Brief report

Extrafine triple therapy and asthma exacerbation seasonality: TRIMARAN and TRIGGER *post hoc* analyses

Alberto Papi, MD,[a] Johann Christian Virchow, MD,[b] Dave Singh, MD,[c] Maxim Kots, MD,[d] Andrea Vele, MSc,[d] George Georges, MD,[d] and Giorgio Walter Canonica, MD[e] *Ferrara, Parma, and Milan, Italy; Rostock, Germany; and Manchester, United Kingdom*

Background: Previous studies have shown seasonal variation in asthma exacerbations, peaking over the winter months. A single-inhaler triple therapy containing extrafine formulations of the inhaled corticosteroid (ICS) beclomethasone dipropionate (BDP), long-acting β_2-agonist formoterol fumarate (FF), and long-acting muscarinic antagonist glycopyrronium (G) is in development for asthma.

Objective: We sought to evaluate whether calendar season impacted the relative effect of BDP/FF/G versus BDP/FF on moderate and severe asthma exacerbations.

Methods: TRIMARAN and TRIGGER were double-blind 52-week studies comparing BDP/FF/G with BDP/FF (TRIMARAN medium-dose ICS; TRIGGER high-dose) in adults with uncontrolled asthma (Asthma Control Questionnaire-7 score ≥1.5), prebronchodilator FEV_1 less than 80% predicted, history of 1 or more asthma exacerbation, who had been receiving ICS/long-acting β_2-agonist for at least 4 weeks before entry. Moderate and severe asthma exacerbations were captured throughout each study. In these *post hoc* analyses, the annual moderate and severe exacerbation rate was calculated for each month, with rate ratios determined from events grouped by season.

Results: In patients who received BDP/FF alone, there was a marked seasonal effect on the occurrence of asthma exacerbations, with the rate highest in the winter months. However, the addition of the long-acting muscarinic antagonist component to BDP/FF reduced this seasonal variation, especially during the winter, such that the relative effect of BDP/FF/G versus BDP/FF was greatest in the winter (significant 20.3% reduction [$P = .0008$]). Reductions in the other seasons ranged between 8.6% and 12.0%.

Conclusions: These *post hoc* analyses indicate that inhaled triple therapy with extrafine BDP/FF/G reduces seasonal peaks in moderate and severe exacerbations, and confirm the overall utility of adding long-acting muscarinic antagonist to ICS/long-acting β_2-agonist in the management of asthma. (J Allergy Clin Immunol 2021;■■■:■■■-■■■.)

Key words: *Asthma, exacerbations, pharmacotherapy, inhaled corticosteroid, long-acting β_2-agonist, long-acting muscarinic antagonist*

INTRODUCTION

A number of studies have evaluated the seasonal trends of asthma exacerbations.[1,2] In a New York database analysis, asthma-related emergency department visits and hospitalizations were most frequent in the winter, and least frequent in the

From [a]the Respiratory Medicine Unit, University of Ferrara, University Hospital S. Anna, Ferrara; [b]Universitätsmedizin Rostock, Zentrum für Innere Medizin, Abteilung für Pneumologie, Rostock; [c]the Medicines Evaluation Unit, The University of Manchester, Manchester University NHS Foundation Trust, Manchester; [d]Global Clinical Development, Chiesi Farmaceutici SpA, Parma; and [e]Humanitas University and Research Hospital IRCCS, Center of Personalized Medicine: Asthma and Allergy, Milan.

The funder of the study, Chiesi Farmaceutici SpA, was responsible for the design of TRIMARAN and TRIGGER, and for conducting the *post hoc* analyses that are reported in this article. Employees of the sponsor (as authors) were involved in the writing of this article, and in the decision to submit for publication. D.S. is supported by the National Institute for Health Research Manchester Biomedical Research Centre.

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Corresponding author: Alberto Papi, MD, Respiratory Medicine Unit, University of Ferrara, University Hospital S. Anna, Ferrara, Italy. E-mail: ppa@unife.it.

