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Title

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

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Abstract

Background

No studies have evaluated the efficacy of single-inhaler triple therapy in asthma. These two studies compared the single inhaler extrafine combination of beclometasone dipropionate (inhaled corticosteroid), formoterol fumarate (long-acting β_2 -agonist), and glycopyrronium (long-acting muscarinic antagonist; BDP/FF/G) versus BDP/FF.

Methods

Two randomised, parallel-group, double-blind, active-controlled studies. Eligible patients were adults with uncontrolled asthma, history of ≥ 1 exacerbation, and previously treated with inhaled corticosteroid (TRIMARAN, medium-dose; TRIGGER, high-dose) plus long-acting β_2 -agonist. After two weeks receiving BDP/FF (TRIMARAN, 100/6 μ g; TRIGGER, 200/6 μ g), patients were randomised (stratifying by country) to 52 weeks with BDP/FF/G 100/6/10 μ g or BDP/FF 100/6 μ g, two inhalations twice-daily in TRIMARAN; and BDP/FF/G 200/6/10 μ g, BDP/FF 200/6 μ g, or open-label BDP/FF 200/6 μ g two inhalations twice-daily plus tiotropium 2.5 μ g two inhalations once-daily in TRIGGER. Co-primary endpoints (BDP/FF/G vs BDP/FF) were: pre-dose FEV₁ at Week 26; rate of moderate-to-severe exacerbations over 52 weeks. Key secondary endpoints included severe exacerbation rate over 52 weeks (using pooled data). ClinicalTrials.gov: NCT02676076, NCT02676089.

Findings

Between February 2016 and May 2018, 1155 patients in TRIMARAN received BDP/FF/G (N=579) or BDP/FF (N=576); between April 2016 and May 2018, 1437 patients in TRIGGER received BDP/FF/G (N=573), BDP/FF (N=576) or BDP/FF+tiotropium (N=288). BDP/FF/G improved Week 26 pre-dose FEV₁ by 57mL (95% CI 15–99; p=0.0080) and 73mL (26–120; p=0.0025) vs BDP/FF in TRIMARAN and TRIGGER, respectively, with reductions in moderate-to-severe exacerbation rate of 15% (rate ratio 0.846 [0.725–0.987]; p=0.0331) and 12% (0.880 [0.751–1.030]; p=0.1102). BDP/FF/G also reduced the severe exacerbation

rate (pooled analysis) vs BDP/FF (0.770 [0.636–0.933]; $p=0.0076$). Adverse events were reported by 410–431 (72–75%) patients with BDP/FF/G, 443–455 (77–79%) with BDP/FF and 210 (73%) with BDP/FF+tiotropium.

Interpretation

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

Funding

Chiesi Farmaceutici SpA.

Keywords

Combination drug therapy; asthma; respiratory function tests; exacerbation

Research in context

Evidence before this study

We searched PubMed for articles published before 4 April 2019, using the search term “*Drug Therapy, Combination*”[MeSH Terms] OR triple AND asthma AND trial NOT theophylline NOT montelukast, with no limits applied. Of the 1068 hits, eight present data from clinical trials that evaluated the efficacy of triple therapy comprising an inhaled corticosteroid plus a long-acting β_2 -agonist plus a long-acting muscarinic antagonist. Of these, six report data in adults (the other two report data in children or adolescents), one of which was a short-term (four week) study, one reports pooled safety data, and one reports subgroup analyses of studies presented in another manuscript. The remaining three manuscripts report 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 manuscripts presents data from two 48-week studies, in which the addition of tiotropium to high-dose inhaled corticosteroid plus 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 manuscript focuses on the long-term (52-week) safety profile of the addition of tiotropium to inhaled corticosteroid plus long-acting β_2 -agonist, which was similar to inhaled corticosteroid plus long-acting β_2 -agonist alone. In the third manuscript, the addition of tiotropium improved airflow limitation and reduced airway wall thickness after 48 weeks. All three studies evaluated the effect of tiotropium plus inhaled corticosteroid plus long-acting β_2 -agonist therapy in patients with spirometric persistent airflow limitation (ratio of forced expiratory volume in 1 second to forced vital capacity <0.7).

Added value of this study

TRIMARAN and TRIGGER are the first studies to evaluate the relative efficacy and safety of single-inhaler triple therapy with those of inhaled corticosteroid plus a long-acting β_2 -agonist in adults with asthma – and in particular are the first long-term studies conducted in patients

1 who had no requirement to demonstrate persistent airflow limitation following short-acting β_2 -
2 agonist use.

3 **Implications of all the available evidence**

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

8

1 Introduction

2 The goals of asthma management are to achieve symptom control and to avoid future risks,
3 especially of exacerbations.¹ Asthma is characterised by the presence of chronic airway
4 inflammation, and as a consequence inhaled corticosteroids are the mainstay of therapy.¹
5 Many patients are able to achieve good disease control, especially from an inhaled
6 corticosteroid/long-acting β_2 -agonist combination.² However, until recently limited options
7 were available for patients who could not achieve controlled asthma with such combinations.

8 The addition of the long-acting muscarinic antagonist tiotropium to inhaled
9 corticosteroid/long-acting β_2 -agonist therapy has been shown to improve lung function, and
10 in longer studies (48-week duration) reduce the risk of exacerbations in patients with
11 asthma, although in a subgroup of patients with persistent airflow limitation.^{3–5} However, this
12 requires patients to use two different inhalers, of different design and with different
13 instructions for use – and often with different dosing regimens. This is not only inconvenient
14 for patients and healthcare providers who provide instruction on correct inhaler use, but can
15 negatively impact treatment adherence and persistence.^{6–9} A single-inhaler triple therapy
16 consisting of an extrafine formulation (i.e., with mass median aerodynamic diameter $<2\ \mu\text{m}$)
17 of the inhaled corticosteroid beclometasone dipropionate (BDP), the long-acting β_2 -agonist
18 formoterol fumarate (FF), and the long-acting muscarinic antagonist glycopyrronium (G)
19 delivered via a pressurised metered-dose inhaler (pMDI) is in development for patients with
20 asthma. Such extrafine formulations result in improved deposition in the small airways,¹⁰
21 which is potentially important given that asthma patients with significant small airways
22 dysfunction tend to have poorer asthma control and quality of life, and are at increased
23 exacerbation risk.¹¹

24 This manuscript describes the results of two Phase III, 52-week studies comparing the
25 efficacy and safety of medium-strength (100/6/10 μg ; TRIMARAN) and high-strength
26 (200/6/10 μg ; TRIGGER) BDP/FF/G with that of the respective strengths of BDP/FF in
27 patients with asthma poorly controlled on medium-dose (TRIMARAN) or high-dose

- 1 (TRIGGER) inhaled corticosteroid/long-acting β_2 -agonist therapy. These are the first studies
- 2 to evaluate single-inhaler triple therapy in a broad asthma population not restricted to those
- 3 with persistent airflow limitation.

Methods

Study design

Both studies were randomised, parallel-group, double-blind and active controlled. The main difference between them was the inhaled corticosteroid dose received prior to and during the study, with patients in TRIMARAN receiving a medium dose, and patients in TRIGGER receiving a high dose (see 'Patients' below).

Patients who met the inclusion and exclusion criteria at screening (Visit 1) had their asthma maintenance therapy switched to extrafine BDP/FF 100/6 µg in TRIMARAN and 200/6 µg in TRIGGER, two inhalations twice daily via pressurised metered-dose inhaler for a two-week open-label run-in period. At the end of the run-in period, patients in TRIMARAN were randomised 1:1 to either (1) continue BDP/FF 100/6 µg two inhalations twice daily, or (2) to receive extrafine BDP/FF/G 100/6/10 µg, two inhalations twice daily via pressurised metered-dose inhaler. Patients in TRIGGER were randomised 2:2:1 to (1) continue BDP/FF 200/6 µg two inhalations twice daily, or to receive (2) extrafine BDP/FF/G 200/6/10 µg two inhalations twice daily via pressurised metered-dose inhaler or (3) open-label BDP/FF 200/6 µg two inhalations twice daily via pressurised metered-dose inhaler plus tiotropium 2.5 µg two inhalations once daily via soft mist inhaler (Respimat®). 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 prior to any visit.

The studies were approved by the ethics committee or institutional review board at each site and were performed 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 impacted any randomised patients. The two protocols had one substantial amendment to the inclusion criteria – to clarify that any long-acting β_2 -

agonist was permitted as prior 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.

Patients

Patients were to be aged 18 to 75 years, inclusive, with a documented history of asthma for at least one year and that was diagnosed prior to the age of 40 years, pre-bronchodilator FEV₁ <80% predicted normal value, and a change in FEV₁ of >12% and >200 mL 10–15 min after inhaling salbutamol 400 µg. Patients were to have uncontrolled asthma (Asthma Control Questionnaire-7 [ACQ-7] ≥1.5), with a history of at least one exacerbation requiring treatment with systemic corticosteroids or emergency department visit or in-patient hospitalisation in the previous 12 months, and were receiving a stable dose of an inhaled corticosteroid plus a long-acting β₂-agonist for at least four weeks prior to entry (TRIMARAN: medium inhaled corticosteroid dose; TRIGGER high dose; see the supplement for the dose equivalents).

