 at week 26, and rate of moderate and severe exacerbations over 52 weeks; (2) peak FEV_1 at week 26; (3) average morning PEF over the first 26 weeks of treatment; and (4) rate of severe exacerbations over 52 weeks in the pooled analysis.

As a first step, we had to show superiority of BDP/FF/G over BDP/FF for both coprimary endpoints. Thereafter, we could only make confirmatory claims when superiority had been shown in all preceding steps. We did not apply multiplicity adjustments to the other secondary endpoints, and so these p values are descriptive, as are the comparisons between BDP/FF/G and BDP/FF plus tiotropium.

We analysed predose and peak FEV_1 at week 26 and average morning PEF over 26 weeks using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, and country as fixed effects, and baseline value and baseline by visit interaction as covariates (visit effect being replaced by between-visit period effect for PEF), and present these data as adjusted means (ie, least squares means) and adjusted mean differences between treatments, with associated 95% CIs and p values. We assumed an unstructured covariance matrix. We analysed the number of asthma exacerbations over the 52-week treatment period using a negative binomial model including treatment, country, and number of exacerbations (1 or >1) in the previous year as fixed effects, and log-time on

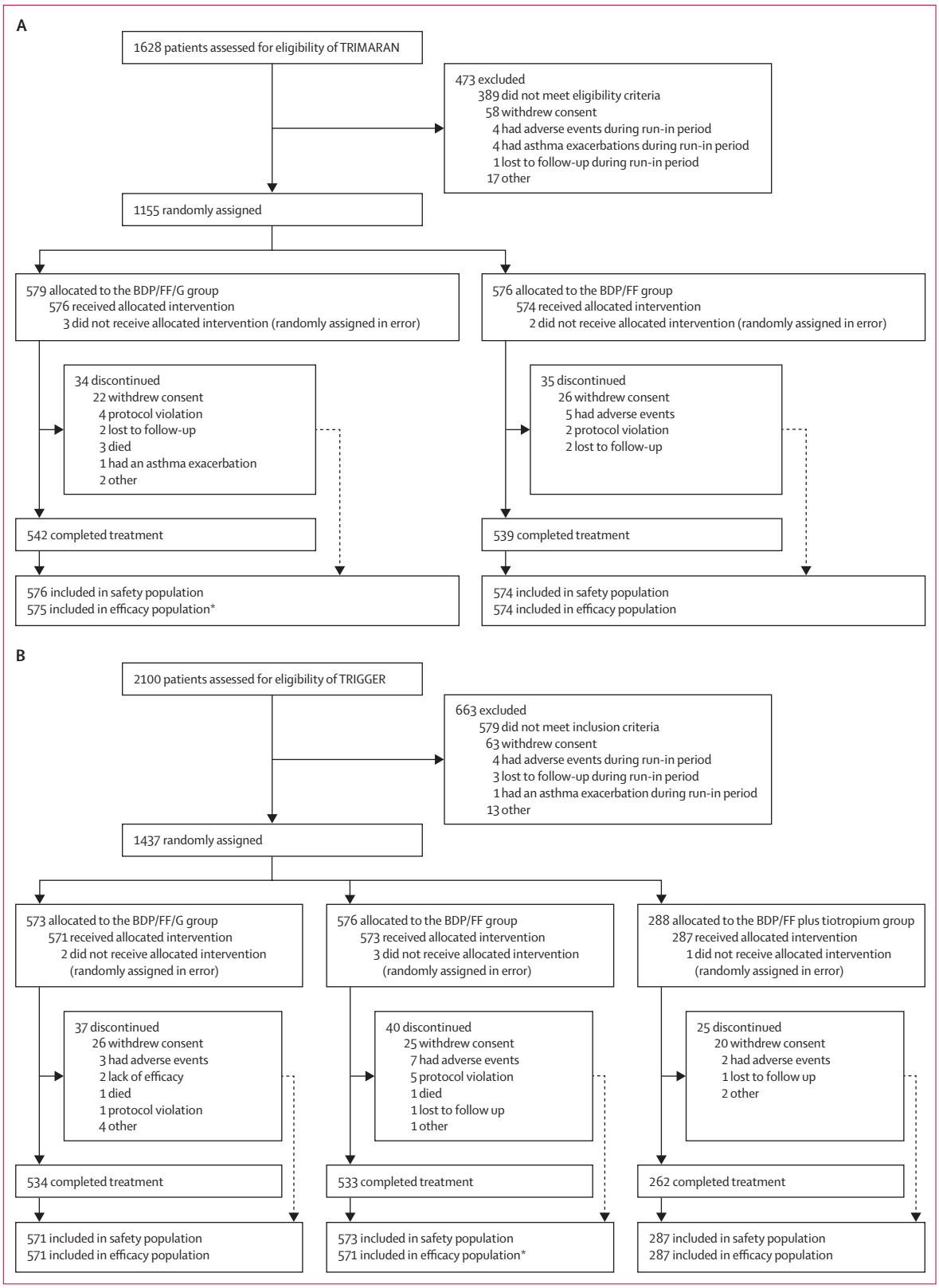


Figure 1: **Study profile for TRIMARAN (A) and TRIGGER (B)**
BDP=beclometasone dipropionate. FF=formoterol fumarate. G=glycopyrronium. TRIGGER=Triple in Asthma High Strength Versus ICS/LABA HS and Tiotropium. TRIMARAN=Triple in Asthma With Uncontrolled Patients on Medium Strength of ICS + LABA study. *One patient in TRIMARAN and two patients in TRIGGER were randomly assigned in error (did not meet inclusion criteria), and received the first dose of study medication before being discontinued from the study without providing any efficacy data after the baseline assessment.

study as offset, and present these data as adjusted rate of asthma exacerbations, and adjusted RRs with 95% CIs and p values.

