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Repeated dose budesonide/formoterol compared to salbutamol in adult asthma: A randomised cross-over trial

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Repeated dose budesonide/formoterol compared to salbutamol in adult asthma: A randomised cross-over trial

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Take Home Message: The comparative bronchodilator responses of repeated administration of salbutamol 200µg and budesonide/formoterol 200/6µg differed depending on the time of measurement; salbutamol caused greater systemic beta2-agonist, cardiovascular and adverse effects.

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Data Sharing Statement: Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) will be available one year after publication until a minimum of 5 years after publication. It will be available to researchers who provide a methodologically sound proposal that has been approved by the study steering committee to achieve the aims outlined in the approved proposal. Data can be obtained through a signed data access agreement. The agreement can be obtained by emailing the Principal Investigator: richard.beasley@mrinz.ac.nz. The study protocol is available publicly on the ANZCTR website.

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ABSTRACT (259)

Objective: To determine the comparative bronchodilator, systemic $beta_2$-agonist, cardiovascular and adverse effects of salbutamol 200µg and budesonide/formoterol 200/6µg when taken repeatedly in stable asthma.

Methods: This open-label, cross-over, single-centre, controlled trial, randomised adults with asthma to different orders of two treatment regimens: salbutamol 200µg via MDI at t=0, 30, 60, 90 minutes, then salbutamol 2.5 mg via nebuliser at t=120, 140, 160 and 420 minutes; or budesonide/formoterol 200/6µg one actuation via Turbuhaler at t=0, 30, 60, 90 minutes, two actuations at t=120, 140, 160 and 420 minutes. The primary outcome measure was FEV_1 after 180 minutes. Secondary outcomes included repeat measures of FEV_1, serum potassium, heart rate, and adverse events

Results: Of 39 patients randomised, two withdrew due to adverse events (QT_{CF} prolongation and T wave abnormalities) after the first intervention with salbutamol. The mean (SD) change from baseline FEV_1 180 minutes after randomisation for salbutamol and budesonide/formoterol regimens was 0.71 (0.46) L, N=38, and 0.58 (0.45) L, N=37, respectively; with a mean (SD) paired difference of -0.10 (0.40) L, N=37, and a model-based estimated difference (95% CI) -0.12 (-0.25 to 0.02) L, P=0.088. In the main secondary analysis, salbutamol resulted in significantly greater FEV_1 from 30 to 240 minutes, but lesser FEV_1 at 360 and 420 minutes. Salbutamol resulted in a significantly lower serum potassium, and a higher heart rate and number of adverse events.

Conclusion: The comparative bronchodilator responses of repeated administration of salbutamol 200µg/dose and budesonide/formoterol 200/6µg differed depending on the time of measurement. Salbutamol caused greater systemic $beta_2$-agonist and cardiovascular effects and more adverse events.

INTRODUCTION

The Global Initiative for Asthma (GINA) recommends that combination inhaled corticosteroid (ICS)-formoterol is the preferred reliever to short acting beta$_2$-agonist (SABA), for adults and adolescents with any severity of asthma.[1,2] This is based on evidence that budesonide-formoterol reliever alone reduces the relative risk of severe exacerbations by at least 60% compared to SABA reliever therapy in mild asthma,[3,4] by 15% compared with maintenance budesonide plus SABA reliever [5], and by about one third in patients taking maintenance ICS/long-acting beta$_2$-agonist (LABA).[6,7] This reduction in severe exacerbation risk is seen with self-administered use by patients in the long-term treatment of asthma in the community setting. In contrast, the relative bronchodilator and anti-inflammatory effects of the repeated administration of budesonide/formoterol compared to SABA's, as may occur in the Emergency Department (ED) setting, are uncertain. This is an important issue as repeated dosing of ICS in acute severe asthma is associated with a substantive improvement in lung function,[8] and a reduced risk of hospital admission.[9]