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Abbreviations used
BDP: Beclomethasone dipropionate
BID: Twice daily
FF: Formoterol fumarate
G: Glycopyrronium
ICS: Inhaled corticosteroid
LABA: Long-acting β_2-agonist
LAMA: Long-acting muscarinic antagonist
PAL: Persistent airflow limitation

summer.[3] Similarly, in a Spanish study, the incidence of both asthma-related emergency department visits and hospitalizations in adults peaked in the winter,[4] and in a study from the United Kingdom, there was a strong correlation between the seasonal pattern of upper respiratory tract infections and asthma-related hospitalization.[5] Results from *post hoc* analyses of clinical trials have shown similar seasonal variation in patients receiving an inhaled corticosteroid (ICS) plus a controller.[6,7] More recently, seasonal variation in "asthma worsening" (described by the authors as "a more moderate and common counterpart to exacerbations") has been analyzed using data pooled from 2 tiotropium 48-week studies (PrimoTinA-asthma).[8] In these studies, tiotropium was compared with placebo, with all patients receiving an ICS/long-acting β_2-agonist (LABA) combination. The occurrence of asthma worsening in the placebo arm peaked in the winter, with lower seasonal variation in the tiotropium arm.

A single-inhaler triple therapy containing extrafine formulations of the ICS beclomethasone dipropionate (BDP), the LABA formoterol fumarate (FF), and the long-acting muscarinic antagonist (LAMA) glycopyrronium (G) has been evaluated for the management of asthma in 2 phase III trials—TRIMARAN and TRIGGER. These were double-blind 52-week studies that compared the efficacy and safety of BDP/FF/G versus BDP/FF; TRIGGER included a third arm in which patients received open-label BDP/FF + tiotropium.[9] Both studies recruited adults with uncontrolled asthma (Asthma Control Questionnaire-7 score ≥1.5), prebronchodilator FEV_1 less than 80% of predicted normal (but no limitation on postbronchodilator FEV_1 or ratio of FEV_1 to forced vital capacity), a history of at least 1 asthma exacerbation in the previous 12 months, and who were receiving a stable dose of an ICS/LABA for at least 4 weeks before entry. The design of these studies was similar, with the main difference being that TRIMARAN used a medium ICS dose (BDP/FF/G 100/6/10 μg and BDP/FF 100/6 μg, both 2 inhalations twice daily [BID]), whereas TRIGGER used a high ICS dose (200/6/10 μg and 200/6 μg, respectively, 2 inhalations BID). Moderate and severe asthma exacerbations were defined in accordance with American Thoracic Society/European Respiratory Society joint statements.[10,11] Overall, BDP/FF/G improved lung function (predose and peak FEV_1 and peak expiratory flow) versus BDP/FF in both studies, with a statistically significant 15% reduction ($P = .033$) in the rate of moderate and severe exacerbations in TRIMARAN, and a 12% reduction in TRIGGER ($P = .11$).[9]

We decided to use data that had been pooled from TRIMARAN and TRIGGER to evaluate whether calendar season impacted the relative effect of single-inhaler triple therapy (BDP/FF/G) versus ICS/LABA (BDP/FF) on moderate and severe exacerbations, both in the overall population and in the subset with "persistent airflow limitation" (PAL). The PAL analyses were to better facilitate comparisons with the tiotropium analyses, because the tiotropium studies limited recruitment to patients with postbronchodilator (salbutamol) FEV_1 less than or equal to 80% predicted and FEV_1/forced vital capacity ratio less than or equal to 0.7[12] (ie, patients with airflow obstruction that failed to normalize postsalbutamol). Full methods are included in this article's Online Repository at www.jacionline.org.

RESULTS AND DISCUSSION

TRIMARAN was conducted between February 17, 2016, and May 17, 2018, with TRIGGER conducted between April 6, 2016, and May 28, 2018. Patients entered into the 2 studies (ie, their screening date) in all 4 seasons, although with a slight tendency toward a fall entry (see Table E1 in this article's Online Repository at www.jacionline.org). Data were analyzed for 1146 patients receiving BDP/FF/G and 1145 receiving BDP/FF (for the patient disposition in the 2 studies, please see Fig 1 in Virchow et al[9]). Of these, 688 (60.0%) and 673 (58.8%) met the PAL definition at screening in the BDP/FF/G and BDP/FF groups, respectively. Overall, BDP/FF/G reduced the annualized rate of moderate and severe exacerbations by 14% versus BDP/FF ($P = .0083$).[9]

In patients who received BDP/FF alone, there was a marked effect of season on the occurrence of moderate and severe asthma exacerbations, with the highest rate in the winter (specifically in December followed by January), with the rate falling during spring and into summer, before increasing again during the fall months (Fig 1, *A*). These results are consistent with previous analyses, in which patients receiving ICS plus a second controller experienced substantial seasonal variation in asthma exacerbations.[6,7] However, the addition of the LAMA component to BDP/FF reduced this seasonal variation, especially during the winter months, with the relative effect of BDP/FF/G versus BDP/FF particularly notable in December and January (Fig 1, *A*). As a consequence, the treatment effect on the rate of moderate and severe exacerbations was greatest in the winter (a significant 20% reduction [$P = .0008$] with BDP/FF/G vs BDP/FF; Fig 1, *B*). Numerical reductions in the other seasons ranged between 9% and 12% (not significant, $P = .1017$ to $.3011$).