Key exclusion criteria were: history of near fatal asthma or a past intensive care unit hospitalisation for asthma that may place the patient at risk; a severe exacerbation in the four weeks prior to entry or during the run-in period; any other significant lung disease that may interfere with study evaluations; current smokers or ex-smokers with ≥10 pack-years exposure or who stopped smoking one year or less prior to screening; treatment with monoclonal antibodies or other biological drugs; clinically significant cardiovascular conditions or laboratory abnormalities; or unstable concurrent disease that may impact efficacy or safety. The full inclusion and exclusion criteria and non-permitted asthma medications are listed in the supplement.

Randomisation and masking

Patients were allocated to treatment by central randomisation stratified by country according to a randomisation list generated by the interactive response technology provider. Patients, investigators, site staff and sponsor personnel were blinded to BDP/FF/G or BDP/FF

assignment for the duration of the studies, with all patients using pressurised metered-dose inhalers. Tiotropium (and BDP/FF in this arm) was administered open-label in TRIGGER.

Procedures

At each visit during the treatment period, data were collected for spirometry (pre-dose and 15 and 30 min, and 1, 2 and 3 h post-dose, with centralised spirometry) and ACQ-7. Asthma exacerbations were captured throughout the study. Each day, pre-dose 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.

Outcomes

The co-primary objectives were to demonstrate superiority of BDP/FF/G over BDP/FF in terms of pre-dose FEV₁ at Week 26, and the rate of moderate to severe exacerbations over 52 weeks in each study. The key secondary objectives were to demonstrate superiority of BDP/FF/G over BDP/FF in terms of peak FEV₁ at Week 26 and average morning PEF over the first 26 weeks of treatment in each study, and in terms of the rate of severe exacerbations using data pooled from the two studies.

Other secondary variables were: FEV₁ peak and predose at all other visits, and FEV₁ area under the curve (AUC) from 0 to 3 h post-dose, and ACQ-7 at all visits; FEV₁ response (change from baseline in pre-dose FEV₁ ≥100 mL) and ACQ-7 response (decrease from baseline score of at least 0.5 units) at Weeks 26 and 52; average morning and evening PEF over each inter-visit period and over 52 weeks, and average evening PEF over the first 26 weeks of treatment; time to first moderate and to first moderate or severe exacerbation; moderate exacerbation rate; and rescue use, rescue-free days, daily asthma symptoms, and asthma control days (days with a total asthma symptoms score of 0 and no rescue use) over each inter-visit period and over the first 26 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 and moderate and severe exacerbations. Severe exacerbations were prespecified to be analysed only in the pooled population as it was anticipated that the occurrence of these events would be relatively low.

A severe asthma exacerbation was defined as an asthma worsening requiring treatment with systemic corticosteroids for at least three days (with any associated emergency room visit or hospitalisation documented). Moderate exacerbations were defined in accordance with an American Thoracic Society/European Respiratory Society joint statement,¹² as one or more of the following criteria:

- nocturnal awakening(s) due to asthma requiring short-acting β_2 -agonist for two consecutive nights or increase ≥ 0.75 from baseline in daily symptom score on two consecutive days;
- increase from baseline in short-acting β_2 -agonist use on two consecutive days (minimum increase four puffs/day);
- $\geq 20\%$ decrease in PEF from baseline on at least two consecutive mornings/evenings or $\geq 20\%$ decrease in FEV₁ from baseline;
- visit to emergency room/study site for asthma treatment not requiring systemic corticosteroids.

Treatment-emergent adverse events (defined as events starting on or after first intake of randomised study medication) were captured throughout the study. Major adverse cardiovascular events were adjudicated by an independent committee, comprising three cardiologists.

Statistical analysis

To demonstrate superiority of BDP/FF/G over BDP/FF in terms of the co-primary and key secondary objectives in both studies, 574 patients needed to be randomised per treatment group. Since patients were randomised 2:2:1 in TRIGGER, 287 patients were needed for the

BDP/FF + tiotropium group. This would give a total of 1148 patients in TRIMARAN and 1435 in TRIGGER. Further details on the sample size calculations are provided in the supplement.

In order to account for multiplicity, the comparisons between BDP/FF/G and BDP/FF in terms of co-primary and key secondary efficacy endpoints were conducted according to the following prespecified hierarchical testing procedure:

1. Pre-dose FEV₁ at Week 26, and moderate and severe exacerbation rate over 52 weeks;
2. Peak FEV₁ at Week 26;
3. Average morning PEF over the first 26 weeks of treatment;
4. Severe exacerbation rate over 52 weeks in the pooled analysis.

At Step 1, superiority of BDP/FF/G over BDP/FF had to be demonstrated for both co-primary endpoints. At each of the next steps, confirmatory claims were to be made only when superiority had been demonstrated in all preceding steps. No multiplicity adjustments were applied to the other secondary endpoints, and so these p-values are descriptive, as are the comparisons between BDP/FF/G and BDP/FF + tiotropium.

Pre-dose and peak FEV₁ at Week 26 and average morning PEF over 26 weeks were analysed 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 inter-visit period effect for PEF), with data presented as adjusted means (i.e., least squares means), and adjusted mean differences between treatments with associated 95% confidence intervals (CIs) and p-values. An unstructured covariance matrix was assumed. The number of asthma exacerbations over the 52-week treatment period was analysed using a negative binomial model including treatment, country and number of exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as offset, and presented as adjusted asthma exacerbation rates, and adjusted rate ratios with 95% CIs and p-values.

Most of the secondary efficacy endpoints were analysed using similar methods to the co-primary and key secondary endpoints. FEV₁ response and ACQ-7 response were compared between treatment groups using a logistic model including treatment and country as factors and the respective baseline values as a covariate. Time to first exacerbation were analysed using a Cox proportional hazards model including treatment, country and number of exacerbations 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 manuscript were prespecified.

All efficacy endpoints were analysed in the intention-to-treat population, defined as all randomised patients 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 randomised patients 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. All analyses presented in this manuscript were done with 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, Chiesi Farmaceutici SpA, was responsible for the design and analysis of the studies, oversaw their conduct and was responsible for study report preparation. All authors had full access to all data, with the lead author (JCV) responsible for the decision to submit for publication.

1 **Results**

2 TRIMARAN was conducted between February 2016 and May 2018 in 171 centres across
3 16 countries, whereas TRIGGER was conducted between April 2016 and May 2018 in 221
4 centres across 17 countries. The sites were a mixture of secondary and tertiary care centres
5 and specialised investigation units. Of the 1155 patients randomised into TRIMARAN, 94%
6 completed treatment in both groups (Figure 1A), whereas of the 1437 patients in TRIGGER,
7 93%, 93% and 91% completed treatment with BDP/FF/G, BDP/FF and BDP/FF + tiotropium,
8 respectively (Figure 1B). Baseline demographics were similar across the five groups (Table
9 1). Patients in TRIGGER had a slightly worse lung function (treatment group mean 51·8–
10 52·1% predicted vs 55·2–55·7%) and higher reversibility (33·2–34·9% vs 30·8–32·5%) than
11 those in TRIMARAN.

Table 1. Baseline characteristics (safety population).

	TRIMARAN		TRIGGER		
	BDP/FF/G 100/6/10 µg (N=576)	BDP/FF 100/6 µg (N=574)	BDP/FF/G 200/6/10 µg (N=571)	BDP/FF 200/6 µg (N=573)	BDP/FF 200/6 µg + tiotropium 2.5 µg (N=287)
Sex, n (%)					
Male	221 (38)	221 (39)	212 (37)	245 (43)	103 (36)
Female	355 (62)	353 (61)	359 (63)	328 (57)	184 (64)
Race, n (%)					
Asian	0	0	2 (<1)	0	0
White	575 (100)	574 (100)	569 (100)	573 (100)	286 (100)
Other	1 (<1)	0	0	0	1 (<1)
Age (years), mean (SD)	52.6 (12.4)	52.5 (12.2)	53.1 (12.2)	54.0 (11.9)	51.6 (12.3)
Body-mass index (kg/m ²), mean (SD)	28.0 (4.81)	27.9 (5.07)	28.4 (5.14)	28.7 (5.87)	28.5 (5.21)
≥30 kg/m ² , n (%)	173 (30)	170 (30)	204 (36)	205 (36)	102 (36)
Smoking status, n (%)					
Ex-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), mean (SD) ^a	4.1 (2.4)	4.8 (2.5)	4.9 (2.4)	4.8 (2.3)	5.6 (2.6)

