Author's response to reviews

Title: Indacaterol improves lung hyperinflation and physical activity in patients with moderate chronic obstructive pulmonary disease - a randomized, multicenter, double-blind, placebo-controlled study

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Author's response to reviews:

Reviewer: Pierre-Regis Burgel
Reviewer's report:
Watz et al. performed a cross over study evaluating three periods of 21 days with indacaterol 150 microgr/day, placebo or open-label tiotropium in 129 subjects with mild to moderate airflow limitations. The authors confirmed that indacaterol and tiotropium reduced hyperinflation and that both treatment effects were within the same range. Measuring physical activity over 1 week with a Sensor armband in patients under indacaterol or placebo, the authors found increase in the number of steps/day (+10.9%; +722 steps) and in the number of minutes of at least moderate physical activity/day (+28 min; +29%).
Overall this is an interesting, well-conducted exploratory study. I have only minor comments:

We thank Prof Burgel for the careful review and the very helpful comments. The ms was changed in light of the comments. For further details please see below.

C1. The authors should provide information on the numbers of patients taking inhaled corticosteroids.
R1: In the methods section (section patients; page 5, line 2) we state that any use of corticosteroids within three months prior to study entry was not allowed. With the revision we now clarify this exclusion criterion by adding the clarification "inhaled or systemic application" in brackets.

C2. The use of physical activity in COPD trials corresponds to a recently introduced outcome that may be of major interest in clinical trials. Although
differences in steps/day and minutes of at least moderate activity/day were statistically significant, and seems rather important in terms of magnitude of the effect, it is difficult to judge whether these improvements were indeed clinically significant. Is there any data in the literature on MCID for physical activity measurement? How much improvement in physical activity translates into better outcome?

R2: We thank for this important comment. We now include a statement in the discussion section, which should help the readers to get an idea about the potentially clinically relevant changes of the physical activity parameters. It reads as follows "A minimal clinically important difference for changes of physical activity is not yet available for patients with COPD. However, our results can be discussed in the context of existing data with regard to mortality that is associated with reduced levels of physical activity. Waschki et al. demonstrated that the decrease of the physical activity level by 0.14 and the decrease of 1845 steps per day in a cohort of patients with mild to very severe COPD is associated with an increase of the relative risk of death by 117% and 104%, respectively [12]. Furthermore, recent data in healthy individuals suggest that 15 min of moderate-intensity exercise (e.g. brisk walking) a day is associated with 14% reduced risk of all-cause mortality [32]."

C3. Was there any correlation between reduction in IC and physical activity?

R3: There was no correlation between changes of IC and physical activity in our study. With the revision we include a sentence in the results section stating "A correlation between changes of IC and changes of any physical activity parameter could not be demonstrated (data not shown)."

Reviewer: James Donohue

Reviewer's report:
This is an interesting study of Indacaterol150mcg and tiotropum18mcg(open label) and placebo on hyperinflation and physical activity. The study was well conducted by expert investigators. The duration of each crossover period of 21 days, the appropriate dosing of indacaterol at 150 and the use of the armband to test physical activity with the lung function data are novel. The hierarchial statistical methods is very good to answer these questions.

We thank Prof Donohue for the careful review and the very helpful comments. The ms was changed in light of the comments. For further details please see below.

Major compulsory Revisions: none
minor none
discretionary revisions
C1). It might be helpful to discuss the MCID for IC and the arm band mentioning
that while no definite standards are established, these results are robust. Some consider 100mls in IC the mcid and there have been discussions on the increased activity time and steps but no mention of a standard. if you have any information on mcid with these tests they might be helpful for readers. Also you report both Peak and trough IC in the figures while many studies do not differentiate.

R1): We thank for this important comment. Regarding MCID for IC we now include with the revision the following sentence in the discussion section "Unlike FEV1, a generally accepted minimal clinically important difference has not yet been identified for changes of IC following a therapeutic intervention, even though an increase of 100 mL can be considered to be potentially clinically meaningful [27] " Regarding MCID for physical activity included the following sentences " A minimal clinically important difference for changes of physical activity is not yet available for patients with COPD. However, our results can be discussed in the context of existing data with regard to mortality that is associated with reduced levels of physical activity. Waschki et al. demonstrated that the decrease of the physical activity level by 0.14 and the decrease of 1845 steps per day in a cohort of patients with mild to very severe COPD is associated with an increase of the relative risk of death by 117% and 104%, respectively [12]. Furthermore, recent data in healthy individuals suggest that 15 min of moderate-intensity exercise (e.g. brisk walking) a day is associated with 14% reduced risk of all-cause mortality [32]. "

C2) You might mention that tiotropium open label is standard and the results generally are the same as when placebo or blinded drug is given (KMBeeh RESPIR Research 2012) line24 on page13 in your report.

R2) Thank you for this advise. We changes this sentence, which now reads as follows " This potential bias from an open label design brought us to the decision not to measure physical activity in our study during open-label treatment with tiotropium, while the lung function measurements might be less affected by open-label therapy with tiotropium in our study [34]. "