The doses of budesonide/formoterol vs salbutamol (or terbutaline) used as reliever therapy in community-based trials has been 200/6µg vs 200µg (and 500µg) respectively.[3-7] This trial compares bronchodilation following repeated administration of budesonide/formoterol compared to salbutamol in this dose ratio of 200/6µg:200µg in adults with stable asthma and moderate to severe airflow obstruction. The primary objective was to compare the magnitude of bronchodilation after 180 minutes of initiation of the two treatments. Our hypothesis was that budesonide/formoterol would have superior bronchodilator efficacy than salbutamol due to the additional genomic and non-genomic effects of repeated doses of ICS.[10-12]

MATERIALS AND METHODS

Study Design and Participants

This was an investigator-led, open-label, cross-over, single-centre, randomised controlled trial comparing salbutamol with budesonide/formoterol conducted at the Medical Research Institute of New Zealand (MRINZ). The trial was run in accordance with Good Clinical Practice guidelines and the declaration of Helsinki, and was approved by the Northern B Health and Disability Ethics Committee (19/NTB/83) and registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12619001083189). Adults with asthma aged 16 to 65 years, with an FEV_1 40 to 70% predicted and bronchodilator reversibility with an FEV_1 ≥12% and >200ml were recruited. Details of inclusion and exclusion criteria are in Table 1 in the online supplement. Written informed consent was obtained from all participants. Participants were required to withhold their SABA inhalers for 6 hours, LABA inhalers for 24 hours and ultra-LABA inhalers for 48 hours prior to each visit.

Procedures

Participants attended an initial screening visit to determine eligibility and then returned on a different day for randomisation and first intervention regimen, followed by reattendance for the second intervention regimen after a minimum washout period of one week. The schedule of assessments and tests is shown in Figure 1; further details can be found in the online supplement.

Intervention regimens

The bronchodilator regimens (Figure 1), were based on the doses of salbutamol self-administered by patients in the community prior to a hospital presentation,[13] and guidelines recommendations for the use of salbutamol in the ED.[14]

The salbutamol regimen was salbutamol [Ventolin 100µg CFC-Free MDI, GlaxoSmithKline] two actuations via a spacer at t=0, 30, 60, 90 minutes, followed by salbutamol [Asthalin 2.5mg/nebule, Rex Medical] nebulised, 1 nebule at 15L/min at t=120, 140, 160 and 420 minutes. The budesonide-

formoterol regimen was budesonide-formoterol [Symbicort Turbuhaler 200µg of budesonide and 6µg of formoterol; AstraZeneca] one actuation at t=0, 30, 60, 90 minutes followed by Symbicort Turbuhaler 200/6, two actuations at t=120, 140, 160 and 420 minutes. In addition, at the eight-hour timepoint, participants randomised to the salbutamol regimen received 12 actuations of budesonide [Pulmicort Turbuhaler 200µg, AstraZeneca] to ensure that they received the same ICS dose on study days with no differential carry-over effects between randomised intervention regimens.

Outcomes

The primary outcome measure was FEV_1 after 180 minutes. Secondary outcome measures were FEV_1, FeNO, and Modified Borg Dyspnoea Scale Score at 30, 60, 90, 120, 150, 210, 240, 300, 360, 420 and 480 minutes; serum potassium, blood eosinophil levels, heart rate and QT_{CF} at 180 and 480 minutes.

Sample Size

Based on the previous cross-over study,[15] the estimated paired SD for this study was an FEV_1 of 0.43L. A sample size of 39 had 90% power to detect a minimally clinical important difference in FEV_1 of 0.23L,[16] with a two-sided alpha of 0.05. Assuming a drop-out rate of 10%, 44 participants were required. A re-estimation of the sample size was done at a planned interim analysis after 15 participants had been randomised. The paired difference (95% CI) change in FEV_1 from baseline for the two treatments was 0.20L (-0.015 to 0.41). The standard deviation (95% CI) for the paired difference in FEV_1 was 0.38 (0.28 to 0.61). Based on the point estimate for the standard deviation, it was calculated that 32 participants would be needed for 90% power to detect a difference in FEV_1 of 0.23L. We therefore continued with the original sample size of 39 participants without consideration of drop-outs.