We analysed most of the secondary efficacy endpoints using similar methods to the coprimary and key secondary endpoints. We compared FEV_1 response and ACQ-7

	TRIMARAN		TRIGGER		
	BDP/FF/G group (n=576)	BDP/FF group (n=574)	BDP/FF/G group (n=571)	BDP/FF group (n=573)	BDP/FF plus tiotropium group (n=287)
Sex					
Male	221 (38%)	221 (39%)	212 (37%)	245 (43%)	103 (36%)
Female	355 (62%)	353 (61%)	359 (63%)	328 (57%)	184 (64%)
Race					
Asian	0	0	2 (<1%)	0	0
White	575 (100%)	574 (100%)	569 (>99%)	573 (100%)	286 (>99%)
Other	1 (<1%)	0	0	0	1 (<1%)
Age, years	52·6 (12·4)	52·5 (12·2)	53·1 (12·2)	54·0 (11·9)	51·6 (12·3)
Body-mass index, kg/m²	28·0 (4·81)	27·9 (5·07)	28·4 (5·14)	28·7 (5·87)	28·5 (5·21)
≥30	173 (30%)	170 (30%)	204 (36%)	205 (36%)	102 (36%)
Smoking status					
Former smoker	92 (16%)	76 (13%)	83 (15%)	80 (14%)	42 (15%)
Non-smoker	484 (84%)	498 (87%)	488 (85%)	493 (86%)	245 (85%)
Smoking history (pack-years)*	4·1 (2·4)	4·8 (2·5)	4·9 (2·4)	4·8 (2·3)	5·6 (2·6)
Duration of asthma, years	24·8 (12·9)	25·2 (12·8)	24·8 (12·2)	26·2 (12·6)	24·5 (12·4)
Exacerbations in the previous year					
1	474 (82%)	473 (82%)	439 (77%)	452 (79%)	229 (80%)
>1	102 (18%)	101 (18%)	132 (23%)	121 (21%)	58 (20%)
Before-salbutamol FEV_1, L†	1·7 (0·56)	1·7 (0·56)	1·6 (0·56)	1·6 (0·57)	1·6 (0·59)
Before-salbutamol FEV_1, % of predicted normal value†	55·2 (12·3)	55·7 (12·0)	51·9 (13·5)	51·8 (13·5)	52·1 (13·2)
Range	17–79	20–79	15–79	16–79	22–79
Reversibility, %	32·5 (24·72)	30·8 (20·53)	33·2 (20·21)	33·9 (21·87)	34·9 (26·99)
Range	12·1–419·2	12·1–163·0	12·1–147·9	12·0–152·5	12·2–234·5
Before-salbutamol FEV_1/FVC ratio†	0·60 (0·12)	0·61 (0·12)	0·59 (0·12)	0·59 (0·13)	0·59 (0·12)
Range	0·26–0·96	0·27–0·94	0·23–0·95	0·27–0·94	0·29–0·88
After-salbutamol FEV_1/FVC ratio‡	0·65 (0·11)	0·65 (0·11)	0·63 (0·12)§	0·63 (0·12)	0·63 (0·12)
Range	0·31–0·97	0·32–0·91	0·27–0·93	0·26–0·92	0·34–0·96
Previous inhaled corticosteroid or long-acting β_2-agonist therapy¶					
Inhaled corticosteroid	61 (11%)	72 (13%)	153 (27%)	144 (25%)	67 (23%)
Inhaled corticosteroid plus long-acting β_2 agonist	531 (92%)	515 (90%)	525 (92%)	520 (91%)	267 (93%)
Long-acting β_2 agonist	55 (10%)	66 (11%)	74 (13%)	71 (12%)	35 (12%)
ACQ-7 score‖	2·3 (0·52)	2·3 (0·53)	2·5 (0·53)§	2·4 (0·54)**	2·4 (0·53)
Peak expiratory flow, L/min††					
Morning	297 (107·5)‡‡	299 (106·0)‡‡	279 (104·2)§§	275 (101·2)¶¶	287 (106·4)
Evening	310 (108·2)‖‖	314 (107·6)‡‡	292 (104·7)¶¶	287 (103·1)‖‖	299 (107·6)
Daily asthma symptom scores††	0·76 (0·49)	0·77 (0·50)	0·81 (0·52)	0·83 (0·51)	0·84 (0·50)
Percentage of asthma symptom-free days††	9·9% (22·78)	11·0% (24·19)	10·2% (23·09)	9·5% (23·14)	10·8% (26·58)
Percentage of asthma control days††	9·1% (21·45)	10·4% (23·48)	9·9% (22·66)	8·9% (22·24)	10·1% (26·22)

Data are n (%), mean (SD), or range. TRIMARAN=Triple in Asthma With Uncontrolled Patients on Medium Strength of ICS + LABA study. TRIGGER=Triple in Asthma High Strength Versus ICS/LABA HS and Tiotropium study. BDP=beclometasone dipropionate. FF=formoterol fumarate. G=glycopyrronium. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. ACQ-7=Asthma Control Questionnaire-7. *Calculated in former smokers only. †Measured at screening before administration of salbutamol. ‡Measured at screening 10–15 min after administration of salbutamol. §Data available for 570 patients. ¶Calculated from asthma therapies being given before study entry (might add up to more than 100% because of changes in asthma therapy in the 3 months before study or multiple therapies reported for the same patient). ‖Measured at the randomisation visit in the intention-to-treat population. **Data available for 568 patients. ††Measured during the run-in period in the intention-to-treat population; the intention-to-treat populations were TRIMARAN n=575 in the BDP/FF/G group, n=574 in the BDP/FF group; TRIGGER n=571 in the BDP/FF/G group, n=571 in the BDP/FF group, and n=287 in the BDP/FF plus tiotropium group. ‡‡Data available for 569 patients. §§Data available for 564 patients. ¶¶Data available for 565 patients. ‖‖Data available for 566 patients.

Table 1: **Baseline characteristics of the safety population**

response between treatment groups using a logistic model including treatment and country as factors and the respective baseline values for these measures as a covariate. We analysed time to first exacerbation using a Cox proportional hazards model including treatment, country, and number of exacerbations (1 or >1) in the previous year as factors. Estimation of the logistic and Cox proportional hazards models was based on events per variable values well above the suggested thresholds, confirming the reliability of the study results.[13–15] All analyses reported in this Article were prespecified in the statistical analysis plan.

