Effects of seasonality and treatment on COPD clinical outcomes: IMPACT *post hoc* analysis

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To the Editor:

COPD exacerbation rates vary during the year, with higher rates and a greater proportion of patients experiencing exacerbations in the winter months [1, 2]. These seasonal effects are driven by a wide range of factors, including host physiology, environmental factors and differing rates of pathogen exposure [3].

The InforMing the PAthway of COPD Treatment (IMPACT) trial investigated the effect of once-daily single-inhaler triple therapy with inhaled corticosteroid (ICS)/long-acting muscarinic receptor antagonist/long-acting β_2-agonist, fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 µg (FF/UMEC/VI), *versus* dual therapy with FF/VI 100/25 µg or UMEC/VI 62.5/25 µg in 10 355 patients with COPD. Eligible patients were required to be ⩾40 years of age with symptomatic COPD (COPD Assessment Test score ⩾10) and have a forced expiratory volume in 1 s (FEV_1) <50% predicted and >1 moderate or severe exacerbations in the prior year, or a FEV_1 50–80% predicted and >2 moderate or >1 severe exacerbations in the prior year. Patients with a diagnosis of asthma were excluded [4, 5]. Moderate exacerbations were defined as those requiring systemic glucocorticoid and/or antibiotic treatment, and severe exacerbations were those resulting in hospitalisation or death. IMPACT demonstrated that FF/UMEC/VI significantly reduced moderate/severe exacerbation rates compared with dual therapy in this patient population [4]. As IMPACT was an international study, comparing data collected by hemisphere will allow the identification of any seasonal trends in exacerbations.

This *post hoc* analysis investigated potential seasonal effects on the rate of moderate and severe exacerbations in 10 038 patients receiving FF/UMEC/VI *versus* FF/VI and UMEC/VI therapy.

Northern Hemisphere countries (primarily located above the Tropic of Cancer) included Austria, Belgium, Canada, China, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Israel, Japan, Korea, the Netherlands, Norway, Poland, Puerto Rico, Romania, Russia, Singapore, Spain, Sweden, Thailand, Turkey, Ukraine, UK, USA and Vietnam. Southern Hemisphere countries (primarily located below the Tropic of Capricorn) included Argentina, Australia, Brazil, Chile, Colombia, New Zealand and South Africa. Peru and the Philippines were excluded due to the lack of seasonality in the Tropics, as these countries are located between the Tropics of Cancer and Capricorn; these 317 (3.1%) patients from IMPACT were excluded. Winter months were defined as December to February for the Northern Hemisphere and June to August for the Southern Hemisphere. Summer months were defined as June to August for the Northern Hemisphere and December to February for the Southern Hemisphere. Exacerbations were assigned to a season based on the start date of the exacerbation.

The annual rate of on-treatment moderate/severe COPD exacerbations by treatment group was analysed using a generalised linear model assuming a negative binomial distribution. The response variable was the number of recorded on-treatment moderate/severe COPD exacerbations per participant, and the explanatory variables were post-bronchodilator % predicted FEV_1, region and treatment group and region by treatment group interaction with log (time on-treatment) as an offset variable.

A seasonality index (mean winter monthly moderate/severe exacerbation rate divided by the mean summer monthly moderate/severe exacerbation rate) and range (upper boundary: highest monthly exacerbation rate

Shareable abstract (@ERSpublications)
IMPACT *post hoc* analysis identified higher COPD exacerbation rates in winter *versus* summer. Exacerbation risk was significantly reduced with FF/UMEC/VI *versus* dual therapy regardless of season, highlighting the durability of response with triple therapy. https://bit.ly/47KAhmK