	TRIMARAN		TRIGGER		
	BDP/FF/G 100/6/10 µg (N=576)	BDP/FF 100/6 µg (N=574)	BDP/FF/G 200/6/10 µg (N=571)	BDP/FF 200/6 µg (N=573)	BDP/FF 200/6 µg + tiotropium 2.5 µg (N=287)
Duration of asthma (years), mean (SD)	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, n (%)					
1	474 (82)	473 (82)	439 (77)	452 (79)	229 (80)
>1	102 (18)	101 (18)	132 (23)	121 (21)	58 (20)
Pre-salbutamol FEV ₁ (L), mean (SD) ^b	1.7 (0.56)	1.7 (0.56)	1.6 (0.56)	1.6 (0.57)	1.6 (0.59)
Pre-salbutamol FEV ₁ % of predicted normal value, mean (SD) ^b	55.2 (12.3)	55.7 (12.0)	51.9 (13.5)	51.8 (13.5)	52.1 (13.2)
Range	17 to 79	20 to 79	15 to 79	16 to 79	22 to 79
Reversibility (%), mean (SD)	32.5 (24.72)	30.8 (20.53)	33.2 (20.21)	33.9 (21.87)	34.9 (26.99)
Range	12.1 to 419.2	12.1 to 163.0	12.1 to 147.9	12.0 to 152.5	12.2 to 234.5
Pre-salbutamol FEV ₁ /FVC, mean (SD) ^b	0.60 (0.12)	0.61 (0.12)	0.59 (0.12)	0.59 (0.13)	0.59 (0.12)
Range	0.26 to 0.96	0.27 to 0.94	0.23 to 0.95	0.27 to 0.94	0.29 to 0.88
Post-salbutamol FEV ₁ /FVC, mean (SD) ^c	0.65 (0.11)	0.65 (0.11)	0.63 (0.12) ^d	0.63 (0.12)	0.63 (0.12)
Range	0.31 to 0.97	0.32 to 0.91	0.27 to 0.93	0.26 to 0.92	0.34 to 0.96
Prior inhaled corticosteroid and/or long-acting β ₂ -agonist therapy, n (%) ^e					

	TRIMARAN		TRIGGER		
	BDP/FF/G 100/6/10 µg (N=576)	BDP/FF 100/6 µg (N=574)	BDP/FF/G 200/6/10 µg (N=571)	BDP/FF 200/6 µg (N=573)	BDP/FF 200/6 µg + tiotropium 2.5 µg (N=287)
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, mean (SD) ^f	2.3 (0.52)	2.3 (0.53)	2.5 (0.53) ^h	2.4 (0.54) ⁱ	2.4 (0.53)
Peak expiratory flow (L/min), mean (SD) ^g					
Morning	297 (107.5) ^j	299 (106.0) ^j	279 (104.2) ^k	275 (101.2) ^l	287 (106.4)
Evening	310 (108.2) ^m	314 (107.6) ⁱ	292 (104.7) ^l	287 (103.1) ^m	299 (107.6)
Daily asthma symptom scores, mean (SD) ^g	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, mean (SD) ^g	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, mean (SD) ^g	9.1 (21.45)	10.4 (23.48)	9.9 (22.66)	8.9 (22.24)	10.1 (26.22)

BDP = beclometasone dipropionate; FF = formoterol fumarate; G = glycopyrronium; SD = standard deviation; FEV₁ = forced expiratory volume in 1 second; ACQ = Asthma Control Questionnaire.

^aCalculated in ex-smokers only. ^bMeasured at screening prior to administration of salbutamol. ^cMeasured at screening 10–15 min after administration of salbutamol (^ddata available for 570 patients).

^eCalculated from asthma prior therapy data (may add up to more than 100% due to changes in asthma therapy in the three months prior to entry and/or multiple therapies reported for the same patient). ^fMeasured at the randomisation visit or ^gduring the run-in period in the intention-to-treat population (TRIMARAN N=575 and 574 for BDP/FF/G and BDP/FF, respectively, TRIGGER N=571, 571 and 287 for BDP/FF/G, BDP/FF and BDP/FF + tiotropium, respectively); data available for ^h570, ⁱ568, ^j569, ^k564, ^l565 and ^m566 patients.

The co-primary endpoint of change in pre-dose FEV₁ at Week 26 was met in both studies, with significant differences between BDP/FF/G and BDP/FF of 57 mL (95% CI 15–99; p=0.0080) in TRIMARAN and 73 mL (26–120; p=0.0025) in TRIGGER (Figure 2A, with absolute values in Supplementary Table 1). BDP/FF/G was not different from BDP/FF + tiotropium (–45 mL [–103 to 13]; p=0.1253). BDP/FF/G reduced the rate of moderate and severe exacerbations by a significant 15% compared with BDP/FF in TRIMARAN (rate ratio 0.846 [0.725–0.987]; p=0.0331; Figure 2B and Supplementary Table 1). The reduction in TRIGGER was 12%, but it did not reach statistical significance (0.880 [0.751–1.030]; p=0.1102). No difference was observed between BDP/FF/G and BDP/FF + tiotropium (1.070 [0.878–1.303]; p=0.5018). Since in TRIGGER statistical significance was not reached for this co-primary endpoint, 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 severe exacerbation rate (pooled analysis). The corresponding p-values should therefore be interpreted descriptively.

For the key secondary endpoints of peak FEV₁ at Week 26 and average morning PEF over 26 weeks, the change from baseline was higher with BDP/FF/G than BDP/FF in both studies (p=0.0002 and p<0.0001 for peak FEV₁ and p=0.0006 and p=0.0014 for morning PEF in TRIMARAN and TRIGGER, respectively), with no differences between BDP/FF/G and BDP/FF + tiotropium (p=0.2709 and 0.9507, respectively; Figure 3A and B, with absolute values in Supplementary Table 1). In the pooled analysis, BDP/FF/G reduced the rate of severe exacerbations vs BDP/FF by 23% (p=0.0076; Figure 3C and Supplementary Table 1), and also reduced the rate of moderate exacerbations by 12% (p=0.0427) and of combined moderate and severe exacerbations by 14% (p=0.0083). In the individual studies, the same trend for a reduced rate with BDP/FF/G was observed for moderate exacerbations (p=0.0864 and 0.2500 in TRIMARAN and TRIGGER, respectively; Supplementary Figure 1).

The time to first moderate or severe exacerbation was prolonged with BDP/FF/G compared with BDP/FF in both TRIMARAN (hazard ratio 0.842 [95% CI 0.727–0.975]; p=0.0217

[Figure 4A]) and TRIGGER (0.799 [0.688–0.929]; $p=0.0035$ [Figure 4B]), and was similar for BDP/FF/G and BDP/FF + tiotropium (0.973 [0.805–1.175]; $p=0.7768$). Likewise, the time to first moderate exacerbation was prolonged with BDP/FF/G vs BDP/FF in both studies (TRIMARAN 0.856 [0.733–0.999]; $p=0.0480$; TRIGGER 0.808 [0.688–0.948]; $p=0.0089$) and was similar for BDP/FF/G and BDP/FF + tiotropium (0.894 [0.733–1.090]; $p=0.2663$). In the pooled analysis, BDP/FF/G prolonged the time to first moderate or severe (0.820 [0.739–0.911]; $p=0.0002$), moderate (0.830 [0.743–0.927]; $p=0.0010$), and severe (0.788 [0.656–0.946]; $p=0.0106$ [Figure 4C]) exacerbation vs BDP/FF. Median times to event are in Supplementary Table 2. In the pooled analyses, the numbers needed to treat for one year with BDP/FF/G rather than BDP/FF to prevent one exacerbation were three for moderate or severe exacerbations, 14 for severe exacerbations and five for moderate exacerbations.

The results for the FEV₁ secondary endpoints in TRIMARAN were consistent with the co-primary and key secondary FEV₁ endpoints, with BDP/FF/G associated with improvements versus BDP/FF in pre-dose FEV₁ at most visits (Supplementary Figure 2), peak FEV₁ and FEV₁ AUC_{0–3h} at all visits (Supplementary Figures 3 and 4), and FEV₁ response at Week 26 (Supplementary Table 3). In TRIGGER, BDP/FF/G improved peak FEV₁, pre-dose FEV₁, and FEV₁ AUC_{0–3h} versus BDP/FF at all visits, and FEV₁ response at Weeks 26 and 52, with no differences between BDP/FF/G and BDP/FF + tiotropium.

BDP/FF/G improved all PEF-based secondary endpoints compared with BDP/FF in both studies (Supplementary Figures 5–7). There were no clinically relevant differences between BDP/FF/G and BDP/FF or BDP/FF + tiotropium in terms of ACQ-7 total score or responders (Supplementary Figure 8 and Supplementary Table 3), or in the rescue medication use endpoints (Supplementary Figure 9 and 10, and Supplementary Table 3). Notably, there was an improvement from baseline in asthma symptoms, control and rescue medication use in all five groups over the duration of the studies, with an improvement in TRIGGER for BDP/FF/G vs BDP/FF in terms of asthma symptom-free days and asthma control days from Week 13 onwards (Supplementary Figures 11–13, and Supplementary Table 3).

Overall, a similar proportion of patients had adverse events in all five groups (Table 2). The majority of events were mild or moderate in severity, and few were considered 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. Four patients experienced treatment-related serious adverse events: atrial fibrillation, in a patient receiving BDP/FF/G 100/6/10 µg, and who had hypertension; oesophageal candidiasis in a patient receiving BDP/FF/G 200/6/10 µg that resolved after therapy; and pneumonia, which resolved after therapy, and angle closure glaucoma, which had not resolved by the end of the study in patients receiving BDP/FF 200/6 µg. All were moderate in severity, and did not require a change in study treatment. Five patients in TRIMARAN experienced major adverse cardiovascular events, as did six patients in TRIGGER, although none of the events in either study were considered related to study treatment (Table 2 and Supplementary Table 4). Three patients in the BDP/FF/G group in TRIMARAN experienced adverse events leading to death (one patient with left ventricular failure, one with acute pancreatitis, and one patient with gastric cancer and acute cardiac failure). In TRIGGER, two patients experienced 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 related to study treatment.

