Response document for **Manuscript ID TAR-21-013**, manuscript titled *'Improvements in lung function with budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler versus dual therapies in patients with COPD: a sub-study of the ETHOS trial'*

Reviewer 1 comments		
General comments		
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 (BFG) 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 -		
Specific comments	**Response**	**Page #**
1. The methods section is unclear whether randomization done for the ETHOS trial was intact for the purposes of this sub-study. Please clarify.	The sub-study was conducted with the same randomized groups, as it was concurrent with the full ETHOS study. We have clarified this in the Methods section: *A subset of study sites was designated for participation in the PFT sub-study, which was conducted concurrently with the full study.*	5
2. Assuming randomization is intact, please present unadjusted results in addition to multivariable regression and report unadjusted FEV1 treatment effect.	We did not present unadjusted results as it is common practice to adjust for important confounders in clinical studies. The unadjusted data would be very similar overall to the adjusted data, and therefore we do not feel it would be useful to report both sets of results for each endpoint. For example, for trough FEV_1 at Week 24 for BGF 320, BGF 160, GFF and BFF, the mean unadjusted changes from baseline were 113 mL, 109 mL, 84 mL, and 36 mL. In comparison, the adjusted mean changes from baseline were 111 mL, 109 mL, 76 mL, and 35 mL. For FEV_1 AUC_{0-4} at Week 24 for BGF 320, BGF 160, GFF and BFF, the unadjusted means were 298 mL, 283 mL, 244 mL, and 171 mL. In comparison, the adjusted means were 290 mL, 279 mL, 237 mL, and 171 mL.	NA
3. Please also clarify what the modified intention to treat population comprised of	We have added the definition of the mITT population to the Methods section:	6

relative to the per protocol population.	*The PFT sub-study population was a subset of the patients in the modified intent-to-treat (mITT) population of the ETHOS study. The overall mITT population included all patients who were randomized and treated and had post-randomization data obtained before discontinuation of treatment.* A per-protocol population analysis would have excluded data obtained after relevant protocol deviations. Such analyses were not included in this manuscript as the primary sub-study analyses used the mITT population, so as to include all treated patients.	
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.	Whereas both analyses use the same dataset, the model allowed for treatment effects to vary by visit, so the at Week 24 data provide the estimated difference at just that time point while over 24 weeks data represent the average effect over that time period. We accounted for the correlation between measurements for the same patient by using a variance-covariance structure in a repeated measures model rather than by using random effects. Thus, all model covariates described in the statistical analysis section of the Methods were analyzed as fixed effects.	NA
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?	The reviewer raises an interesting point. While it is correct that most of the treatment group differences were <100 mL, it is important to note that this MCID for FEV_1 was proposed to evaluate the efficacy of monotherapy in comparison to placebo, and adding one additional active treatment (e.g., the comparison of triple therapy versus dual therapy) would not necessarily be expected to produce an improvement exceeding the MCID (Jones et al, Am J Resp Crit Care Med 2014; 189: 250-255). The magnitude of the treatment benefit also depends on disease severity at baseline, with less severe patients demonstrating a greater capacity to improve with triple therapy (as shown in Table 3). Overall, the benefits of BGF in ETHOS were similar to other studies of triple therapy including TRIBUTE and IMPACT, which also reported treatment differences for triple vs dual therapies of <100 mL (Papi et al, Lancet 2018;391:1076-1084; Lipson et al, N Engl J Med 2018;378:1671-1680). Data for transition dyspnea index (TDI), St George's Respiratory Questionnaire (SGRQ), rescue medication	NA

	use, and the EXAcerbations of Chronic pulmonary disease Tool (EXACT), which were secondary endpoints in ETHOS, have been reported in brief in the supplementary appendix of the primary publication (Rabe et al, N Engl J Med 2020; 383:35-48) and will be comprehensively described in an upcoming secondary manuscript focusing on symptoms and quality of life endpoints. Hence, they are not included in this manuscript which focuses on lung function. Both doses of BGF significantly improved these outcomes in comparison with both dual therapies (GFF and BFF).	
Reviewer 2 comments		
General comments		
The sub-study of ETHOS trial to evaluate the impact of triple therapy in comparison to dual therapies on lung function is very well designed, written and addresses an important issue. This study can become foundation for future prospective studies to compare triple therapy to dual therapies in COPD patients.		
Specific comments	**Response**	**Page #**
- It mentioned in the article that patients without FEV1 baseline stability (those with >20% or 200 mL change in their FEV1) were excluded from randomization. Given that those with rapid decline in their FEV1 are high risk patients for recurrent and severe exacerbations, they have high likelihood of ending up on triple therapy. Also, being able to have better management of the disease in this sub-group and potentially slow the slope of FEV1 reduction can have significant impact on preventing recurrent admissions. The reason behind this exclusion was not explained in the paper. I suggest authors consider providing the reason in the manuscript.	Because all FEV_1 comparisons were made to the baseline values (mean of 60 and 30 minutes prior to dosing) obtained at Visit 4 (randomization), it was important to ensure that these values were stable and reflective of the patient's COPD severity prior to being randomized into the study so that any improvements could be estimated precisely. We have added rationale for these criteria in the Methods section: *In order to ensure that baseline FEV_1 values were stable and reflective of their true COPD severity during the screening period but prior to randomization, patients who did not meet FEV_1 baseline stability criteria were also excluded; this was defined as the average of the 60- and 30-minute pre-dose FEV_1 assessments at the randomization visit being within ±20% or 200 mL of the mean pre-dose FEV_1 obtained at the two previous visits.* These criteria specified that the baseline FEV_1 at Visit 4 had to be within ±20% or 200 mL of the mean of the pre-dose FEV_1 obtained at Visit 2 and Visit 3. It should be noted that Visits 2–4 took place within the screening period of 1–4 weeks. Any instability over	5