In the subset of patients with PAL, the seasonal pattern of exacerbations in the BDP/FF treatment group was similar to that observed in the overall population, with the highest rates in the winter months (Fig 2, *A*). As with the overall population, the seasonal peaks were attenuated in the triple therapy group, such that the greatest rate reduction with BDP/FF/G versus BDP/FF was in the winter, with a significant 29% reduction ($P < .0001$; Fig 2, *B*). The reductions in the other seasons ranged from 14% ($P = .1327$) to a significant 19% ($P = .0369$). Of note, the rate reductions were numerically larger in the PAL subset than in the overall population in all 4 seasons, primarily driven by the BDP/FF treatment group, in which the exacerbation rates were higher in the PAL subset than in the overall group; in contrast, in the BDP/FF/G treatment group, rates were similar in the overall population and the PAL subset.

These are the first analyses to demonstrate such a pronounced seasonal benefit on exacerbations from the addition of a LAMA to ICS/LABA therapy. We confirmed results from a number of previous analyses, with a marked seasonal variation in the occurrence of exacerbations in patients receiving ICS/LABA alone, with the highest risk in the 3 winter months, followed by spring and fall. The key finding of our analyses was that the main

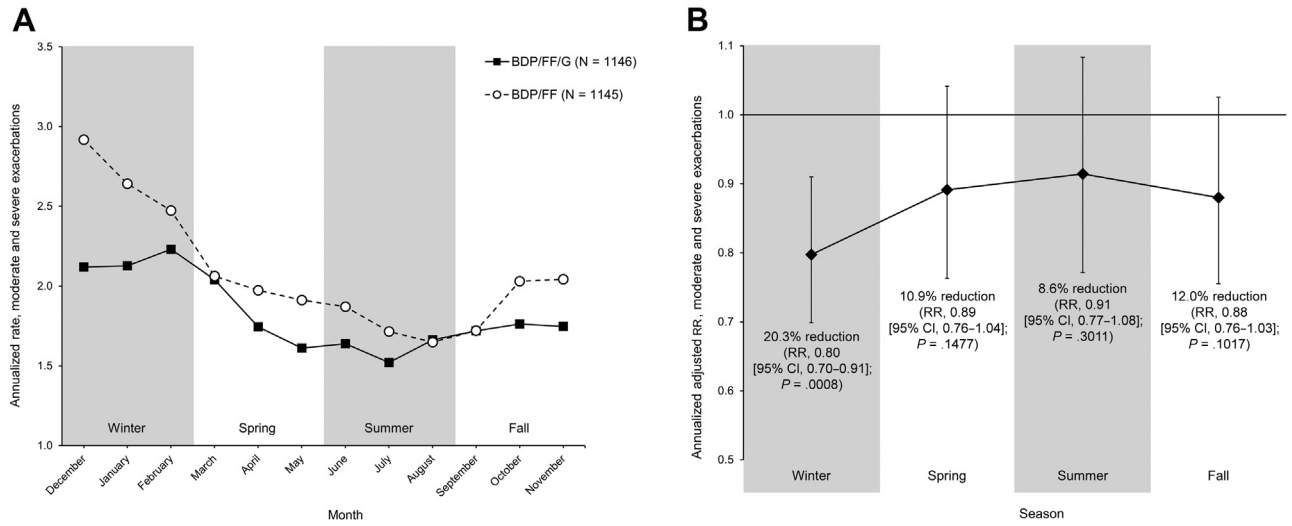

FIG 1. A, Rate of moderate and severe exacerbations by the month of onset. **B,** Adjusted RR BDP/FF/G vs BDP/FF by season (overall population). *RR,* Rate ratio.