Table 2. Treatment-emergent adverse events and serious adverse events (safety population).

Number (%) of patients	TRIMARAN			TRIGGER	
	BDP/FF/G 100/6/10 µg (N=576)	BDP/FF 100/6 µg (N=574)	BDP/FF/G 200/6/10 µg (N=571)	BDP/FF 200/6 µg (N=573)	BDP/FF 200/6 µg + tiotropium 2.5 µg (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)

Number (%) of patients	TRIMARAN			TRIGGER	
	BDP/FF/G 100/6/10 µg (N=576)	BDP/FF 100/6 µg (N=574)	BDP/FF/G 200/6/10 µg (N=571)	BDP/FF 200/6 µg (N=573)	BDP/FF 200/6 µg + tiotropium 2.5 µg (N=287)
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)

Number (%) of patients	TRIMARAN			TRIGGER	
	BDP/FF/G 100/6/10 µg (N=576)	BDP/FF 100/6 µg (N=574)	BDP/FF/G 200/6/10 µg (N=571)	BDP/FF 200/6 µg (N=573)	BDP/FF 200/6 µg + tiotropium 2.5 µg (N=287)
Major adverse cardiovascular events	4 (1)	1 (<1)	3 (1)	3 (1)	0
Adverse events leading to study drug discontinuation	4 (1)	5 (1)	4 (1)	8 (1)	2 (1)
Adverse events leading to death	3 (1)	0	1 (<1)	1 (<1)	0

- 1 Data are number of patients (percentage). Preferred terms are listed where the occurrence is $\geq 2.5\%$ in any treatment group for
- 2 adverse events and $\geq 0.5\%$ in either group for serious adverse events and treatment-related adverse events. BDP =
- 3 beclometasone dipropionate; FF = formoterol fumarate; G = glycopyrronium.

Discussion

TRIMARAN and TRIGGER are the first studies to evaluate the efficacy and safety of single-inhaler triple therapy in the management of asthma. The lung function (pre-dose FEV₁) co-primary endpoint was met in both studies, with a slightly larger effect size in TRIGGER.

Furthermore, the moderate and severe exacerbations co-primary endpoint was met in TRIMARAN, with a significant 15% reduction for BDP/FF/G vs BDP/FF; although there was similar effect size in TRIGGER, with a 12% reduction, statistical significance was not achieved. In the prespecified 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 secondary exacerbations endpoints, in the pooled analyses BDP/FF/G reduced the rate of moderate and combined moderate and severe exacerbations by 12 and 14%, respectively, and prolonged the time to first moderate or severe, moderate, and severe exacerbation compared with BDP/FF. The totality of the exacerbations data therefore suggest that BDP/FF/G prevents these events to a greater degree than BDP/FF.

Although care should be taken comparing studies, the 23% reduction in the rate of severe exacerbations along with the 21% risk reduction (hazard ratio 0.79 for time to first severe exacerbation) are consistent with the results of two long-term studies in which tiotropium was added as a free combination to any inhaled corticosteroid and long-acting β_2 -agonist (where there was a 20% rate reduction and a 21% risk reduction for tiotropium vs placebo).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 FEV₁ \leq 80% and FEV₁ to forced vital capacity (FVC) ratio \leq 70%,³ compared with pre-bronchodilator FEV₁ $<$ 80% in TRIMARAN and TRIGGER and no limitation on the FEV₁/FVC ratio. Another key difference is that the earlier studies administered triple therapy via multiple inhalers, and did not supply or monitor the daily concomitant use of inhaled corticosteroid/long-acting β_2 -agonist. The use of single-inhaler triple therapy in TRIMARAN and TRIGGER ensured the delivery of all three

1 components and should potentially optimise treatment adherence and persistence. We
2 acknowledge, however, that in TRIGGER for FEV₁ and moderate-to-severe exacerbations,
3 BDP/FF + tiotropium (administered open-label via separate inhalers) exhibited numerically
4 greater improvements vs BDP/FF (although not statistically significant) than single inhaler
5 (and double-blind) BDP/FF/G.

6 The majority of exacerbations in TRIMARAN and TRIGGER were moderate in severity,
7 which by definition were predominantly self-managed by patients. To our knowledge, this is
8 the first study to evaluate the effect of inhaled therapy on such exacerbations by applying the
9 American Thoracic Society/European Respiratory Society joint statement definition.¹²

10 Although there was a consistent trend in favour of triple therapy, there was no significant
11 treatment effect for the rate of moderate exacerbations in the individual studies, yet the time
12 to first moderate exacerbation was extended with BDP/FF/G vs BDP/FF, both in the pooled
13 analysis and in each individual study. The reasons for this are unclear – although it may be
14 associated with the variability of symptoms in asthma (the worsening of which defines a
15 moderate exacerbation episode), so making it challenging to assess this outcome precisely.
16 In addition, neither study was powered to evaluate the effect of treatment on moderate
17 exacerbations. The effect of triple therapy on the objective lung function endpoints, FEV₁
18 and PEF, was consistent, within and between studies, with both BDP/FF/G doses improving
19 these endpoints vs BDP/FF for the duration of the studies.

20 Asthma control, symptom endpoints and rescue medication use improved from baseline with
21 all treatments. Interestingly, in TRIMARAN BDP/FF/G and BDP/FF resulted in similar
22 improvements in symptom-free days and asthma control days, whereas in TRIGGER there
23 was a separation between BDP/FF/G and BDP/FF, particularly over the second half of the
24 study. These results are similar to those of the previous tiotropium studies, in which
25 tiotropium administered separately to inhaled corticosteroid plus a long-acting β_2 -agonist
26 resulted in consistent improvements in lung function, but less consistent improvements in
27 ACQ-7 score,^{3,4} and with a dissociation in effect between severe exacerbations and asthma

1 control.³ For the populations that we recruited (who had uncontrolled disease despite
2 medium or high-dose inhaled corticosteroid plus a long-acting β_2 -agonist), the prevention of
3 future exacerbations (especially severe exacerbations) is arguably the more important
4 treatment goal.

5 We acknowledge that the improvement in asthma control and decrease in symptoms in all
6 groups, including in those patients who continued BDP/FF therapy from the run-in period
7 across the 52-week trial duration, suggests a clinical trial effect in both studies, which can
8 arise at least in part due to improved adherence. This clinical trial effect also appeared to
9 impact severe exacerbations, with a low rate observed during the trial (0.310 in the pooled
10 BDP/FF group), despite all patients being required to have a history of at least one
11 exacerbation requiring treatment with systemic corticosteroids or emergency department
12 visit or in-patient hospitalisation. In this context, the much lower rate of severe exacerbations
13 observed during the studies compared to the historic data is similar to a number of clinical
14 trials that recruited similar populations,^{16–20} potentially also reflecting increased adherence to
15 therapy or improved care as a result of clinical trial participation. Importantly, when the study
16 was designed, it was anticipated that the rate of these more clinically relevant exacerbations
17 would be lower than that of moderate exacerbations – which is why the only prespecified
18 analysis of severe exacerbation rate was in the pooled population. It is notable, therefore,
19 that despite this low rate, there was still a 23% reduction with BDP/FF/G vs BDP/FF.

20 It is always challenging to interpret the clinical relevance of results when evaluating the
21 additive effect of a therapy on top of therapies that are known to be effective. It could be
22 argued that the differences that we observed between BDP/FF/G and BDP/FF for some of
23 the endpoints were numerically small (with the differences in pre-dose FEV₁ at Week 26 and
24 in morning PEF over 26 weeks lower than those included in the powering assumptions), and
25 indicate only a modest effect of triple therapy. However, the populations that we studied
26 (adults with uncontrolled asthma despite receiving a long-acting β_2 -agonist plus either a
27 medium- or high-dose inhaled corticosteroid) have limited treatment options available, and

1 so even modest incremental improvements can be valuable. Uncontrolled asthma is
2 associated with a substantial (and growing) economic and health burden,²¹ especially due to
3 exacerbations, and so additional therapies are needed. In this context, a key finding is that
4 all treatments were similarly well tolerated. This is again consistent with the results of a
5 number of other triple therapy studies in asthma, in which the addition of long-acting
6 muscarinic antagonist did not impact the overall adverse event profile.^{3-5,22}

7 Given the broad inclusion criteria of these two studies, the results should be generalisable to
8 adults with asthma that is uncontrolled by an inhaled corticosteroid plus a long-acting β_2 -
9 agonist (although we recognise that the recruited populations were predominantly of white
10 race). The Global Initiative for Asthma (GINA) report already includes recommendations for
11 add-on long-acting muscarinic antagonist use for patients whose asthma is not well
12 controlled on inhaled corticosteroid plus long-acting β_2 -agonist therapy.¹ For such patients,
13 escalation of therapy to inhaled triple therapy has been shown to be cost-effective compared
14 to an inhaled corticosteroid plus a long-acting β_2 -agonist,²³⁻²⁷ and is likely to be cost-effective
15 compared to the addition of systemic biological therapy.²⁵ Since BDP/FF/G delivers the three
16 molecules via one device, and based on the magnitude of reduction in the annual rate of
17 severe asthma exacerbations observed in the prespecified pooled analysis of TRIMARAN
18 and TRIGGER, it is expected that BDP/FF/G will provide an attractive treatment option,
19 fulfilling a significant unmet need at both the individual patient and the overall health system
20 levels.

