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

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PII: S0091-6749(21)00086-5

DOI: <https://doi.org/10.1016/j.jaci.2021.01.007>

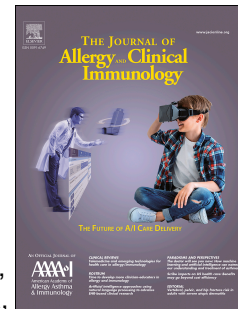
Reference: YMAI 14935

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 3 November 2020

Revised Date: 10 December 2020

Accepted Date: 12 January 2021



Please cite this article as: Papi A, Virchow JC, Singh D, Kots M, Vele A, Georges G, Canonica Extrafine triple therapy and asthma exacerbation seasonality: TRIMARAN and TRIGGER post-hoc analyses, *Journal of Allergy and Clinical Immunology* (2021), doi: <https://doi.org/10.1016/j.jaci.2021.01.007>.

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Extrafine triple therapy and asthma exacerbation

seasonality: TRIMARAN and TRIGGER post-hoc analyses

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Funding

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.

Disclosure statement

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.

JCV reports personal fees from Chiesi during the conduct of the studies. 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 Gemeinsame Bundesausschuss (GBA).

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

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

GG is an employee of Chiesi USA, Inc.

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

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54 **Abstract**

55 **Background**

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

61 **Objective**

62 To evaluate whether calendar season impacted the relative effect of BDP/FF/G versus
63 BDP/FF on moderate-and-severe asthma exacerbations.

64 **Methods**

65 TRIMARAN and TRIGGER were double-blind 52-week studies comparing BDP/FF/G with
66 BDP/FF (TRIMARAN medium-dose ICS; TRIGGER high-dose) in adults with uncontrolled
67 asthma (Asthma Control Questionnaire-7 ≥ 1.5), pre-bronchodilator FEV₁ <80% predicted,
68 history of ≥ 1 asthma exacerbation, who had been receiving ICS/LABA for ≥ 4 weeks prior to
69 entry. Moderate and severe asthma exacerbations were captured throughout each study. In
70 these *post-hoc* analyses, the annual moderate-and-severe exacerbation rate was calculated
71 for each month, with rate ratios determined from events grouped by season.

72 **Results**

73 In patients who received BDP/FF alone, there was a marked seasonal effect on the
74 occurrence of asthma exacerbations, with the rate highest in the winter months. However,
75 the addition of the LAMA component to BDP/FF reduced this seasonal variation, especially
76 during the winter, such that the relative effect of BDP/FF/G versus BDP/FF was greatest in

the winter (significant 20.3% reduction [$p=0.0008$]). 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 LAMA to ICS/LABA in the management of asthma.

Clinical trial registration

ClinicalTrials.gov: TRIMARAN, NCT02676076; TRIGGER, NCT02676089.

86

87 **Clinical implications**

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

91 **Capsule summary**

92 There is seasonal variation in asthma exacerbations. In these *post-hoc* analyses, inhaled
93 triple therapy reduced seasonal peaks (demonstrating particular efficacy in winter),
94 confirming the overall utility of adding LAMA to ICS/LABA as asthma maintenance therapy.

95 **Keywords**

96 Asthma; exacerbations; pharmacotherapy; inhaled corticosteroid; long-acting beta2-agonist;
97 long-acting muscarinic antagonist.

98

99

100 **Abbreviations**

101 BDP, beclomethasone dipropionate

102 BID, twice daily

103 CI, confidence interval

104 ED, emergency department

105 FEV₁, forced expiratory volume in 1 second

106 FF, formoterol fumarate

107 FVC, forced vital capacity

108 G, glycopyrronium

109 ICS, inhaled corticosteroid

110 LABA, long-acting β_2 -agonist

111 LAMA, long-acting muscarinic antagonist

112 PAL, persistent airflow limitation

113 PEF, peak expiratory flow

114 pMDI, pressurized metered dose inhaler

115 RR, rate ratio

116

117

118 **Introduction**

119 A number of studies have evaluated the seasonal trends of asthma exacerbations.^{1,2} In a
120 New York database analysis, asthma-related emergency department (ED) visits and
121 hospitalizations were most frequent in the winter, and least frequent in the summer.³
122 Similarly, in a Spanish study the incidence of both asthma-related ED visits and
123 hospitalizations in adults peaked in the winter,⁴ and in a study from the UK, there was a
124 strong correlation between the seasonal pattern of upper respiratory infections and asthma-
125 related hospitalization.⁵ Results from *post-hoc* analyses of clinical trials have shown similar
126 seasonal variation in patients receiving an inhaled corticosteroid [ICS] plus a controller.^{6,7}
127 More recently, seasonal variation in 'asthma worsening' (described by the authors as 'a
128 more moderate and common counterpart to exacerbations') has been analyzed using data
129 pooled from two tiotropium 48-week studies (PrimoTinA-asthma).⁸ In these studies,
130 tiotropium was compared with placebo, with all patients receiving an ICS/long-acting β_2 -
131 agonist (LABA) combination. The occurrence of asthma worsening in the placebo arm
132 peaked in the winter, with lower seasonal variation in the tiotropium arm.