Additionally, we did a number needed to treat analysis for the number of patients who would need to be treated with BDP/FF/G rather than BDP/FF for 1 year to prevent one moderate or severe exacerbation, one moderate exacerbation, or one severe exacerbation.

We analysed all efficacy endpoints in the intention-to-treat population, defined as all patients randomly assigned to treatment who received at least one dose of the study treatment and with at least one available evaluation of efficacy (primary or secondary efficacy variables) after baseline. Safety data were analysed in the safety population, which comprised all patients randomly assigned to treatment who received at least one dose of study treatment. An independent Data Safety Monitoring Board composed of three independent clinicians and one independent biostatistician provided a quarterly independent scrutiny of the study.

We did all analyses presented in this manuscript using SAS software, version 9.4. The studies are registered with ClinicalTrials.gov: TRIMARAN, NCT02676076; TRIGGER, NCT02676089.

Role of the funding source

The funder of the study had a role in the study design and data analysis, oversaw study conduct, and was responsible for study report preparation. All authors had full access to all data and the corresponding author had final responsibility for the decision to submit for publication.

Results

TRIMARAN was undertaken between Feb 17, 2016, and May 17, 2018, during which time 1628 patients were assessed for eligibility, of whom 1155 patients were randomly assigned to the BDP/FF/G group (n=579) or the BDP/FF group (n=576); 542 (94%) patients in the BDP/FF/G group and 539 (94%) in the BDP/FF group completed treatment (figure 1A). TRIGGER was undertaken between April 6, 2016, and May 28, 2018, during which time 2100 patients were assessed for eligibility, of whom 1437 were randomly assigned to the BDP/FF/G group (n=573), BDP/FF group (n=576), or BDP/FF plus tiotropium group (n=288); 534 (93%) patients in the BDP/FF/G group, 533 (93%) in the BDP/FF group, and 262 (91%) in the BDP/FF plus tiotropium group completed treatment (figure 1B). Baseline demographic characteristics were similar across the five groups (table 1). Patients in TRIGGER had a slightly worse lung function (as measured by before-salbutamol FEV_1) and higher reversibility than those in TRIMARAN.

The coprimary endpoint of change in predose FEV_1 at week 26 was met in both studies, with significant differences between the BDP/FF/G and BDP/FF groups of 57 mL (95% CI 15 to 99; p=0·0080) in TRIMARAN and 73 mL (26 to 120; p=0·0025) in TRIGGER (figure 2A;

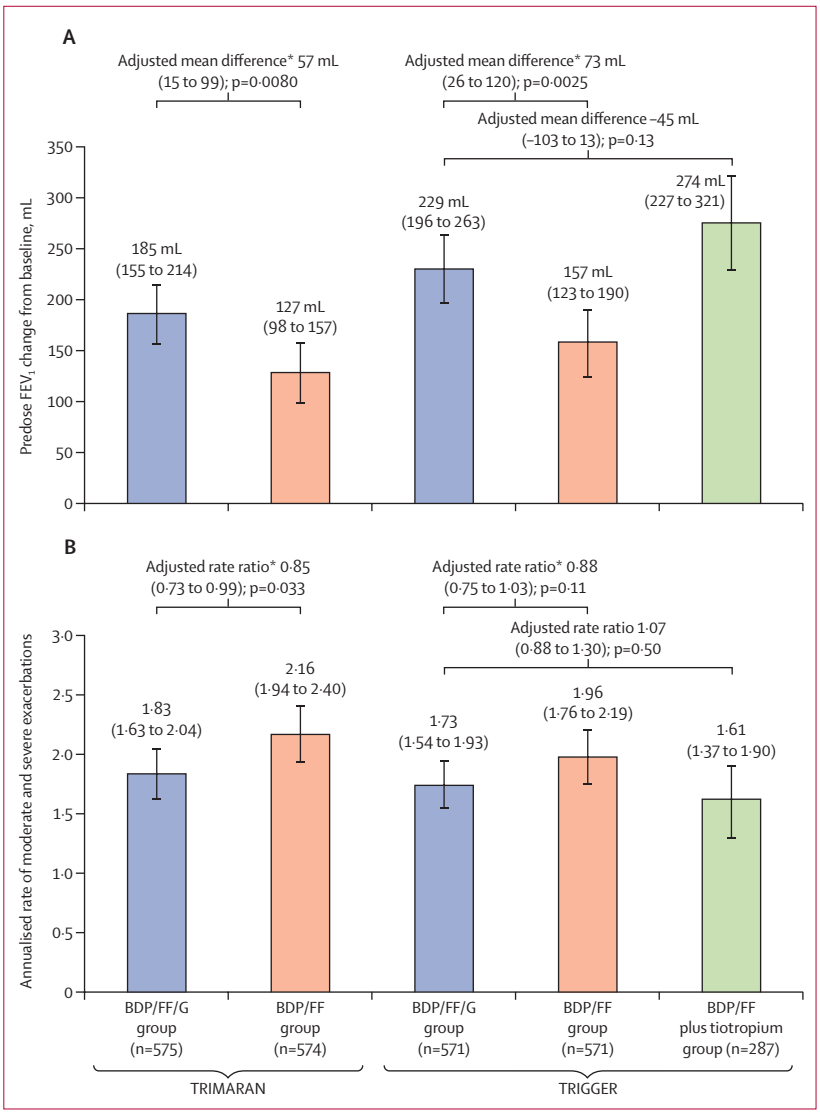
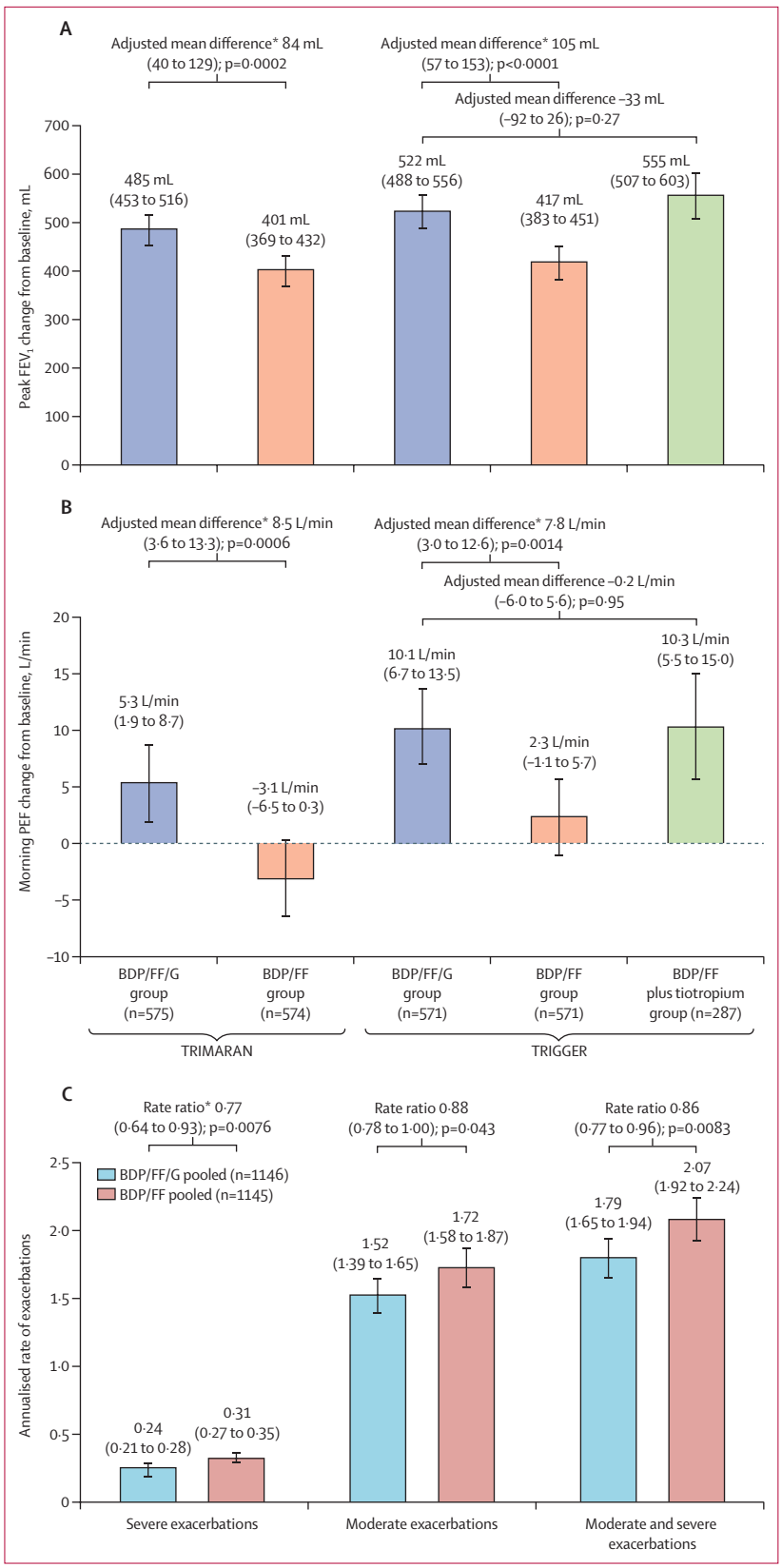


