previously on inhaled corticosteroids, for whom there was a small number of events [$n = 5$–8 across groups], preventing meaningful conclusions), and across a broad range of eosinophil counts (1), suggesting that it is highly unlikely that this was a chance finding influenced by confounding.

We disagree with the suggestion that there may have been a different level of effort in retrieving deaths between groups. Our supplemental follow-up retrieved 52-week vital status for 99.65% of patients in the intent-to-treat population. For the 30 patients whose 52-week vital status remained unknown in the final retrieved dataset (including $n = 10$ on BGF 320 and $n = 5$ on GFF), we reported tipping-point analyses to examine the possible impact of these patients. If all 5 missing patients on GFF were alive and up to 8 of 10 patients on BGF 320 died the day after we last knew they were alive, the treatment comparison would remain significant (1). It is correct that not all retrieved deaths were included in the analysis and that the percentage of excluded deaths varied across groups. This is because the analysis only included deaths up to 52 weeks, and a greater percentage of deaths in the dual-therapy groups occurred within 52 weeks. We performed a sensitivity analysis including all retrieved deaths, regardless of how late they occurred (i.e., 37 deaths for BGF 320 and 64 deaths for GFF); this produced a hazard ratio of 0.46 (95% confidence interval, 0.30–0.71; $P = 0.0004$).

Overall, we agree that further trials assessing the benefits of triple therapy on mortality would be welcome. However, there would be substantial practical difficulties in conducting such trials, including the fact that two large studies (IMPACT [Informing the Pathway of Chronic Obstructive Pulmonary Disease Treatment] and ETHOS) have now shown a benefit of triple therapy on mortality, raising ethical questions on the appropriateness of randomizing this patient population to long-term dual therapy. As mentioned by Rogliani and Calzetta, clinical trial populations are only partially representative of real-life populations, and any future trials would have this same limitation. Nevertheless, many studies have now provided evidence that triple therapy reduces exacerbations and improves lung function and patient-reported outcomes compared with dual therapies (3). The findings from IMPACT and ETHOS on mortality add support for the benefit of these therapies in improving the lives of patients with chronic obstructive pulmonary disease. ■

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Reply to López-Campos *et al.*

From the Authors:

We read with interest the comments by Dr. López-Campos and colleagues on our manuscript demonstrating a reduction in all-cause mortality (ACM) with triple therapy using fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) in patients with chronic obstructive pulmonary disease (COPD) (1). Although we agree that the terminology can be confusing, on-treatment and on/off-treatment data provide different information, and both should be evaluated. The on-treatment analysis (which describes the benefit expected from a medication while the patient is receiving the medication) demonstrated a 42% reduction in ACM ($P = 0.011$), while the on/off-treatment ACM analysis (which is the analysis of efficacy including data even after patients have stopped receiving their assigned medication) demonstrated a 28% reduction in ACM ($P = 0.042$) when comparing FF/UMEC/VI with UMEC/VI (1, 2). This on/off-treatment analysis is an intention-to-treat (ITT) analysis. In both on- and on/off-treatment analyses, all patients were analyzed according to their original randomized medication. The ITT analysis is important to help understand the effects of treatment policy and differential dropout. However, this analysis is perhaps most important when the test article (the treatment in question) has poor tolerance causing more people to drop from the study. This was not the case in IMPACT (Informing the Pathway of COPD Treatment), in which fewer patients on FF/UMEC/VI than patients on UMEC/VI stopped therapy.

We acknowledge that ACM in IMPACT was a prespecified endpoint without adjustment for multiplicity. However, it is important to note that multiplicity adjustments are performed to avoid a study being declared successful when only a few endpoints achieve a P value <0.05 without the context of how many endpoints were tested. Importantly, inferences may still be

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made about results that are not adjusted for multiplicity when this context is understood. We have not singled out ACM because it occurred by chance. In fact, 33 of 34 predefined efficacy endpoints directionally favored FF/UMEC/VI over UMEC/VI in the overall IMPACT population, with 29 of the 33 having a P value <0.05 and 23 of these 29 having a P value <0.001.

The IMPACT study provides confidence in the reduction in ACM with FF/UMEC/VI treatment compared with long-acting muscarinic antagonist/long-acting β_2-agonist treatment. IMPACT was a well-designed, well-conducted, large, global, multicenter trial. ACM was a predefined endpoint with a prespecified analysis plan. These data were reliable and of high quality, with independent adjudication of deaths and minimal missing data (0.4% of the 10,355 subjects in the ITT population).

In addition, we demonstrated clinical plausibility between ACM and reduction of severe (hospitalized) COPD exacerbations. Indeed, in IMPACT, there was a 34% reduction in the rate of severe COPD exacerbations with FF/UMEC/VI compared with UMEC/VI, further supporting the plausibility that the risk of death would also be reduced (2).

Similar findings in reduction in ACM more recently shown in the ETHOS (Efficacy and Safety of Triple Therapy in Obstructive Lung Disease) study (3) also strongly support that the IMPACT findings were not due to chance. ■

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Erratum: Culture Conversion in Patients Treated with Bedaquiline and/or Delamanid: A Prospective Multicountry Study

Because of an error by our compositor, an incorrect affiliation was inadvertently inserted for Dr. Nino Chumburidze in the January 1, 2021 article by Franke and colleagues (1). Dr. Chumburidze should have been listed as being a member of the Medical Department, Doctors Without Borders, in Tbilisi, Georgia (not Sokhumi, Georgia). The *Journal* has replaced the online version of the article with a corrected version. ■

Reference

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