	this short time period likely reflects changes in lung function following discontinuation of bronchodilator maintenance treatments at the screening visit rather than being a marker of rapid decline in FEV_1, which takes many weeks or months to be observed.	
- Patients with other respiratory diseases including asthma were excluded from the study. However, the reversibility post albuterol with mean of 15-17 and SD of 15-16 in the subgroups raises the question if there were patients with ACOS (asthma COPD overlap syndrome) among the patients. How would that impact the external validity of the results in COPD patients?	Based on the characteristics of our patient population, we do not feel that patients with ACOS (or asthma-like features such as high eosinophil counts and bronchodilator reversibility) made a substantial contribution to our study results. Overall, only 16.2% of patients in the PFT sub-study had blood eosinophil counts ≥300 cells/mm^3, and 34.1% had reversibility to albuterol ≥12% and ≥200 mL. Patients with a current diagnosis of asthma were excluded from the study, and investigators were advised not to enrol patients who had received a diagnosis of active asthma within the past 5 to 10 years. The number of patients with a history of asthma was very low (78/3088 in the PFT population; ~2.5%). As shown in Table S1, while patients with eosinophil counts ≥300 cells/mm^3 experienced the largest benefits of triple therapy, nominally significant differences versus dual therapy were also observed in patients with eosinophil counts 100–<300 cells/mm^3. Therefore, we do not believe that our results were driven by patients with asthma-like features.	NA
- Although the benefits of BGF vs BFF maintained at week 52, in comparison to week 24 the improvement had declined. How would authors explain that specially comparing to BGF vs GFF that the LSM improvement at week 52 were higher than week 24 for BGF vs GFF.	We thank the reviewer for this interesting observation. These findings are reflective of the results in Table 5, which show that the rate of decline over 52 weeks was larger with GFF vs the ICS-containing therapies. Although these rate of decline analyses were exploratory, they suggest that ICS-containing therapies such as BGF and BFF may slow the decline in FEV_1 over the long term. This may explain why the treatment difference with BGF increased over time vs GFF. Regarding the smaller benefit for BGF vs BFF at week 52, it can also be seen in Table 5 that all treatment groups experienced some level of decline over the full study duration. This results in smaller absolute values of FEV_1 at the 52-week time point, and therefore correspondingly smaller treatment differences might be expected.	NA
Reviewer 3 comments		

General comments		
Well written and designed. Interesting findings You are correct that it would be speculative/premature to use triple therapy to prevent/slow lung decline. However, would appreciate a few sentences in the discussion related to your thoughts on the following:		
Specific comments	**Response**	**Page #**
How do your findings potentially impact current GOLD recs for triple therapy (if at all). If not, what further data would be necessary for that to happen?	In line with our findings, the current GOLD report notes that triple therapy has been shown to improve lung function versus dual LAMA/LABA and ICS/LABA therapies. We have added a sentence in the Discussion to mention this: *The findings of this 4-hour PFT sub-study of ETHOS demonstrated the benefit of BGF versus GFF and BFF on both morning pre-dose trough FEV_1 and FEV_1 $AUC_{0–4}$ for the first 24 weeks of treatment. These improvements in lung function were sustained at Week 52. These findings are in line with the recommendations in the GOLD report, which notes that triple therapy can improve lung function versus dual LAMA/LABA and ICS/LABA therapies.*[3] Our subgroup analyses also support the current recommendation to consider eosinophil count when prescribing ICS-containing therapy. However, the GOLD report also notes that "there is no conclusive clinical trial evidence that any existing medications for COPD modify the long-term decline in lung function." While our study does not provide conclusive evidence, it suggests that further studies are warranted to specifically assess the impact of ICS on lung function decline in COPD.	11
There is not a strong correlation of PFTs to symptoms typically. What is the clinical significance (if any) to the changes observed in lung function? Would have been nice to link these lung function numbers to the CAT scores in the original ETHOS study.	We only measured CAT score at baseline, so unfortunately, we are unable to correlate changes in lung function with CAT score over time. However, we have assessed improvements in lung function according to CAT score at baseline. In these analyses, we see that there were slighter larger increases from baseline across all treatment groups in those patients with more impaired (higher) CAT scores at baseline. These results will be included in a forthcoming publication and thus cannot be included in this manuscript.	NA

Reviewer 4 comments		
General comments		
I've read the manuscript entitled "Improvements in lung function with budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler versus dual therapies in patients with COPD: a sub-study of the ETHOS trial" by Rabe and colleagues that aimed to investigate the effect of triple therapy on pulmonary function test in a subset of ETHOS patients. ETHOS is a randomized controlled study recently published in the literature, conducted in a population of moderate-to-very severe COPD patients treated with triple therapy (LABA/LAMA/ICS), that clearly demonstrated a significant reduction in the rate of moderate/severe COPD exacerbation as well as improved symptoms and quality of life compared either with LABA/LAMA and LABA/ICS therapeutic regimen. In this manuscript, Authors demonstrated the improvement in lung function of triple therapy (vs LAMA/LABA and LABA/ICS) in a subset of the ETHOS protocol patients. The study protocol was elegantly designed and the manuscript is very well written, with results clearly described, helping in assessing the superiority of triple therapy in lung function improvements vs LABA/LAMA and LABA/ICS, in moderate-to-very severe patients with frequent exacerbation rate. In conclusion, I suggest the manuscript to be accepted for publication.	We thank the reviewer for their positive evaluation of our manuscript.	NA