21 In conclusion, taken together these data indicate that in adults with uncontrolled asthma
22 treated with a medium-to-high dose inhaled corticosteroid plus a long-acting β_2 -agonist the
23 addition of a long-acting muscarinic antagonist in a single inhaler BDP/FF/G triple therapy
24 mainly improves lung function with an associated positive impact on severe exacerbations,
25 and a less marked benefit in terms of asthma symptoms or control.

Contributors

The studies were conceived and designed by JCV, AP, MK, SP and GWC. The data were acquired by JCV, PK, PP and GWC, analysed by AV, and interpreted by JCV, PK, PP, AP, DS, SC, FZ, AV, MK, GG, SP and GWC. MK and GG contributed to the medical data integrity. SC and FZ contributed to the conduct of the studies. SC and FZ were Chiesi clinical operation project managers, AV was Chiesi statistician, SP was Head of Chiesi global clinical development, and GG was the Clinical Program Leader. JCV and GWC were principal investigators of TRIMARAN and TRIGGER, respectively. The manuscript was revised for intellectual content and approved for publication by JCV, PK, PP, AP, DS, SC, FZ, AV, MK, GG, SP and GWC.

Declaration of interests

JCV reports personal fees from Chiesi during the conduct of the study. In the past JCV has lectured and received honoraria from AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer-Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, Leti, MEDA, Merck, MSD, Mundipharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sanofi/Regeneron, Sandoz-Hexal, Stallergens, TEVA, UCB/Schwarz-Pharma, Zydus/Cadila and possibly others, and participated in advisory boards and received honoraria from Avontec, Boehringer-Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, MEDA, MSD, Mundipharma, Novartis, Paul-Ehrlich Institut, Regeneron, Revotar, Roche, Sanofi-Aventis, Sanofi/Regeneron, Sandoz-Hexal, TEVA, UCB/Schwarz-Pharma and possibly others, and received funding for research from Deutsche Forschungsgesellschaft, Land Mecklenburg-Vorpommern, GSK, 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, all outside the submitted work.

PP reports grants and personal fees from AstraZeneca and Chiesi, and personal fees from GSK, Menarini, Mundipharma, Novartis and Sanofi, all outside the submitted work.

AP reports grants, personal fees, non-financial support and payment for advisory board membership, consultancy, payment for lectures, grants for research, and travel expenses reimbursement from Chiesi, Astrazeneca, GlaxoSmithKline, Boehringer Ingelheim, Mundipharma and TEVA, and personal fees and non-financial support from Menarini, Novartis, Zambon and Sanofi, all outside the submitted work.

DS reports personal fees from Chiesi during the conduct of the study. Outside the submitted work, he reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, GlaxoSmithKline, Glenmark, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Therevance, and Verona.

SC, FZ, AV, MK and SP are employees of Chiesi, the sponsor of the studies.

GG is an employee of Chiesi USA, Inc.

GWC reports personal fees from A. Menarini, Alk-Abello, Allergy Therapeutics, AstraZeneca-Medimmune, Boehringer Ingelheim, Chiesi Farmaceutici, Genentech, Guidotti-Malesci, Glaxo Smith Kline, Hal Allergy, Merck Sharp & Dome, Mundipharma, Novartis, Orion, Sanofi-Aventis, Sanofi Genzyme/Regeneron, Stallergenes-Greer, Uriach Pharma, Teva, Valeas, ViforPharma, all outside the submitted work.

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1 **Data sharing**

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

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Figure legends

Figure 1. Patient disposition in A) TRIMARAN and B) TRIGGER.

BDP = beclometasone dipropionate; FF = formoterol fumarate; G = glycopyrronium

Figure 2. Co-primary endpoints: A) Pre-dose FEV₁ change from baseline at Week 26 and B) annualised moderate and severe exacerbation rate (intention-to-treat population).

Panel A: Data are adjusted means and adjusted mean differences (95% confidence interval). Panel B: Data are adjusted exacerbation rates per patient per year and adjusted rate ratios (95% confidence interval). BDP = beclometasone dipropionate; FF = formoterol fumarate; G = glycopyrronium; FEV₁ = forced expiratory volume in 1 second.

Figure 3. Key secondary endpoints: A) Peak FEV₁ change from baseline at Week 26 (intention-to-treat population), B) average morning PEF change from baseline over 26 weeks (intention-to-treat population), and C) annualised severe, moderate, and moderate and severe exacerbation rate (pooled analysis, intention-to-treat population).

Panels A and B: Data are adjusted means and adjusted mean differences (95% confidence interval). Panel C: Data are adjusted exacerbation rates per patient per year and adjusted rate ratios (95% confidence interval). BDP = beclometasone dipropionate; FF = formoterol fumarate; G = glycopyrronium; FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow.

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

BDP = beclometasone dipropionate; FF = formoterol fumarate; G = glycopyrronium; HR = hazard ratio; CI = confidence interval.