Randomisation

Participants were randomised 1:1 to different orders of the intervention regimens in an AB/BA cross-over design. The randomisation method involved a computer-generated sequence supplied

by the study statistician, independent of the investigators. The sequence was uploaded into the Research Electronic Data Capture (REDCap) system by an individual who was otherwise uninvolved in study processes. REDCap concealed the allocations until after randomisation. Investigators enrolled participants and both were not masked to group assignment.

Statistical Methods

For the primary analysis of the FEV_1 after 180 minutes a mixed linear model was used with fixed effects for the baseline FEV_1, order of treatments, and treatment; and a random effect based on the participant with an unstructured variance-covariance matrix. For the sensitivity analyses all measurement times were used, denoted as a 'full' mixed linear model. In these models an overall P value tests the hypothesis that the difference between treatments is different at the different measurement times, which is a time by treatment interaction. The 'full' models can also estimate comparisons of treatments at each time point, with associated P values of differences between treatments within each measurement time. The estimates of treatment differences within each time period from the 'full' mixed model may differ from simpler analyses because more data is used in their estimation.

The analysis of serum potassium, blood eosinophil count, heart rate, and QTc_F used the same models as for the logarithm FeNO and Borg score. FeNO had a strongly skewed distribution and was analysed on the logarithm transformed scale. The exponent of the difference in logarithms is interpreted as the ratio of geometric means. McNemar's test for paired contingency tables and an appropriate estimate of the difference in paired proportions was used to assess for the difference in proportion of participants with adverse events. Further details are available in the online supplement.

RESULTS

There were 39 participants recruited (Figure 2) between 2 October 2019 and 1 November 2020. The trial was paused from 23 March 2020 to 8 June 2020 in accordance with the New Zealand government's COVID-19 response. Two participants were withdrawn during the first intervention regimen due to adverse events (QT_{CF} prolongation and T wave abnormalities) following administration of salbutamol. All participants were included in the intention-to-treat analysis. Baseline characteristics are shown in Table 1. At baseline, participants had a mean (SD) FEV_1 percent predicted 60.7% (9.1) and FeNO 44.6 ppb (48.4).

Table 1: Baseline characteristics of study population

Characteristic	N=39
Age; mean years (SD)	46.0 (14.3)
Sex (%)	
Female	20 (51.3)
Male	19 (48.7)
Ethnicity[a] (%)	
European	33 (84.6)
Māori	3 (7.7)
Pacific Peoples	1 (2.6)
Asian	2 (5.1)
Smoking status	
Ex-smoker (%)	11 (28.2)
Never (%)	28 (71.8)
Pack years; mean (SD)	1.4 (2.4)
Age at asthma diagnosis; mean years (SD)	10.9 (11.1)
Medication use (%)	
Patient-reported use of SABA only at enrolment	5 (12.9)
Patient-reported use of ICS + SABA at enrolment	8 (20.5)
Patient use of ICS/LABA only at enrolment	10 (25.6)
Patient use of ICS/LABA + SABA at enrolment	16 (41.0)
Lung Function; mean (SD)	
FEV_1 (L)	2.06 (0.67)
FEV_1 (percent predicted)	60.7 (9.1)
FeNO (ppb); mean (SD)	44.6 (48.4)
Log_e FeNO (ppb); mean (SD)	3.40 (0.85)
Modified Borg Dyspnoea Score; mean (SD)	1.9 (1.3)
Serum Potassium (mmol/L); mean (SD)	4.5 (0.37)
Blood Eosinophils ($x10^9$/L); mean (SD)	0.34 (0.22)
Resting heart rate (/min); mean (SD)	69.7 (11.8)
[b]QT_{CF} (ms); mean (SD)	415.1 (18.1)

[a]Prioritised ethnicity using Level 1 codes [17]