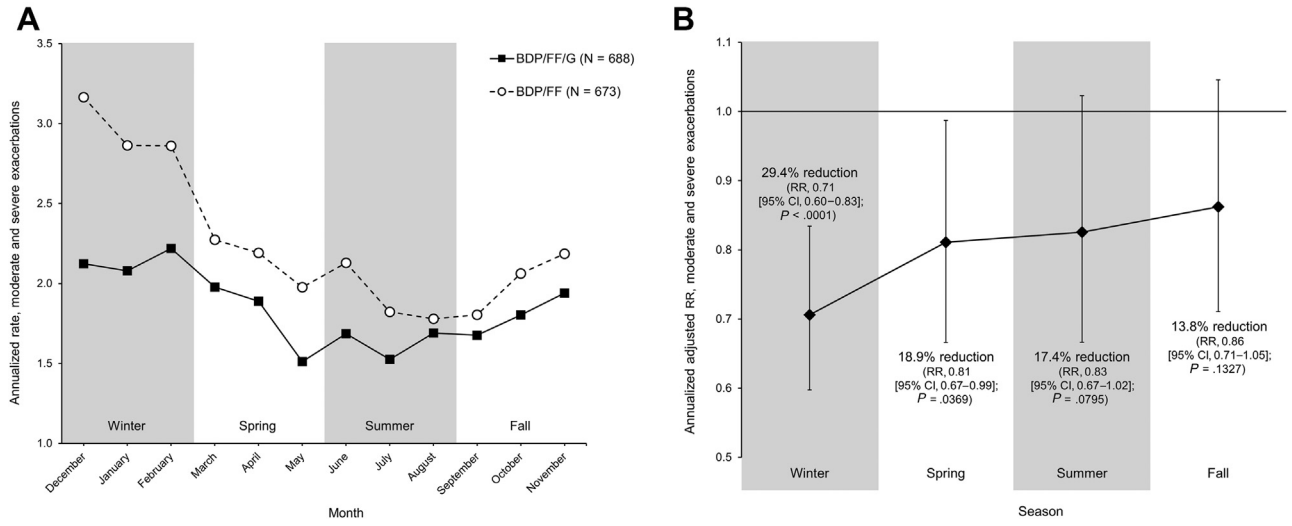

FIG 2. A, Rate of moderate and severe exacerbations by the month of onset. **B,** Adjusted RR BDP/FF/G vs BDP/FF by season (PAL subset). *RR,* Rate ratio

benefit from the addition of a LAMA was in smoothing out this winter peak, although there was some benefit across the full calendar. It is considered that there are different types of asthma exacerbations, with some involving eosinophilic inflammation, which are responsive to corticosteroid therapy.[2] For example, airborne allergen exposure, which is highest from spring to fall across Europe, typically triggers ICS-responsive exacerbations.[13] Other types of exacerbation (especially those associated with infections) tend to be corticosteroid resistant[2,14]; for these less ICS-responsive exacerbations, additional bronchodilation could be more relevant. In addition, a number of *in vitro* studies have demonstrated a direct inhibitory effect of the LAMA tiotropium on respiratory syncytial virus replication and activity.[15-17] Although most common during the winter months, infective exacerbations (especially due to viral infections, primarily human rhinovirus and to a lesser extent influenza) can occur throughout the year, which may help to explain why there was a benefit from the use of BDP/FF/G in terms of exacerbations in all 4 seasons (especially in the PAL subset). Furthermore, the value of BDP/FF/G over BDP/FF was not restricted to exacerbations—in the overall analyses, BDP/FF/G also improved lung function (predose and peak FEV_1 and peak expiratory flow) versus BDP/FF in both studies.[9] Unfortunately, the design of TRIMARAN and TRIGGER, with only 6 clinic visits over the 52-week follow-up period, does not facilitate an examination of the seasonal variation of these routinely assessed end points.

These analyses do have some limitations, of course, in particular that they are *post hoc*. In addition, our conclusions are drawn on mean data, rather than individual patient analyses, and do not provide a comprehensive mechanistic explanation for the results that we observed. However, they may be of particular relevance in some patients—especially in those individuals who are more prone to exacerbations in the winter. The key strength is the prolonged recruitment periods of the 2 studies

(TRIMARAN recruited patients between February 2016 and May 2017, with TRIGGER recruiting between April 2016 and May 2017), which permitted us to conduct these analyses.

In conclusion, these *post hoc* analyses of data from two 12-month studies indicate that inhaled triple therapy with extrafine BDP/FF/G reduces seasonal peaks in moderate and severe exacerbations, and confirm the overall utility of adding LAMA to ICS/LABA as maintenance therapy in the management of asthma.

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Clinical implications: Studies have demonstrated substantial seasonal variation in asthma exacerbations. In these *post hoc* analyses, we show that inhaled triple therapy reduces this seasonal variation, demonstrating particular efficacy in the winter.