Figure 1A

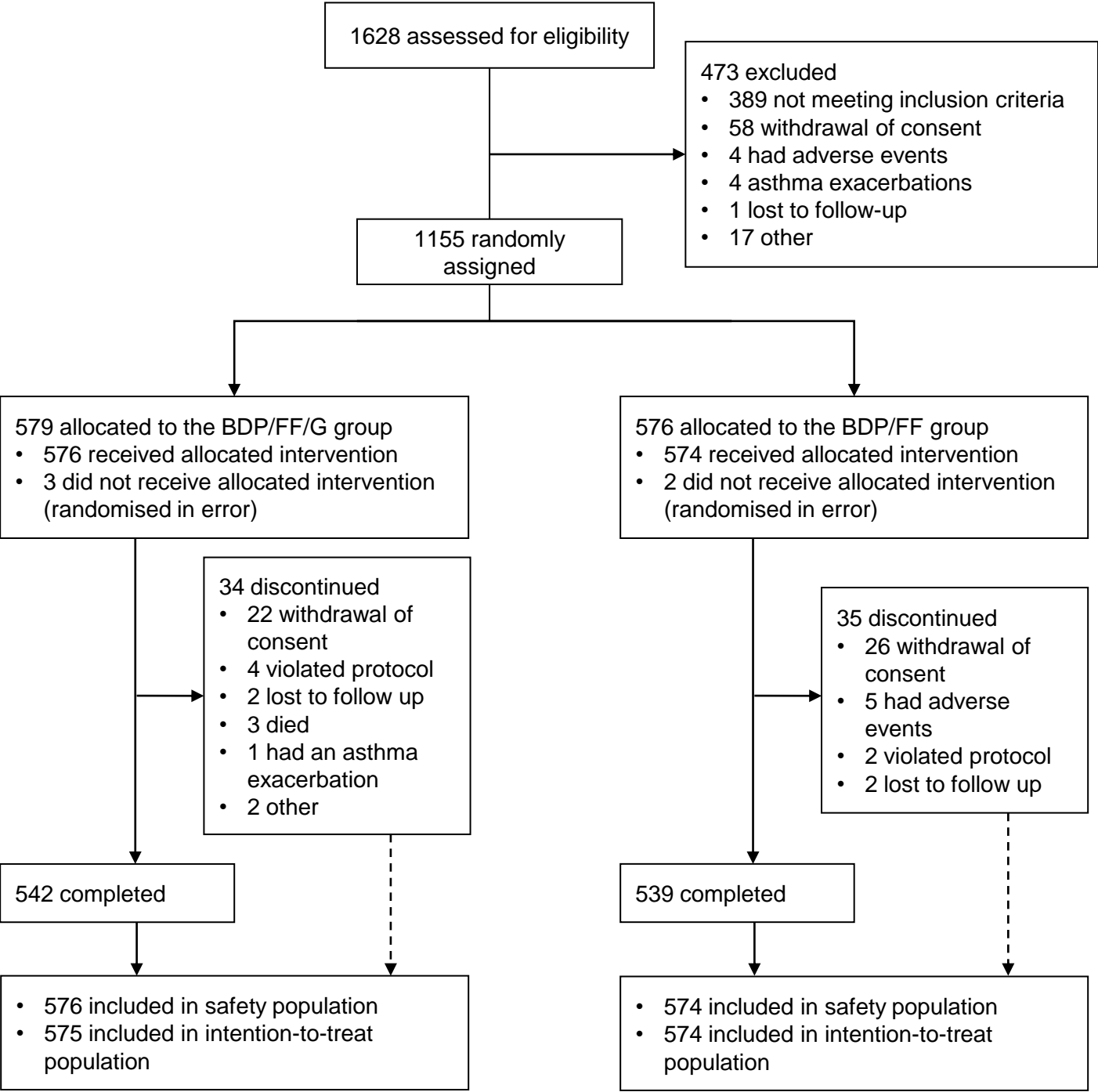


Figure 1B

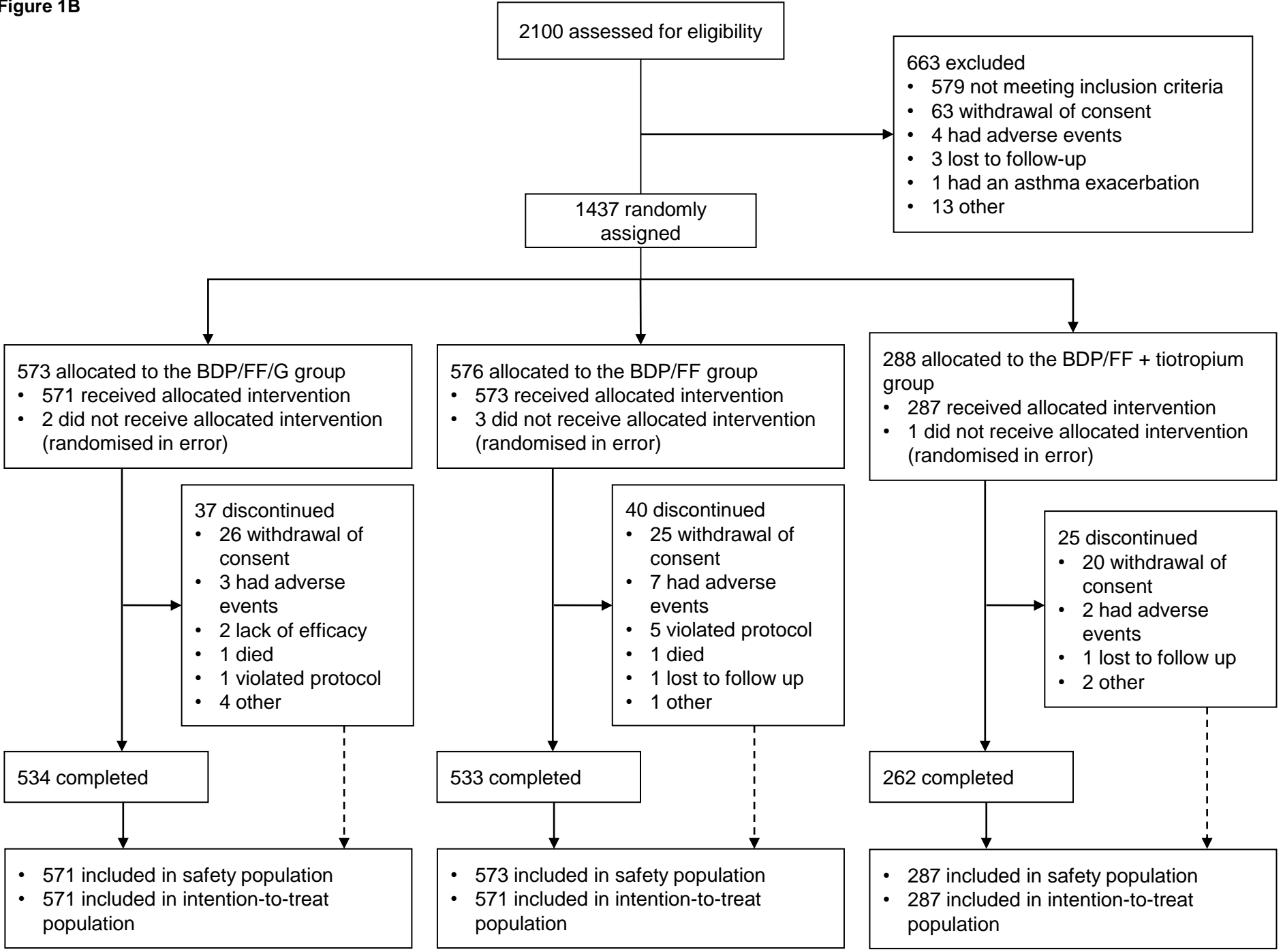


Figure 2A

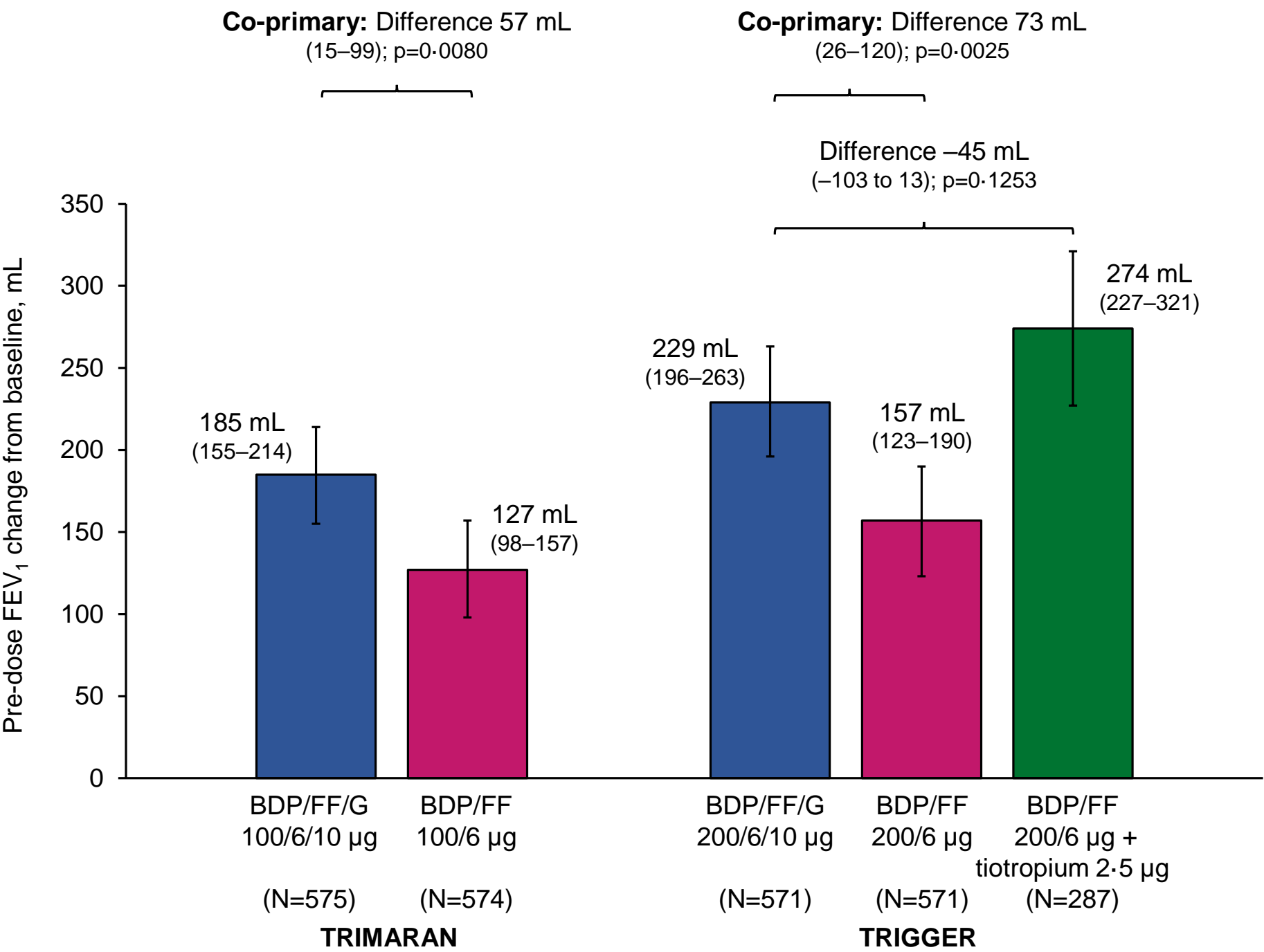


Figure 2B

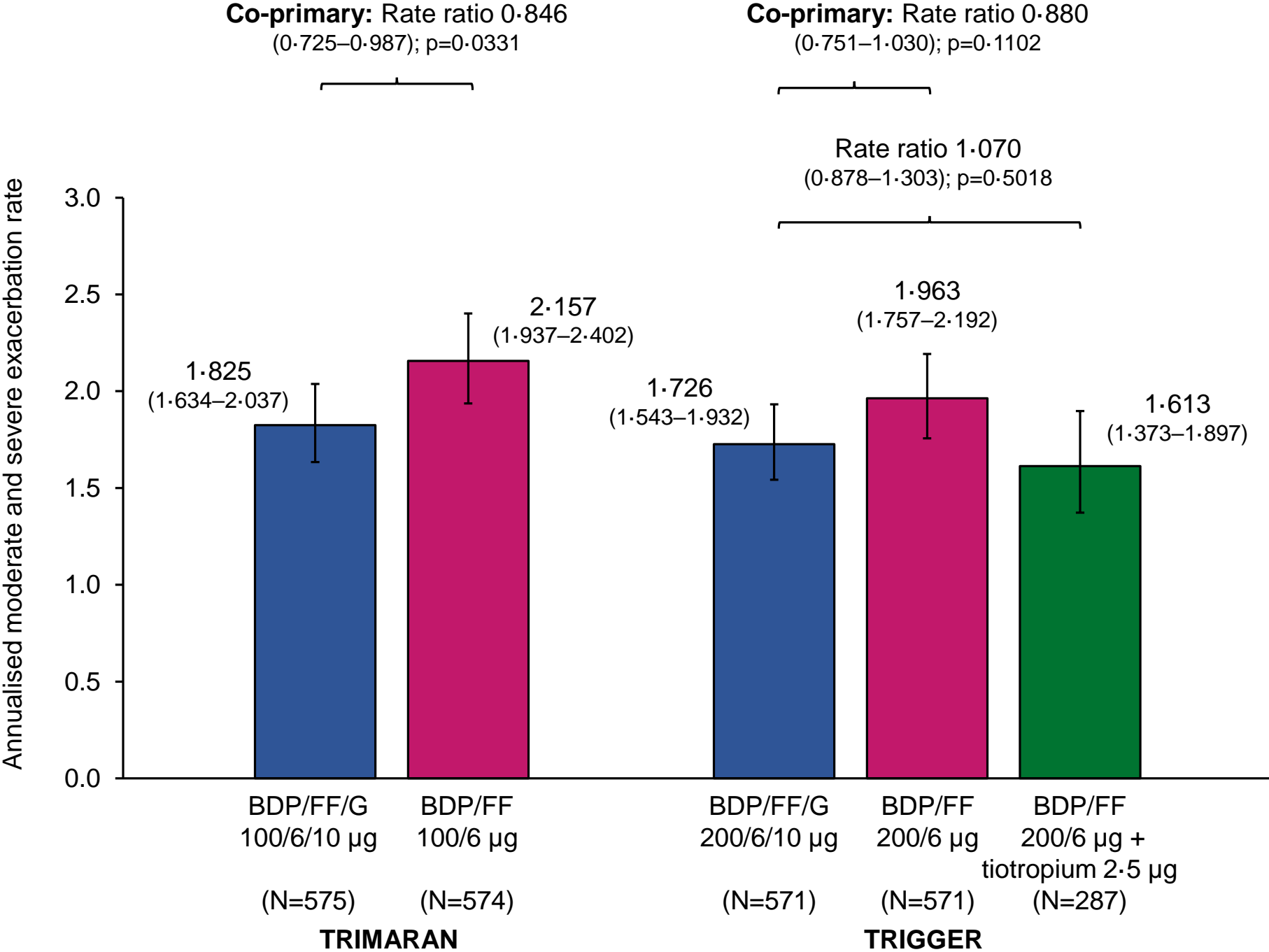


Figure 3A

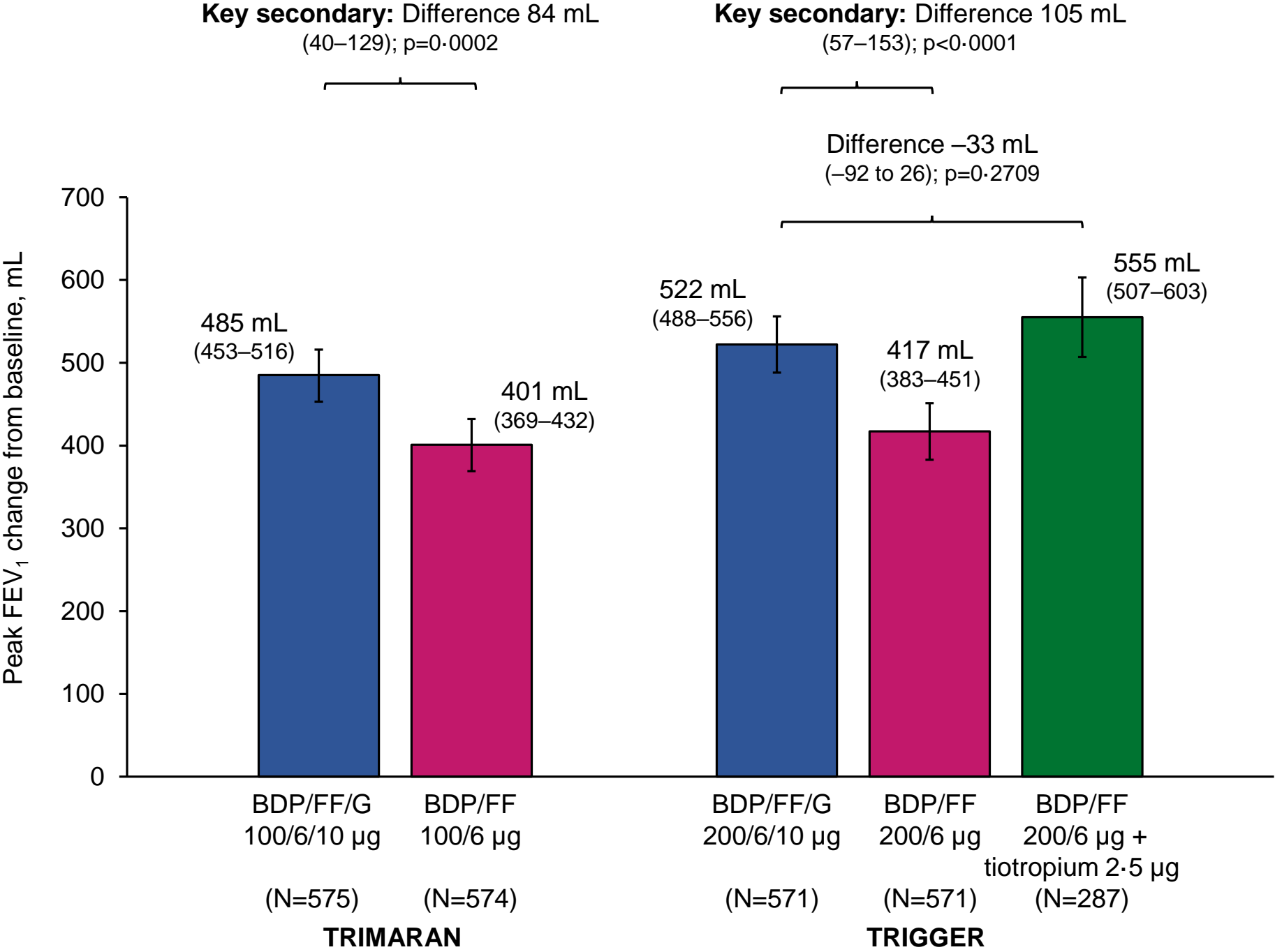


Figure 3B

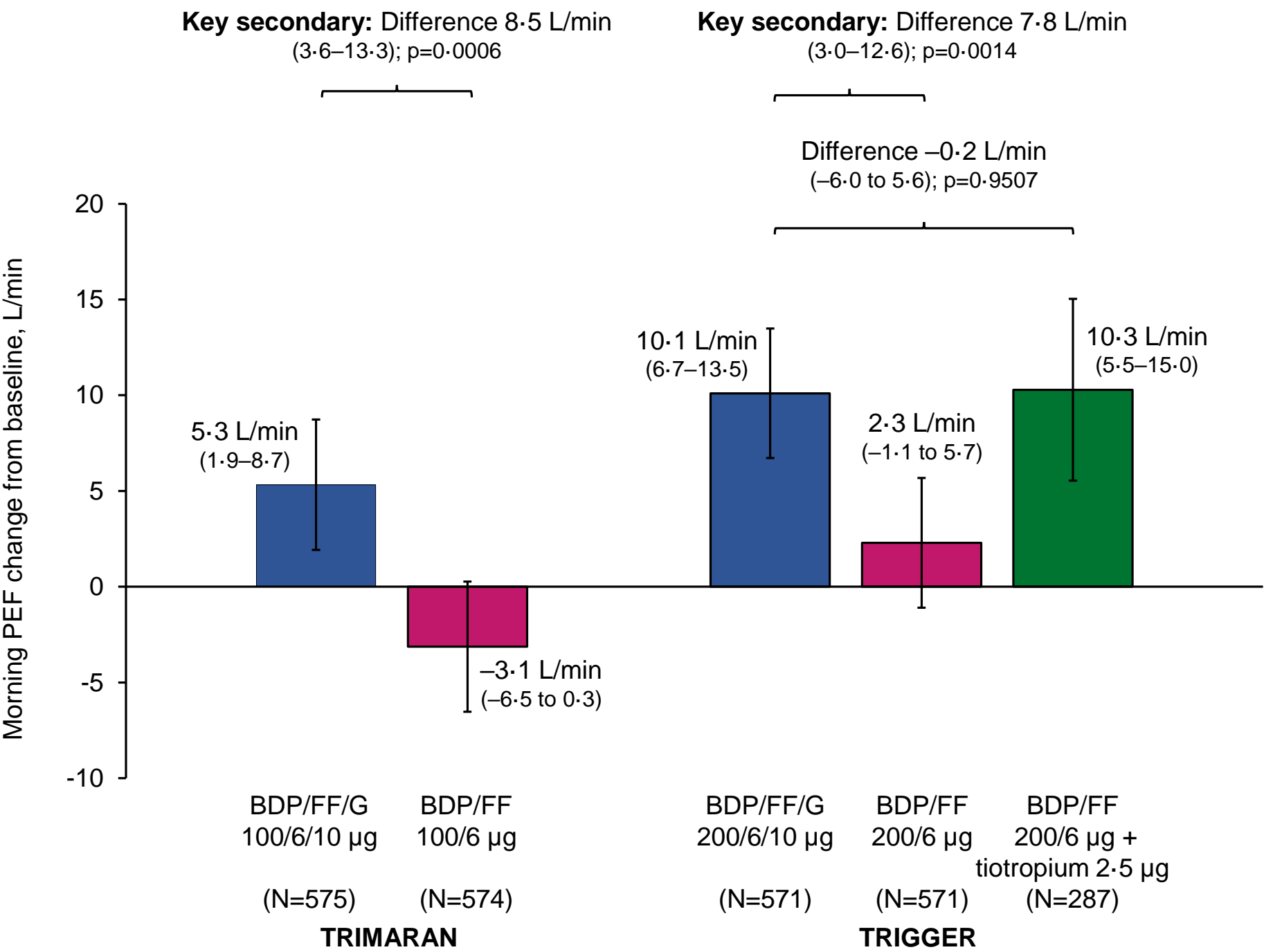


Figure 3C

