in the editorial is therefore questionable, as it does not correspond to the actual TORCH data.

Missing data represent a problem for any statistical analysis of clinical trial data and no statistical method can completely compensate. However, the methods used in the TORCH rate of decline analysis [3] correspond to those currently recommended by leading statistical experts [7] and are based on the same underlying principles as those employed in the statistical analysis of the UPLIFT and other large trials.

The analysis using random coefficient regression accounts for the early dropout in the placebo group, assuming that those who drop out would have progressed in a similar way to those in the placebo arm with similar observed data (baseline and on-treatment FEV₁ measurements) who remained in the study. For the analysis to be valid, every observation does not need to be observed for every subject and the analysis does not assume that the measurements were in any way “a random sample”. In this model, correlation of intercept and slope of the lines representing the decline in FEV₁ is expected and is in fact an intrinsic part of the model; for example, if those with the highest baseline have the greatest decline this would be accounted for. Therefore, the objections of SUISSA [1] to the analysis on these grounds are unfounded.

SUISSA [1] particularly focuses on subjects with data only at baseline and those with no data beyond 24 weeks. These patients provided baseline FEV₁ data as well as baseline demographic data that are used as covariates in the analysis. In the primary analysis, we included patients with data from at least one post-treatment time-point and, therefore, the model corrected for any imbalance in the treatment groups in terms of their baseline and first on-treatment FEV₁. In response to a suggestion from DECRAMER and MOLENBERGHS [8], we have performed an analysis including subjects with only baseline data [9]. This analysis, which adjusts for differences in baseline values between those with no further data and the remainder, shows very similar results to the previously published analysis [3]. Those patients who discontinued treatment in the TORCH trial may, on average, have more severe disease than those who remained on treatment, but it is reasonable to assume that this will be reflected in their baseline FEV₁ and demography, which have been allowed for in these analyses.

In conclusion, the editorial by SUISSA [1] singles out TORCH for criticism with regard to missing data when this is a universal feature of all long-term chronic obstructive pulmonary disease trials. The methods used to analyse rate of decline in TORCH represent current best practice and there is no evident justification for his assertion that the results may be influenced by regression to the mean. The illustration he has provided does not correspond to the actual TORCH data. We therefore stand by our conclusion regarding reduction compared with placebo in rate of decline in forced expiratory volume in one second with salmeterol, fluticasone and the combination of both treatments.

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STATEMENT OF INTEREST

Statements of interest for all authors of this manuscript can be found at www.erj.ersjournals.com/misc/statements.shtml

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From the authors:

I thank KEENE *et al.* for their comments and this opportunity to clarify the concepts presented in my editorial [1]. First, I am reassured that they agree that the principle of intent-to-treat (or intention-to-treat) analysis is fundamental in order to avoid bias in randomised trials. This is particularly crucial for trials leading to such extensive missing data problem issues that 18% of placebo patients in TORCH (Toward a Revolution in Chronic Obstructive Pulmonary Disease (COPD) Health) did not have a single measure of forced expiratory volume in one second (FEV₁) and that by the end of the trial over 45% were not having their FEV₁ measured [2]. It is questionable whether

one can reliably measure lung function decline in such situations. To then compare groups having differential missing numbers is bound to introduce bias, particularly if the measure is subject to regression to the mean. Unless it is able to accurately predict what the missing FEV₁ value would have been at that time (not at baseline as in the table presented by KEENE *et al.*) or the number of missing data is small, no statistical model, however sophisticated, can eliminate this bias.

It is rather unfortunate that all trials conducted to date in COPD have not been able to provide more complete data on lung function over time for a proper intent-to-treat analysis and, thus, an accurate assessment of the effect of these drugs on lung function decline. The TORCH study has greatly enhanced the conduct of randomised trials by its complete follow-up for mortality [3], a paradigm followed by the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) study [4], thus allowing proper intent-to-treat analyses for this outcome. Putting aside other methodological issues encountered in past trials [5], it is now time to consider in the design of future trials that data on other outcomes, such as exacerbations and lung function, be collected more extensively.

In the meantime, we should refrain from over-interpreting analyses based on outcomes with such widespread missing data to draw conclusions regarding the effectiveness of medications in chronic obstructive pulmonary disease.

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