Figure 2: **Coprimary endpoints**

(A) Predose FEV_1 change from baseline to week 26. (B) Annualised rate of moderate and severe exacerbations. Results are from the intention-to-treat population. In panel A, data are adjusted means with 95% CIs shown as error bars and in parentheses, and adjusted mean differences with 95% CIs in parentheses. In panel B, data are adjusted exacerbation rates per patient per year with 95% CIs shown as error bars and in parentheses, and adjusted rate ratios with 95% CIs in parentheses. BDP=beclometasone dipropionate. FEV_1=forced expiratory volume in 1 s. FF=formoterol fumarate. G=glycopyrronium. TRIGGER=Triple in Asthma High Strength Versus ICS/LABA HS and Tiotropium study. TRIMARAN=Triple in Asthma With Uncontrolled Patients on Medium Strength of ICS + LABA study. *Coprimary endpoints.



absolute values are in the appendix [pp 19–20]). In TRIGGER, the predose FEV_1 at week 26 was not different between the BDP/FF/G and the BDP/FF plus tiotropium groups (–45 mL, –103 to 13; p=0·13). The rate of moderate and severe exacerbations in the BDP/FF/G group was significantly reduced by 15% compared with the BDP/FF group in TRIMARAN (RR 0·85, 95% CI 0·73–0·99; p=0·033; figure 2B; appendix pp 19–20). The reduction in TRIGGER was 12% but was not significant (0·88, 95% CI 0·75–1·03; p=0·11). No difference was seen between the BDP/FF/G group and BDP/FF plus tiotropium group in TRIGGER (1·07, 0·88–1·30; p=0·50). Since this coprimary endpoint was not significantly reduced in TRIGGER, in accordance with the prespecified hierarchical testing procedure, no formal claim of superiority can be made, either in this study or for the key secondary endpoint of rate of severe exacerbations (pooled analysis). Therefore, the corresponding p values should be interpreted descriptively.

For the key secondary endpoints of peak FEV_1 at week 26 and average morning PEF over 26 weeks, the change from baseline was higher in the BDP/FF/G group than in the BDP/FF group in both studies (p=0·0002 for peak FEV_1 and p=0·0006 for morning PEF in TRIMARAN, and p<0·0001 for peak FEV_1 and p=0·0014 for morning PEF in TRIGGER), with no differences between the BDP/FF/G group and the BDP/FF plus tiotropium group in TRIGGER (p=0·27 for peak FEV_1 and p=0·95 for morning PEF; figure 3A and 3B; absolute values are in the appendix [pp 19–20]). In the pooled analysis, patients in the BDP/FF/G groups had a reduced rate of severe exacerbations compared with those in the BDP/FF groups (23%; p=0·0076; figure 3C; appendix pp 19–20).