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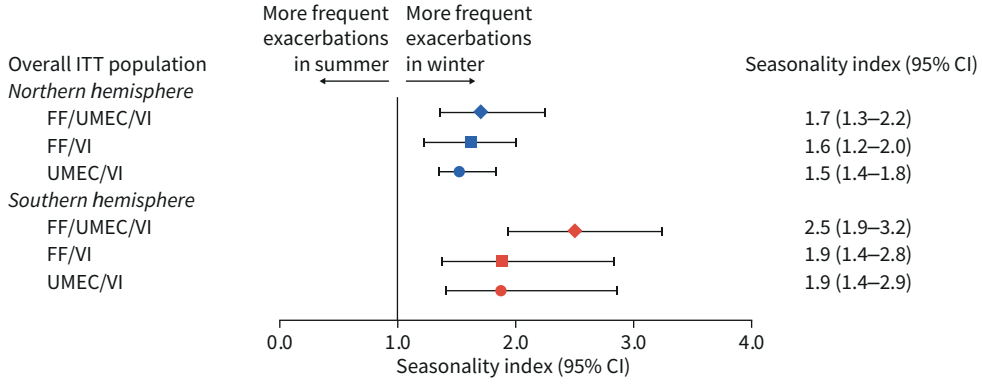
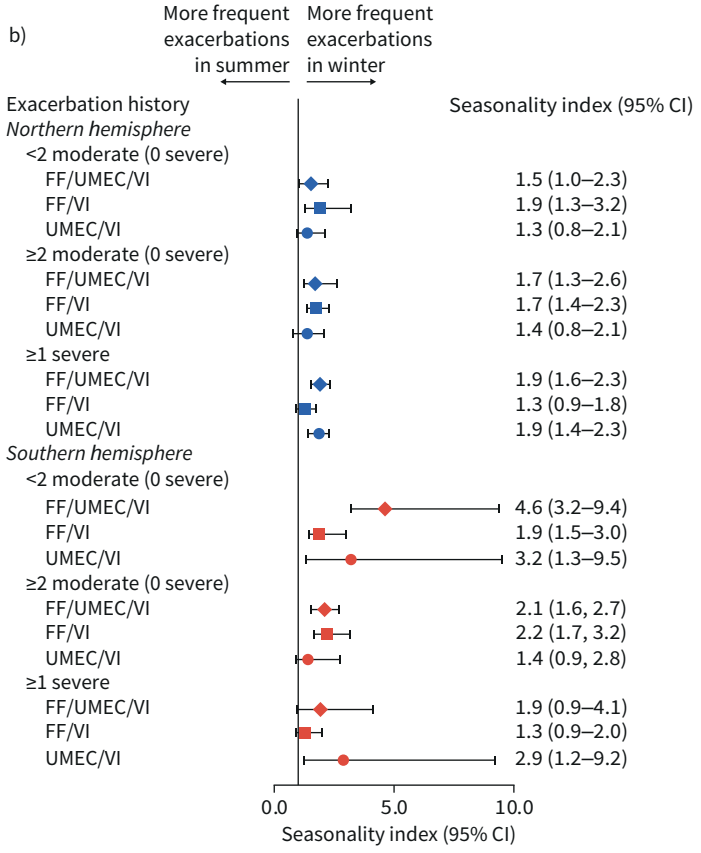
a)



b)