[b]Corrected QT interval using Fridericia's formula

In the primary analysis, the mean (SD) change from baseline FEV_1 180 minutes after randomisation for salbutamol and budesonide/formoterol regimens was 0.71 (0.46) L, N=38, and

0.58 (0.45) L, N=37, respectively; with a mean (SD) paired difference of -0.10 (0.40) L, N=37, and a model-based estimated difference (95% CI) -0.12 (-0.25 to 0.02) L, P=0.088. A box-plot of the FEV_1 change from baseline is shown in Figure 3 and the FEV_1 at each time point for the salbutamol and budesonide/formoterol interventions are shown in Figure 4. In the secondary analysis, using all measurement times in a 'full' mixed linear model, there was evidence that the differences in FEV_1 between treatments depended on the time of measurement, P interaction <0.001. The estimates and P values in this table are derived from the individual treatment comparisons within time from the 'full' mixed linear model, and differ from the simpler analyses as they incorporate the full data (Table 2).

Table 2: Secondary analyses of FEV_1 comparison at all time-points

Time (minutes)	Budesonide/Formoterol minus Salbutamol Difference (95% CI)	P value
30	-0.22 (-0.29 to -0.15)	<0.001
60	-0.22 (-0.29 to -0.15)	<0.001
90	-0.18 (-0.25 to -0.11)	<0.001
120	-0.16 (-0.23 to -0.09)	<0.001
150	-0.13 (-0.20 to -0.06)	<0.001
180	-0.15 (-0.22 to -0.07)	<0.001
210	-0.10 (-0.17 to -0.03)	0.004
240	-0.13 (-0.20 to -0.06)	<0.001
300	0.0 (-0.07 to 0.07)	0.96
360	0.16 (0.09 to 0.23)	<0.001
420	0.16 (0.09 to 0.23)	<0.001
480	-0.06 (-0.13 to 0.01)	0.11

There was no evidence that the FeNO in the two intervention regimens was different at the different time points (Figure 5). When averaged over all the time points, the FeNO was lower in the salbutamol group compared to the budesonide/formoterol group, ratio of geometric means (95% CI) 1.04 (1.02 to 1.06), P<0.001. There was no evidence of a difference in Borg score between treatments (Figure 1 online supplement).

The serum potassium was lower in the salbutamol intervention at both time points (Table 3). In a model without a time by treatment interaction term, the mean serum potassium over both time points was lower in the salbutamol intervention (point estimate of difference 0.21 mmol/L, (0.13 to 0.28), P<0.001).

Table 3: Analysis of Serum Potassium

Time (minutes)	Budesonide/Formoterol minus Salbutamol Difference (95% CI)	P value
180	0.26 (0.16 to 0.37)	<0.001
480	0.15 (0.05 to 0.25)	0.004

The blood eosinophil count was higher in the budesonide/formoterol regimen after 180 minutes, estimate (95% CI) 0.065 $x10^9$/L (0.022 to 0.11), P<0.004, but not after 480 minutes; -0.02 x 10^9/L (-0.06 to 0.024), P=0.36. There was strong evidence of time-treatment interaction; P=0.007.

The heart rate was lower in the budesonide/formoterol regimen and the size of the difference depended on time, 10 bpm lower (-12.6 to -7.4), P<0.001 after 180 minutes and 4 bpm lower (-6.5 to -1.4), P=0.003, after 480 minutes. The QTc_F was shorter in the budesonide/formoterol regimen with no evidence of a time-treatment interaction: 4.4ms shorter (-7.9 to -0.1), P=0.013.

There were 79 adverse events in total with no serious adverse events (Table 2 online supplement). There were significantly more adverse events during the salbutamol regimen compared to the budesonide/formoterol regimen, estimated difference (95% CI) in paired proportions 37.8 (22.2 to 53.5), P<0.001. There were significantly higher proportions of tremor and light-headedness in the salbutamol regimen compared to the budesonide/formoterol regimen, estimated difference (95% CI) in paired proportions 37.8 (22.1 to 53.5), P<0.001 and 18.9 (6.3 to 31.5), P=0.003 respectively.