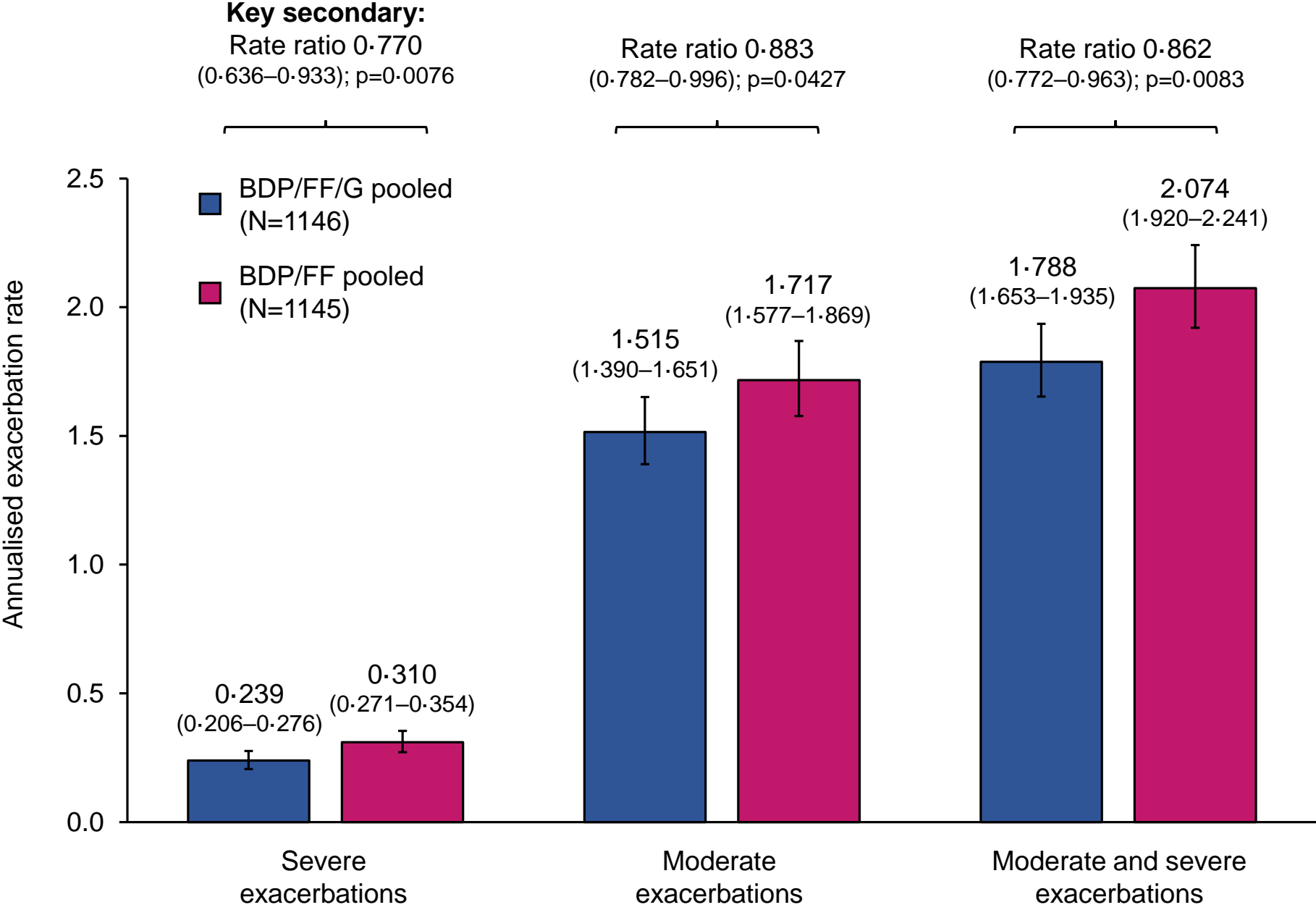
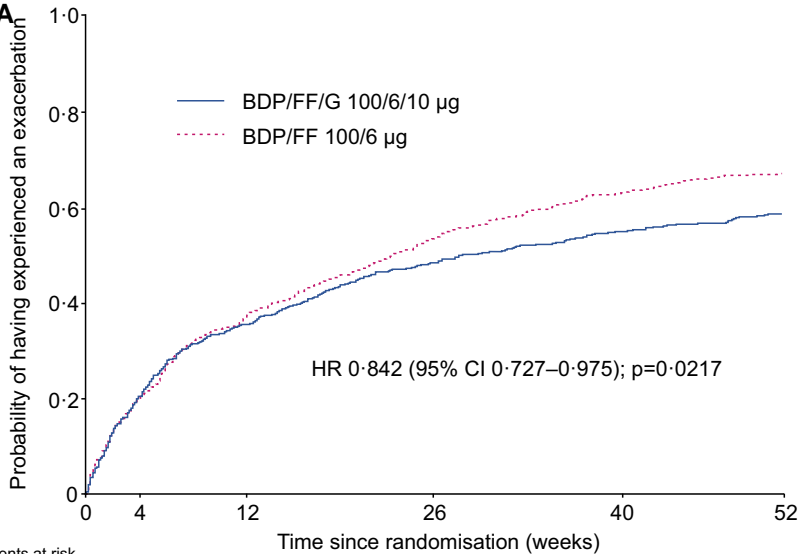
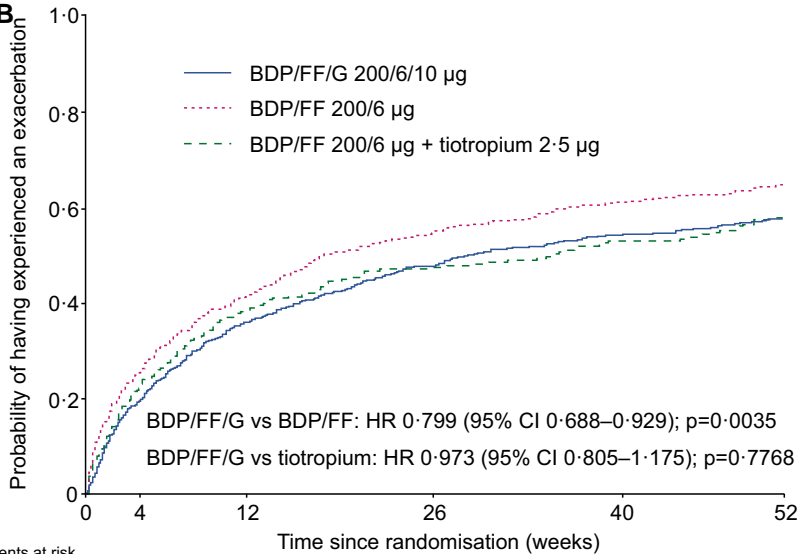


Figure 4A

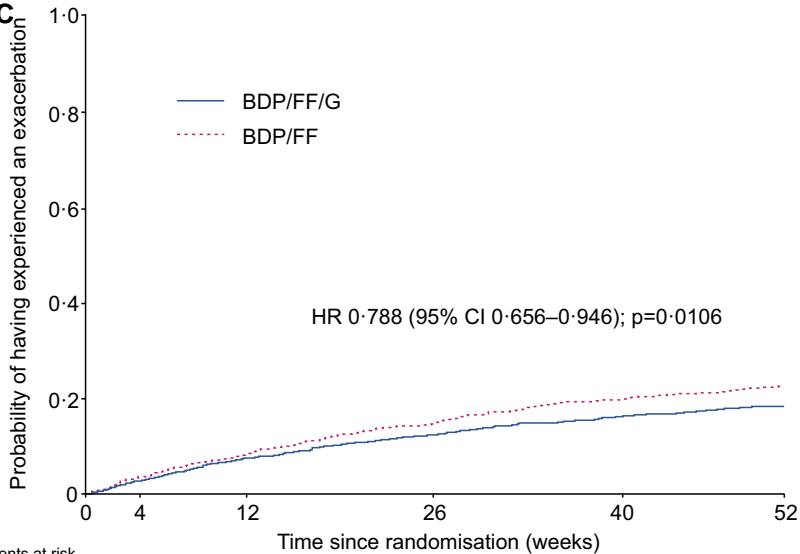
Number of patients at risk

BDP/FF/G	n=575	455	368	293	252	155
BDP/FF	n=574	457	354	257	199	121

Figure 4B

Number of patients at risk

BDP/FF/G	n=571	460	363	292	253	148
BDP/FF	n=571	421	331	252	213	129
BDP/FF + tiotropium	n=287	222	175	146	128	76

Figure 4C

Number of patients at risk

BDP/FF/G	n=1146	1109	1048	984	924	590
BDP/FF	n=1145	1098	1031	942	871	544

Supplementary Material

[Click here to download Supplementary Material: TRIMARAN and TRIGGER manuscript supplement \(21 Aug 2019\).pdf](#)