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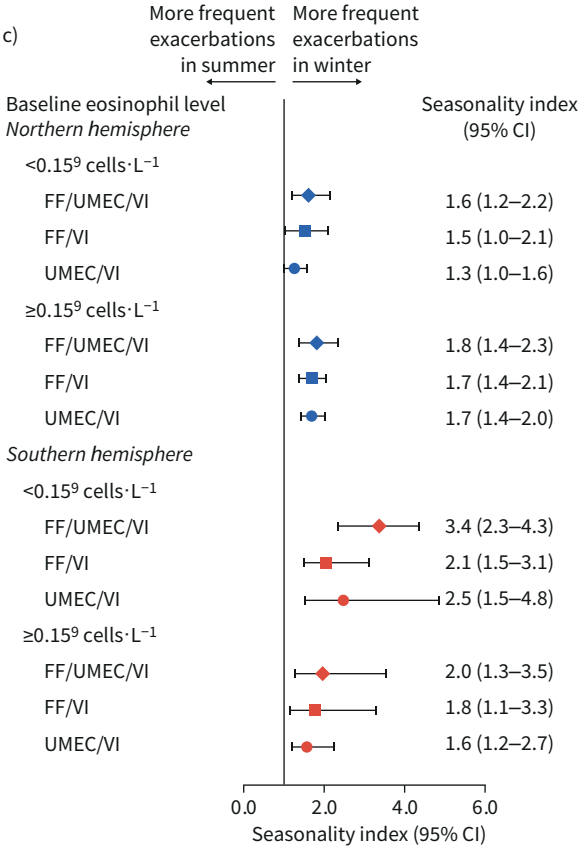
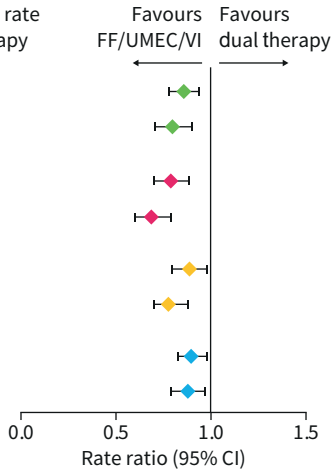


d)



	Mean annual exacerbation rate FF/UMEC/VI	Mean annual exacerbation rate dual therapy	Rate ratio (95% CI)	p-value
Spring				
FF/UMEC/VI (n=3744) *versus* FF/VI (n=3579)	0.89	1.05	0.86 (0.78–0.94)	0.002
FF/UMEC/VI (n=3744) *versus* UMEC/VI (n=1759)	0.89	1.12	0.80 (0.71–0.90)	<0.001
Summer				
FF/UMEC/VI (n=3724) *versus* FF/VI (n=3544)	0.60	0.76	0.79 (0.70–0.89)	<0.001
FF/UMEC/VI (n=3724) *versus* UMEC/VI (n=1729)	0.60	0.87	0.69 (0.60–0.79)	<0.001
Autumn				
FF/UMEC/VI (n=3763) *versus* FF/VI (n=3564)	0.95	1.07	0.89 (0.80–0.98)	0.015
FF/UMEC/VI (n=3763) *versus* UMEC/VI (n=1780)	0.95	1.21	0.78 (0.70–0.88)	<0.001
Winter				
FF/UMEC/VI (n=3759) *versus* FF/VI (n=3587)	1.22	1.35	0.90 (0.83–0.98)	0.017
FF/UMEC/VI (n=3759) *versus* UMEC/VI (n=1787)	1.22	1.39	0.88 (0.79–0.97)	0.013

FIGURE 1 Mean patient seasonality index by subgroup in the Northern and Southern Hemispheres in a) the overall ITT population by b) exacerbation rate, c) baseline eosinophil level, and d) annual rate of on-treatment moderate/severe exacerbations in patients receiving fluticasone furoate/umeclidinium/vilanterol *versus* fluticasone furoate/vilanterol or umeclidinium/vilanterol. Seasonality index is calculated as the mean monthly exacerbation rate in winter (Northern Hemisphere: December to February, Southern Hemisphere: June to August) divided by the mean monthly exacerbation rate in summer (Northern Hemisphere: June to August, Southern Hemisphere: December to February). Upper boundary: highest monthly winter rate of moderate/severe exacerbations divided by the lowest monthly summer rate of moderate/severe exacerbations. Lower boundary: lowest monthly winter rate of moderate/severe exacerbations divided by highest monthly summer rate of moderate/severe exacerbations. Higher moderate/severe exacerbation rates in winter than summer result in a lower boundary of >1. Baseline levels were measured at screening. FF: fluticasone furoate; ITT: intent-to-treat; UMEC: umeclidinium; VI: vilanterol.

in winter divided by lowest monthly exacerbation rate in summer; lower boundary: lowest monthly exacerbation rate in winter divided by highest monthly exacerbation rate in summer) were calculated for the intent-to-treat (ITT) population and stratified by exacerbation history subgroups (<2 moderate (0 severe), ⩾2 moderate (0 severe) and ⩾1 severe) and eosinophil level (<0.15×10^9 L^{-1} and ⩾0.15×10^9 L^{-1}).