For the other secondary endpoints, patients in the BDP/FF/G group had a reduced rate of moderate exacerbations (12%; p=0·043), and combined moderate and severe exacerbations (14%; p=0·0083) compared with those in the BDP/FF group (pooled analysis, figure 3C; appendix pp 19–20). In the individual studies, the same trend for the reduced rate of exacerbations in the BDP/FF/G group was observed for moderate exacerbations (p=0·086 in TRIMARAN and p=0·25 in TRIGGER; appendix p 6).

Figure 3: **Key secondary endpoints**
(A) Peak FEV_1 change from baseline at week 26. (B) Average morning PEF change from baseline over 26 weeks. (C) Annualised rate of severe, moderate, and moderate and severe exacerbations (pooled analysis). Results are from the intention-to-treat population. Data in panels A and B are adjusted means with 95% CI shown as error bars and in parentheses, and adjusted mean differences with 95% CIs in parentheses. Data in panel C are adjusted annualised rate of exacerbations per patient, with 95% CIs as error bars and in parentheses, and adjusted rate ratios with 95% CIs in parentheses. BDP=beclometasone dipropionate. FEV_1=forced expiratory volume in 1 s. FF=formoterol fumarate. G=glycopyrronium. PEF=peak expiratory flow. TRIGGER=Triple in Asthma High Strength Versus ICS/LABA HS and Tiotropium study. TRIMARAN=Triple in Asthma With Uncontrolled Patients on Medium Strength of ICS + LABA study. *Key secondary endpoints.

The time to first moderate or severe exacerbation was longer in the BDP/FF/G group than in the BDP/FF group in both TRIMARAN (hazard ratio [HR] 0·84, 95% CI 0·73–0·98; p=0·022; figure 4A) and TRIGGER (0·80, 0·69–0·93; p=0·0035), and was similar for the BDP/FF/G and BDP/FF plus tiotropium groups in TRIGGER (0·97, 0·81–1·18; p=0·78; figure 4B). Likewise, the time to first moderate exacerbation was longer in the BDP/FF/G group than in the BDP/FF group in both studies (TRIMARAN HR 0·86, 95% CI 0·73–1·0; p=0·048; TRIGGER 0·81, 0·69–0·95; p=0·0089) and was similar for the BDP/FF/G group and BDP/FF plus tiotropium group in TRIGGER (0·89, 0·73–1·09; p=0·27). In the pooled analysis, time to first moderate or severe exacerbation was longer in the BDP/FF/G group than in the BDP/FF group (HR 0·82, 95% CI 0·74–0·91; p=0·0002), as was time to first moderate exacerbation (0·83, 0·74–0·93; p=0·0010), and time to first severe exacerbation (0·79, 0·66–0·95; p=0·011; figure 4C). Median times to first exacerbation are in the appendix (p 21). In the pooled analyses, the numbers needed to treat for 1 year with BDP/FF/G rather than BDP/FF to prevent one moderate or severe exacerbation was three, to prevent one severe exacerbation was 14, and to prevent one moderate exacerbation was five.

The results for the FEV_1 secondary endpoints in TRIMARAN were consistent with the coprimary and key secondary FEV_1 endpoints, with improvements seen in the BDP/FF/G group compared with the BDP/FF group in predose FEV_1 at most visits, peak FEV_1 and FEV_1 $AUC_{0–3h}$ at all visits, and FEV_1 response at week 26 (appendix pp 7–9, 22–26). In TRIGGER, improvements were seen in the BDP/FF/G group for predose FEV_1, peak FEV_1, and FEV_1 $AUC_{0–3h}$ at all visits, and FEV_1 response at weeks 26 and 52 compared with the BDP/FF group, with no differences between the BDP/FF/G group and BDP/FF plus tiotropium group (appendix pp 7–9, 22–26).

All PEF-based secondary endpoints improved in the BDP/FF/G group compared with the BDP/FF group in both studies (appendix pp 10–12). We saw no clinically relevant differences between the BDP/FF/G group and the BDP/FF or BDP/FF plus tiotropium group in TRIGGER in terms of ACQ-7 total score or response (appendix pp 13, 22–26), or in the rescue medication use endpoints (appendix pp 14–15, 22–26). Notably, we saw an improvement from baseline in asthma symptoms, asthma control, and rescue medication use in all five groups over the duration of the studies, with similar improvements seen in TRIMARAN for both the BDP/FF/G and BDP/FF groups and an improvement seen in TRIGGER for the BDP/FF/G group compared with the BDP/FF group in terms of asthma symptom-free days and asthma control days from week 13 onwards (appendix pp 16–18, 22–26).

Overall, a similar proportion of patients had adverse events in all five groups (table 2). Most events were mild or moderate in severity, and few were considered to be related to treatment. The most common adverse event in all groups was asthma exacerbation, the occurrence of which was lower with triple therapy than with BDP/FF in both studies. Four patients had treatment-related serious adverse events: atrial fibrillation in a patient given

