

Reviewer 1 v.1

Comments to the Author

Rabe et al have presented a sub-study of the ETHOS trial assessing lung function over 52 weeks of follow-up among participant receiving budesonide/glycopyrrolate/formoterol (BGF) v/s two dual-therapy arms: glycopyrrolate/formoterol (GFF) and budesonide/formoterol (BFF). While the study and analysis are well conceived and presented, a lack of clinically meaningful improvement in lung function parameters in the BGF arm v/s GFF and BFF may dampen the enthusiasm for BGF use as a disease modifying therapy. I have minor comments to this manuscript -

1. The methods section is unclear whether randomization done for the ETHOS trial was intact for the purposes of this sub-study. Please clarify.
2. Assuming randomization is intact, please present unadjusted results in addition to multivariable regression and report unadjusted FEV1 treatment effect.
3. Please also clarify what the modified intention to treat population comprised of relative to the per protocol population.
4. Please specify the difference in statistical methods for calculating "at week-24" and "over week-24" outcomes. Please also specify the fixed- and random-effects components for assessing the above outcomes.
5. While the improvement in FEV1 did not reach the generally accepted MCID threshold, can the authors comment on changes in respiratory questionnaire scores and/or functional status for BGF relative the the other arms?