DISCUSSION

This randomised controlled trial showed that there was no significant difference in the magnitude of bronchodilation between repeated doses of budesonide/formoterol 200/6µg and salbutamol 200µg at the primary outcome time point of 180 minutes. In the secondary analysis however, there were significant differences between treatments depending on the time of measurement, with salbutamol resulting in a greater magnitude of bronchodilation over the first four hours, and budesonide/ formoterol achieving a greater magnitude of bronchodilation at 360 and 420 minutes. Salbutamol resulted in a greater fall in serum potassium, a systemic $beta_2$-agonist effect,[18] consistent with a lesser $beta_2$-agonist effect for budesonide/formoterol 200/6 compared to than salbutamol 200µg. Also consistent with these findings, salbutamol resulted in a higher heart rate and greater prolongation of the QTc_F, and adverse effects occurred more frequently. This study was not designed to determine dose equivalence of the two treatments but to compare bronchodilation and adverse effects at commonly used doses.

Previous studies reporting differences between formoterol and salbutamol at the dose ratio used in our study are difficult to interpret because those studies do not report differences in point estimates and confidence intervals for differences in FEV_1, and all have different time points for primary evaluation. In a study of acute presentations to ED,[19] in which formoterol 6µg x 4 and salbutamol 200µg x 4 were taken three times over one hour, the primary measurement time was 75 minutes and although the actual FEV_1 at this time was not reported, the change from baseline FEV_1 of 37% and 28% respectively are consistent with a change from baseline of 0.39 and 0.30 L; a difference of 0.09L favouring the formoterol group. In another ED study,[20] in which budesonide/formoterol 400/12 x 2 and salbutamol 100µg x 8 were taken twice 5 minutes apart, and for the primary outcome was Area under the Curve normalised for time to 90 minutes, the measures were 1.38 and 1.52 L respectively, consistent with difference of 0.135L, favouring the salbutamol arm. Finally in a third study in ED,[21] in which formoterol 6µg x 4 and salbutamol 200µg x 4 were taken twice 30 minutes apart, the primary measurement time was FEV_1 after 45 minutes however, the results were reported as % change from baseline FEV_1 and the point estimate for this favoured salbutamol

although the confidence intervals were wide and included the pre-specified clinically important difference to detect.

There are a number of methodological issues relevant to the interpretation of the findings. Firstly, the study was open label and so this introduced potential bias. Secondly, we used a model of adults with moderate to severe reversible airflow obstruction in an outpatient clinic situation, rather than the acute asthma setting in the ED. This had the potential advantage of allowing for a cross-over study design and prevent confounding due to beta$_2$-agonist self-administration and/or systemic corticosteroid treatment prior to the administration of the randomised treatments in the ED setting. However, this means that the findings are not necessarily generalisable to patients presenting to ED with a severe exacerbation.

The salbutamol dosing schedule was consistent with the New Zealand adult asthma guideline recommendations.[14] The corresponding budesonide/formoterol doses were based on the 200/6 vs salbutamol 200µg therapeutic dose ratio used in the community clinical trials, and the 6:1 dose bronchodilator equivalence between nebuliser and MDI with spacer administration,[22] to account for the lack of a nebuliser product for budesonide/formoterol. This also meant that the study could not be blinded which has the potential to introduce bias.