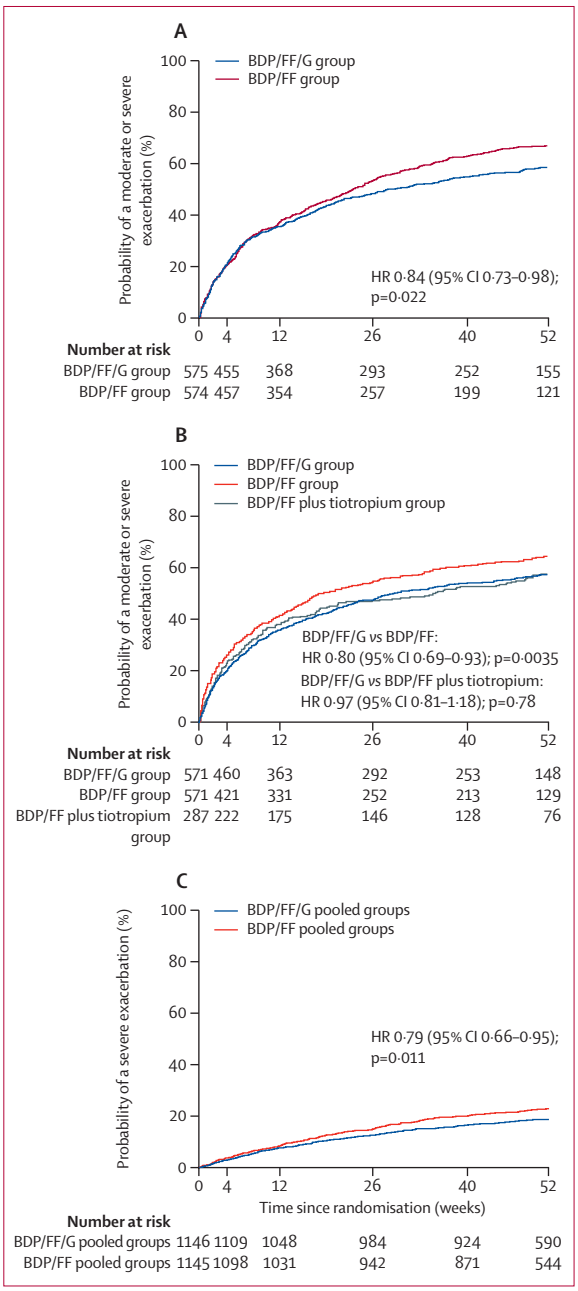


Figure 4: **Time to first moderate or severe exacerbation in TRIMARAN (A) and TRIGGER (B; intention-to-treat populations), and pooled analysis of time to first severe exacerbation (C)**

BDP=beclometasone dipropionate; FF=formoterol fumarate. G=glycopyrronium. HR=hazard ratio. TRIGGER=Triple in Asthma High Strength Versus ICS/LABA HS and Tiotropium study. TRIMARAN=Triple in Asthma With Uncontrolled Patients on Medium Strength of ICS + LABA study.

	TRIMARAN		TRIGGER		
	BDP/FF/G group (n=576)	BDP/FF group (n=574)	BDP/FF/G group (n=571)	BDP/FF group (n=573)	BDP/FF plus tiotropium (n=287)
Adverse events	431 (75%)	455 (79%)	410 (72%)	443 (77%)	210 (73%)
Asthma exacerbation	337 (59%)	379 (66%)	323 (57%)	364 (64%)	162 (56%)
Nasopharyngitis	71 (12%)	79 (14%)	46 (8%)	63 (11%)	34 (12%)
Headache	38 (7%)	46 (8%)	25 (4%)	27 (5%)	13 (5%)
Respiratory tract infection viral	15 (3%)	26 (5%)	17 (3%)	28 (5%)	14 (5%)
Bronchitis	18 (3%)	22 (4%)	18 (3%)	18 (3%)	12 (4%)
Pharyngitis	12 (2%)	16 (3%)	10 (2%)	12 (2%)	4 (1%)
Viral upper respiratory tract infection	12 (2%)	16 (3%)	4 (1%)	8 (1%)	3 (1%)
Hypertension	16 (3%)	9 (2%)	10 (2%)	7 (1%)	7 (2%)
Upper respiratory tract infection	11 (2%)	10 (2%)	9 (2%)	15 (3%)	7 (2%)
Treatment-related adverse events	22 (4%)	19 (3%)	28 (5%)	24 (4%)	16 (6%)
Dysphonia	9 (2%)	1 (<1%)	10 (2%)	8 (1%)	2 (1%)
Cough	1 (<1%)	0	0	1 (<1%)	2 (1%)
Oral candidiasis	1 (<1%)	4 (1%)	3 (1%)	3 (1%)	3 (1%)
Dry mouth	4 (1%)	0	3 (1%)	1 (<1%)	2 (1%)
Electrocardiogram QT prolonged	1 (<1%)	3 (1%)	1 (<1%)	1 (<1%)	0
Muscle spasms	0	0	3 (1%)	3 (1%)	0
Serious adverse events	28 (5%)	22 (4%)	28 (5%)	33 (6%)	15 (5%)
Asthma exacerbation	7 (1%)	4 (1%)	11 (2%)	11 (2%)	6 (2%)
Pneumonia	0	3 (1%)	3 (1%)	5 (1%)	2 (1%)
Treatment-related serious adverse events	1 (<1%)	0	1 (<1%)	2 (<1%)	0
Severe adverse events	34 (6%)	38 (7%)	35 (6%)	55 (10%)	13 (5%)
Major adverse cardiovascular events	4 (1%)	1 (<1%)	3 (1%)	3 (1%)	0
Adverse events leading to study treatment discontinuation	4 (1%)	5 (1%)	4 (1%)	8 (1%)	2 (1%)
Adverse events leading to death	3 (1%)	0	1 (<1%)	1 (<1%)	0

Data are n (%). Preferred terms are listed when occurrence was 2·5% or higher in any treatment group for adverse events and when occurrence was 0·5% or higher in any group for serious adverse events and treatment-related adverse events. TRIMARAN=Triple in Asthma With Uncontrolled Patients on Medium Strength of ICS + LABA study. TRIGGER=Triple in Asthma High Strength Versus ICS/LABA HS and Tiotropium study. BDP=beclometasone dipropionate. FF=formoterol fumarate. G=glycopyrronium.

Table 2: **Treatment-emergent adverse events and serious adverse events in the safety population**

BDP/FF/G in TRIMARAN and who had hypertension; oesophageal candidiasis in a patient given BDP/FF/G in TRIGGER that resolved after therapy; pneumonia in a patient given BDP/FF in TRIGGER that resolved after therapy; and angle closure glaucoma in a patient given BDP/FF in TRIGGER that had not resolved by the time they completed the study. All these treatment-related serious adverse events were moderate in severity and did not require a change in study treatment. Five patients in TRIMARAN and six in TRIGGER had major adverse cardiovascular events, although none of the events in either study were considered as related to study treatment (table 2; appendix p 27). Three patients in the BDP/FF/G group in TRIMARAN had an adverse event or events leading to death (one patient with left ventricular failure, one with acute pancreatitis, and one with gastric cancer and acute cardiac failure). In TRIGGER, two patients had an adverse event leading to death, one in the BDP/FF/G group (cerebral haemorrhage) and one in the BDP/FF group (sudden death). None of the deaths in either study was considered as related to study treatment.