133 A single-inhaler triple therapy containing extrafine formulations of the ICS beclomethasone
134 dipropionate (BDP), the LABA formoterol fumarate (FF) and the LAMA glycopyrronium (G)
135 has been evaluated for the management of asthma in two Phase III trials – TRIMARAN and
136 TRIGGER. These were double-blind 52-week studies that compared the efficacy and safety
137 of BDP/FF/G versus BDP/FF; TRIGGER included a third arm in which patients received
138 open-label BDP/FF + tiotropium.⁹ Both studies recruited adults with uncontrolled asthma
139 (Asthma Control Questionnaire-7 ≥ 1.5), pre-bronchodilator forced expiratory volume in 1
140 second (FEV₁) <80% of predicted normal (but no limitation on post bronchodilator FEV₁ or
141 ratio of FEV₁ to forced vital capacity [FVC]), a history of at least one asthma exacerbation in
142 the previous 12 months, and who were receiving a stable dose of an ICS/LABA for at least

four weeks prior to 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 two inhalations twice daily [BID]), whereas TRIGGER used a high ICS dose (200/6/10 µg and 200/6 µg, respectively, two 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 (pre-dose and peak FEV₁ and peak expiratory flow [PEF]) versus BDP/FF in both studies, with a statistically significant 15% reduction (p=0.033) in the rate of moderate-and-severe exacerbations in TRIMARAN, and a 12% reduction in TRIGGER (p=0.11).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, since the tiotropium studies limited recruitment to patients with post-bronchodilator (salbutamol) FEV₁ ≤80% predicted and FEV₁/FVC ratio ≤0.7,¹² (i.e., patients with airflow obstruction that failed to normalize post-salbutamol). Full methods are included in the supplement.

Results and discussion

TRIMARAN was conducted between Feb 17, 2016, and May 17, 2018, with TRIGGER conducted between April 6, 2016, and May 28, 2018. Patients entered into the two studies (i.e., their screening date) in all four seasons, although with a slight tendency towards a fall entry (Supplementary Table 1). Data were analyzed for 1146 patients receiving BDP/FF/G and 1145 receiving BDP/FF (please see published Figure 1)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 ($p=0.0083$).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 (Figure 1A). 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 (Figure 1A). As a consequence, the treatment effect on the rate of moderate-and-severe exacerbations was greatest in the winter (a significant 20% reduction [$p=0.0008$] with BDP/FF/G versus BDP/FF; Figure 1B). Numerical reductions in the other seasons ranged between 9 and 12% (not significant, $p=0.1017$ to 0.3011).

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 (Figure 2A). 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 ($p<0.0001$; Figure 2B).

The reductions in the other seasons ranged from 14% ($p=0.1327$) to a significant 19% ($p=0.0369$). Of note, the rate reductions were numerically larger in the PAL subset than in the overall population in all four 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 three winter months, followed by spring and fall. The key finding of our analyses was that the main 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 four 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 (pre-dose and peak FEV₁ and PEF) versus BDP/FF in both studies.⁹ Unfortunately, the design of

TRIMARAN and TRIGGER, with only six clinic visits over the 52-week follow-up period, does not facilitate an examination of the seasonal variation of these routinely-assessed endpoints.

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 two 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.

230

231 **Acknowledgements**

232 Dave Singh is supported by the National Institute for Health Research (NIHR) Manchester

233 Biomedical Research Centre (BRC).

234 The authors would like to thank the investigators and patients at the investigative sites for

235 their support of these studies.

236 Writing support was provided by David Young of Young Medical Communications and

237 Consulting Ltd. This support was funded by Chiesi Farmaceutici SpA.

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293

294 **Figure legends**

295 *Figure 1. A) Rate of moderate-and-severe exacerbations by the month of onset, and B)*
296 *adjusted rate ratio BDP/FF/G versus BDP/FF by season (overall population).*

297 *BDP, beclomethasone dipropionate; FF, formoterol fumarate; G, glycopyrronium ; RR, rate ratio; CI, confidence interval.*

298

299 *Figure 2. A) Rate of moderate-and-severe exacerbations by the month of onset, and B)*
300 *adjusted rate ratio BDP/FF/G versus BDP/FF by season (PAL subset).*

301 *PAL, persistent airflow limitation; BDP, beclomethasone dipropionate; FF, formoterol fumarate; G, glycopyrronium ; RR, rate*
302 *ratio; CI, confidence interval.*

303