The annual rate of moderate/severe exacerbations was higher in winter (Northern Hemisphere: 1.30 (n=7220); Southern Hemisphere: 1.31 (n=1913)) and lower in summer (Northern Hemisphere: 0.74 (n=7174); Southern Hemisphere: 0.59 (n=1823)), though the interaction between treatment and season was not statistically significant (winter: p=0.89; summer: p=0.61). The mean seasonality index and lower boundaries were >1 for all treatment groups in the ITT population, indicating higher exacerbation rates in winter compared with summer (figure 1a). Similarly, for both subgroups of eosinophil level and all prior exacerbation history subgroups at screening, trends for differences in exacerbation rates were observed between seasons, when the mean seasonality index was >1 for all subgroups and the lower boundaries were >1 for most subgroups (figure 1b and c). Patients receiving FF/UMEC/VI had significantly lower exacerbation rates than patients receiving dual therapy in all seasons for the ITT population (figure 1d). No significant interactions were identified between treatment and region for any season.

These results align with the TORCH (TOwards a Revolution in COPD Health) and POET-COPD (Prevention Of Exacerbations with Tiotropium in COPD) analyses, which demonstrated that exacerbations occur more frequently in winter than in summer [1, 2]. This reduction in exacerbation rate in summer was seen across all treatment groups; however, FF/UMEC/VI therapy resulted in lower exacerbation rates compared with FF/VI and UMEC/VI therapy, regardless of season. This suggests that the effectiveness of FF/UMEC/VI to reduce exacerbations compared with dual therapy is durable regardless of the triggering event that, for example, might be impacted by seasonality, viral infections or air pollution; however, it should be noted that the IMPACT study was conducted before the COVID-19 pandemic. Seasonality patterns of COPD-related emergency department visits have been found to differ post-COVID-19 compared with pre-pandemic data, possibly due to changing patterns of respiratory virus circulation post-lockdowns [6].

Reductions in exacerbation rate in summer compared with winter were observed regardless of eosinophil level or exacerbation history, although low numbers of exacerbations may have reduced the power of the analysis to assess the association between eosinophil levels and exacerbations. Although eosinophil levels may indicate potential for an exacerbation at screening, this may not be a durable indicator for future events. These results are in agreement with the overall findings of IMPACT that moderate to severe exacerbations were reduced with FF/UMEC/VI *versus* dual therapy; however, our subgroup analysis findings differ from a previously published analysis from the IMPACT trial, in which moderate and severe exacerbations were found to increase in proportion with blood eosinophil count in patients not taking ICS-containing medication throughout the trial [7]. A trend for greater exacerbation reduction with FF/UMEC/VI than with UMEC/VI in summer over winter was observed in this study. Triggering events for exacerbations between the seasons may differ as the prevalence of respiratory pathogens is higher in winter [8]; therefore, a higher proportion of exacerbations in summer may be triggered by other factors, such as exposure to environmental pollutants [9, 10]. Regardless, triple therapy was significantly favoured over dual therapy in all seasons, highlighting the benefits of FF/UMEC/VI regardless of the triggering event. However, it is important to weigh the implications of these findings with the size of the effect; it may be unwise to draw firm conclusions from these data. As this was a *post hoc* analysis, limitations should be considered, such as the fact that the distribution of patients between the hemispheres was not considered in the original IMPACT cohort. It should also be noted that the Northern Hemisphere countries here cover a wider range of latitudes compared with the Southern Hemisphere countries. Additionally, tropical and temperate climates were not separately analysed, so specific effects of these regions cannot be extrapolated here.

In conclusion, these data demonstrate the increased frequency of moderate and/or severe exacerbations during the winter months in patients with COPD and highlight the durability of the triple-therapy treatment paradigm regardless of the seasonality of triggering events.

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Ethics statement: All patients provided written informed consent. The study was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki and received approval from local ethics review boards of all participating sites.

Author contributions: All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to *ERJ Open Research*; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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