Discussion

TRIMARAN and TRIGGER are the first studies to assess the efficacy and safety of single-inhaler triple therapy in the management of asthma. The lung function (predose FEV_1) coprimary endpoint was met in both studies, with a slightly larger effect size in TRIGGER. Furthermore, the rate of moderate and severe exacerbations coprimary endpoint was met in TRIMARAN, with a significant 15% reduction for BDP/FF/G versus BDP/FF, and although a similar effect size was seen in TRIGGER, with a 12% reduction, it was not significant. In the key secondary endpoint analysis of data pooled from the two studies, BDP/FF/G reduced the rate of the more clinically relevant severe exacerbations by 23%. Furthermore, for the other secondary exacerbation endpoints, in the pooled analyses, BDP/FF/G reduced the rate of moderate exacerbations by 12% and combined moderate and severe exacerbations by 14% and the time to first moderate or severe exacerbation, first moderate exacerbation, and first severe exacerbation was longer with BDP/FF/G than with BDP/FF. Overall, these exacerbation data therefore suggest that BDP/FF/G prevents these events to a greater degree than BDP/FF.

Although care should be taken when comparing studies, the 23% reduction in the rate of severe exacerbations along with the 21% reduction in risk (time to first severe exacerbation HR 0·79) are consistent with the results of two long-term studies[3] in which tiotropium was added as a free combination to any inhaled corticosteroid and long-acting β_2 agonist (with a 20% rate reduction and a 21% risk reduction for tiotropium *vs* placebo on severe exacerbations).[3] Importantly, however, TRIMARAN and TRIGGER had less strict exclusion criteria than these studies and so enrolled broader patient populations. Specifically, the tiotropium studies were limited to a subgroup of patients with post-bronchodilator FEV_1 of 80% or less and FEV_1 to forced vital capacity (FVC) ratio of 70% or less,[3] compared with pre-bronchodilator FEV_1 of less than 80% in TRIMARAN and TRIGGER and no limitation on the FEV_1 to FVC ratio. Another key difference is that in the long-term tiotropium studies triple therapy was administered via multiple inhalers and they did not supply or monitor the daily concomitant use of inhaled corticosteroids or long-acting β_2 agonists.[3] The use of single-inhaler triple therapy in TRIMARAN and TRIGGER ensured the delivery of all three components and should potentially optimise treatment adherence and persistence. However, we acknowledge that in TRIGGER for FEV_1 and moderate-to-severe exacerbations, patients in the BDP/FF plus tiotropium group

(treatment administered open-label via separate inhalers) had non-significant, numerically greater improvements than those in the single inhaler (double-bind) BDP/FF/G group.

Most exacerbations in TRIMARAN and TRIGGER were moderate in severity, and hence were predominantly self-managed by patients. To our knowledge, this is the first study to assess the effect of inhaled therapy on such exacerbations by applying the American Thoracic Society and European Respiratory Society joint statement definition.[12] Although we saw a consistent trend in favour of triple therapy, we saw no significant treatment effect on the rate of moderate exacerbations in the individual studies, yet the time to first moderate exacerbation was longer in the BDP/FF/G group than in the BDP/FF group, both in the pooled analysis and in each individual study. The reasons for this finding are unclear, although it might be due to the variability of symptoms in asthma (the worsening of which defines a moderate exacerbation episode), so making precise assessment of this outcome is a challenge. Additionally, neither study was powered to assess the effect of treatment on moderate exacerbations. The effect of triple therapy on the objective lung function endpoints of FEV_1 and PEF was consistent, within and between studies, with both BDP/FF/G doses improving these endpoints compared with BDP/FF for the duration of the studies.

Asthma control, symptom endpoints, and rescue medication use improved from baseline with all treatments. In TRIMARAN, both the BDP/FF/G and BDP/FF groups had similar improvements in symptom-free days and asthma control days, whereas in TRIGGER we saw a separation between the BDP/FF/G and BDP/FF groups, particularly over the second half of the study. These results are similar to those of the previous tiotropium studies, in which tiotropium administered separately to an inhaled corticosteroid plus a long-acting β_2 agonist resulted in consistent improvements in lung function, but less consistent improvements in ACQ-7 score,[3,4] and with a dissociation in effect between severe exacerbations and asthma control.[3] For the populations that we recruited (who had uncontrolled disease despite medium-dose or high-dose inhaled corticosteroid plus a long-acting β_2 agonist), the prevention of future exacerbations (especially severe exacerbations) is arguably the more important treatment goal.

We acknowledge that the improvement in asthma control and decrease in symptoms in all groups, including in those patients who continued BDP/FF therapy from the run-in period across the 52-week trial period, suggests a clinical trial effect in both studies, which can occur at least in part because of improved adherence. This clinical trial effect also appeared to affect severe exacerbations, with a low rate observed during the trial (0·31 in the pooled BDP/FF group), despite all patients being required to have a history of at least one exacerbation in the previous year requiring treatment with systemic corticosteroids, emergency department visit, or inpatient admission to hospital. In this context, the much lower rate of severe exacerbations observed during the studies than reported in historical data (ie, the patient's history of at least one exacerbation in the previous year) is similar to what has been found in several clinical trials that recruited similar populations,[16–20] potentially also reflecting increased adherence to therapy or improved care as a result of clinical trial participation. Importantly, when TRIMARAN and TRIGGER were designed, the rate of these more clinically relevant exacerbations was anticipated to be lower than that of moderate exacerbations, which is why the only prespecified analysis of rate of severe exacerbations was in the pooled population. Therefore, despite this low rate, a notable 23% reduction in severe exacerbations was seen with BDP/FF/G compared with BDP/FF.