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METHODS

Trial design and participants

The full design and inclusion/exclusion criteria of TRIMARAN and TRIGGER have been previously published.[E1] Both studies recruited men or women aged 18 to 75 years, inclusive, with a documented history of asthma for at least 1 year and diagnosed before the age of 40 years, prebronchodilator FEV_1 less than 80% of the predicted normal value (the patients actually recruited into TRIMARAN had prebronchodilator FEV_1 ranging from 17% to 79%, with TRIGGER ranging from 15% to 79%), and a change in FEV_1 of more than 12% and more than 200 mL 10 to 15 minutes after inhaling albuterol. Patients were to have uncontrolled asthma (Asthma Control Questionnaire-7 score ≥1.5), a history of at least 1 exacerbation requiring treatment with systemic corticosteroids or an emergency department visit or in-patient hospitalization in the previous 12 months, and were receiving a stable dose of an ICS/LABA for at least 4 weeks before entry (TRIMARAN: medium ICS dose; TRIGGER: high dose). Patients were excluded if they had a diagnosis of chronic obstructive pulmonary disease, or if they were current smokers, or ex-smokers with total cumulative exposure greater than or equal to 10 pack-years or who had stopped smoking within 1 year before entry. Neither study applied phenotypic (eg, blood eosinophils or persistent airflow limitation status) or allergen sensitization criteria to recruitment or randomization stratification.

Patients who met the inclusion/exclusion criteria at screening had their asthma maintenance therapy switched to extrafine BDP/FF 100/6 μg in TRIMARAN and 200/6 μg in TRIGGER, 2 inhalations BID via pressurized metered dose inhaler for a 2-week open-label run-in period. At the end of the run-in period, patients were randomized to either continue BDP/FF (100/6 μg in TRIMARAN or 200/6 μg in TRIGGER) or receive extrafine BDP/FF/G (100/6/10 μg in TRIMARAN or 200/6/10 μg in TRIGGER), all 2 inhalations BID via pressurized metered dose inhaler. A third treatment group was included in TRIGGER: open-label BDP/FF 200/6 μg 2 inhalations BID plus tiotropium once daily in separate inhalers; these patients are not included in the current analyses.

All patients provided written informed consent before any study-related procedure. The study was approved by the independent ethics committees at each institution, and was performed in accordance with the principles of the Declaration of Helsinki, and the International Conference on Harmonization notes for guidance on Good Clinical Practice (ICH/CPMP/135/95). The studies are registered with ClinicalTrials.gov: TRIMARAN, NCT02676076; TRIGGER, NCT02676089.

Outcomes

The occurrence of asthma exacerbations was captured throughout the 52-week study duration. One of the 2 coprimary end points of TRIMARAN and TRIGGER was the rate of moderate to severe exacerbations. Severe exacerbations were defined as asthma worsening requiring treatment with systemic corticosteroids for at least 3 days, whereas moderate exacerbations were episodes of asthma worsening that were self-managed, defined in accordance with an American Thoracic Society/European Respiratory Society joint statement.[E2]

Statistical methods

No adjustment for multiplicity was applied to the analyses in this study. To analyze the impact of seasonality, data from TRIMARAN and TRIGGER were pooled. For each treatment and month, the annual rate of moderate to severe exacerbations was calculated by dividing the total number of events (for each treatment and month) by the total number of study days (for each treatment and month) × 365.25, with events grouped by date of onset. Rate ratios were determined with events grouped by season: events that had onset between December 1 and February 28 (29 in leap years) were grouped as "winter," those between March 1 and May 31 were grouped as "spring," June 1 and August 31 as "summer," and September 1 and November 30 as "fall." Data for sites in Argentina (the only southern hemisphere country included in these studies) were all shifted by 6 months.

The number of asthma exacerbations in each season was analyzed using a negative binomial model including treatment, country, and number of exacerbations in the previous year (1 or >1) as fixed effects, and log-season-time on study as offset, and presented as adjusted rate ratios with 95% CIs and *P* values.

RESULTS

See Table E1.

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TABLE E1. Season of screening visit

Season of screening visit, n (%)	BDP/FF/G (N = 1146)	BDP/FF (N = 1145)
Winter	228 (19.9)	231 (20.2)
Spring	252 (22.0)	243 (21.2)
Summer	311 (27.1)	311 (27.2)
Fall	355 (31.0)	360 (31.4)

This table presents the proportion of patients who entered TRIMARAN and TRIGGER according to the season of the initial (screening) visit: "Winter" indicates that the screening visit was in December, January, or February, "Spring" indicates March, April, or May, "Summer" indicates June, July, or August, and "Fall" indicates September, October, or November. Data for the southern hemisphere were shifted by 6 months.