Interpreting the clinical relevance of results when assessing the additive effect of a therapy on top of therapies that are known to be effective is challenging. The differences that we observed between the BDP/FF/G group and BDP/FF group for some of the endpoints could be argued to be numerically small (with the differences in predose FEV_1 at week 26 and morning PEF over 26 weeks being lower than those included in the powering assumptions), and indicate only a moderate effect of triple therapy. However, the populations that we studied have few treatment options available, and so even moderate incremental improvements can be valuable. Uncontrolled asthma is associated with a substantial (and increasing) economic and health burden,[21] especially because of exacerbations, and so additional therapies are needed. In this context, a key finding is that all treatments were similarly well tolerated. This finding is again consistent with the results of several other triple therapy studies in asthma, in which the addition of a long-acting muscarinic antagonist did not affect the overall adverse event profile.[3–5,22]

Given the broad inclusion criteria of TRIMARAN and TRIGGER, the results should be generalisable to adults with asthma that is uncontrolled by an inhaled corticosteroid plus a long-acting β_2 agonist, although we recognise that the recruited populations were predominantly of white race. The Global Initiative for Asthma report already includes recommendations for add-on long-acting muscarinic antagonist use for patients whose asthma is not well controlled on inhaled corticosteroid plus long-acting β_2-agonist therapy.[1] For such patients, escalation of therapy to inhaled triple therapy has been shown to be cost-effective compared with an inhaled corticosteroid plus a long-acting β_2 agonist,[23–27] and is likely to be cost-effective compared with the addition of systemic biological therapy.[25] Since BDP/FF/G delivers the three molecules via one device, and based on the magnitude of reduction in the annual rate of severe asthma exacerbations observed in the prespecified pooled analysis of TRIMARAN and TRIGGER, we expect that BDP/FF/G

will provide an attractive treatment option and fulfil a substantial unmet need at both the individual-patient and the overall health system level.

Taken together, these data indicate that in adults with uncontrolled asthma treated with a medium-to-high dose of inhaled corticosteroid plus a long-acting β_2 agonist the addition of a long-acting muscarinic antagonist in a single inhaler BDP/FF/G triple therapy mainly improves lung function with an associated positive effect on severe exacerbations and some benefit in terms of asthma symptoms and control.

Contributors

The studies were conceived and designed by JCV, AP, MK, SP, and GWC. Data were acquired by JCV, PK, PP, and GWC, analysed by AV, and interpreted by all authors. MK and GG contributed to the medical data integrity. SC and FZ contributed to the conduct of the studies. SC and FZ were Chiesi Farmaceutici clinical operation project managers, AV was a Chiesi Farmaceutici statistician, SP was head of Chiesi Farmaceutici global clinical development, and GG was the Clinical Program Leader for BDP/FF/G. JCV was the principal investigator for TRIMARAN and GWC was the principal investigator for TRIGGER. The manuscript was revised for intellectual content and approved for publication by all authors.

Declaration of interests

JCV reports personal fees from Chiesi Farmaceutici during the conduct of the study. JCV has previously lectured and received honoraria from AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer Ingelheim, Chiesi, Essex/Schering-Plough, GlaxoSmithKline, Janssen-Cilag, Leti, MEDA, Merck, MSD, Mundipharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sanofi/Regeneron, Sandoz-Hexal, Stallergens, TEVA, UCB/Schwarz-Pharma, and Zydus/Cadila; participated in advisory boards and received honoraria from Avontec, Boehringer Ingelheim, Chiesi, Essex/Schering-Plough, GlaxoSmithKline, Janssen-Cilag, MEDA, MSD, Mundipharma, Novartis, Paul-Ehrlich Institut, Regeneron, Revotar, Roche, Sanofi-Aventis, Sanofi/Regeneron, Sandoz-Hexal, TEVA, and UCB/Schwarz-Pharma; received funding for research from Deutsche Forschungsgesellschaft, Land Mecklenburg-Vorpommern, GlaxoSmithKline, and MSD; and has advised the Bemeinsame Bundesausschuss (GBA). PK reports personal fees from Chiesi, Novartis, AstraZeneca, Boehringer Ingelheim, Berlin Chemie Menarini, Adamed, Polpharma, and Lekam outside of the submitted work. PP reports grants and personal fees from AstraZeneca and Chiesi, and personal fees from GlaxoSmithKline, Menarini, Mundipharma, Novartis, and Sanofi outside of the submitted work. AP reports grants, personal fees, non-financial support, payment for advisory board membership, payment for consultancy, payment for lectures, grants for research, and travel expenses reimbursement from Chiesi Farmaceutici, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Mundipharma, and TEVA; and personal fees and non-financial support from Menarini, Novartis, Zambon, and Sanofi outside of the submitted work. DS reports personal fees from Chiesi Farmaceutici during the conduct of the study and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Cipla, Genentech, GlaxoSmithKline, Glenmark, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Therevance, and Verona outside of the submitted work. SC, FZ, AV, MK, and SP are employees of Chiesi Farmaceutici. GG is an employee of Chiesi USA. GWC reports personal fees from A Menarini, Alk-Abello, Allergy Therapeutics, AstraZeneca-Medimmune, Boehringer Ingelheim, Chiesi Farmaceutici, Genentech, Guidotti-Malesci, GlaxoSmithKline, Hal Allergy, MSD, Mundipharma, Novartis, Orion, Sanofi-Aventis, Sanofi Genzyme/Regeneron, Stallergenes-Greer, Uriach Pharma, TEVA, Valeas, and ViforPharma outside of the submitted work.

Data sharing

Chiesi Farmaceutici is committed to conducting legitimate research and sharing with qualified scientific and medical researchers the anonymised patient-level and study-level data, clinical protocol, and full clinical study report of Chiesi Farmaceutici sponsored interventional clinical trials in patients for medicines and indications approved by the European Medicines Agency or the US Food and Drug Administration, or both, after Jan 1, 2015, following the approval of any received research proposal and the signature of a Data Sharing Agreement. Chiesi Farmaceutici provides access to clinical trial information consistently with the principle of safeguarding commercially confidential information and patient privacy. Other information on Chiesi's data sharing commitment, access, and research request approval process are available in the Clinical Trial Transparency section at http://www.chiesi.com/en/research-and-development/.

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