We chose FEV_1 after 180 minutes as the primary outcome measure, as this time point corresponded to the end of the intensive bronchodilator regimen, at which stage a decision would be made in clinical practice as to whether to discharge or admit the patient to hospital. The repeated measures of FEV_1 over the 8-hour time period allowed an assessment of the time course, during which we observed that the differences between treatments depended on the time of measurement. The greatest difference in FEV_1 occurred during the first 60 minutes, with the FEV_1 following salbutamol being 0.22L greater, close to our pre-specified difference to detect of 0.23L.[16] The FEV_1 remained around 0.10 to 0.18L higher with salbutamol until 240 minutes, 80 minutes after the end of the intensive cumulative dosing period. The FEV_1 was 0.16L higher with budesonide/formoterol at 360 and 420 minutes, an effect presumably due to the longer duration of

action of formoterol.[23,24] These differences suggest that whereas salbutamol may lead to greater efficacy in the acute ED setting, when used in these comparative doses, the more prolonged bronchodilation with budesonide/formoterol may contribute to its greater efficacy with self-administration in the community setting.[25] Many statistical tests have been carried out and so conclusions based on the secondary and sensitivity analyses should be viewed with caution as they are not adjusted for potential type I error inflation.

The finding that the serum potassium with salbutamol was 0.26 and 0.15 mmol/L lower at 180 and 480 minutes demonstrates that budesonide/formoterol 200/6 has lesser systemic $beta_2$-agonist effect than salbutamol 200µg. This is consistent with the finding of a non-significant 0.26 vs 0.16 mmol/L mean fall in serum potassium over 180 minutes with salbutamol 200µg x 8 vs budesonide/formoterol 200/6 x 8 respectively in severe asthma,[20] the non-significant 0.06 mmol/L greater fall between 45 and 240 minutes with salbutamol 200µg x 8 vs formoterol 6µg x 8, in another ED study,[21] but not the third ED study [19] in which the mean minimum serum potassium with formoterol 6µg x 12 was lower than salbutamol 200µg x 12; 3.2 vs 3.5 mmol/L respectively.

To broaden assessment heart rate and QTc_F interval were measured, representing cardiovascular $beta_1$/$beta_2$, and cardiac electrophysiological $beta_2$ effects. We observed that repeated doses of salbutamol 200µg caused a greater increase in heart rate and QTc_F interval prolongation than budesonide/formoterol 200/6µg, changes which increase the risk of ventricular arrhythmias.[26] The clinical relevance of the differences is borne out by the observation that tremor and light-headedness occurred more frequently with salbutamol, and the requirement for two patients to be withdrawn due to adverse effects including QTc prolongation and T wave abnormalities.

FeNO was measured to assess potential acute airways anti-inflammatory effects, following the demonstration that in stable asthma, budesonide 2,400µg reduced sputum eosinophils at 6 hours, an effect which was associated with a reduction in bronchial hyperresponsiveness.[27] In contrast to these findings, we observed no reduction in FeNO with budesonide/formoterol, despite a

budesonide dose of 2,000µg over 3 hours. When averaged over time, the FeNO was slightly greater with the budesonide/formoterol intervention, a finding most likely due to chance. The mean baseline FeNO of the participants was 45ppb, and it remains to be determined whether adults presenting with a severe exacerbation and a higher FeNO might obtain anti-inflammatory effects with the repeated use of budesonide/formoterol. The other potential benefit with the ICS component of budesonide/formoterol is the acute non-genomic vasoconstrictor effects within the airways, considered to be responsible for the substantive improvement in lung function with the repeated use of ICS in the ED treatment of exacerbations.[8-12] It is possible that these effects may have contributed to the bronchodilator response observed with the repeated use of budesonide/formoterol in this study.

The blood eosinophil count in our study was higher in the budesonide/formoterol regimen after 180 minutes which is likely a chance finding unrelated to the systemic absorption of budesonide. A previous study [28] demonstrated that the peak plasma concentration of budesonide was achieved five to ten minutes after a single dose administration of 1200 µg of budesonide via Turbuhaler in moderate to severe asthma. In another study, [29] peak plasma concentration was achieved within 20 minutes of administration of 1600 µg of budesonide via Turbuhaler in mild to moderate asthma. The effect of repeated, cumulative dosing of budesonide over an eight-hour period on plasma concentrations is unknown, however our observation of a time by treatment interaction with blood eosinophil levels may be due to the accumulation of plasma concentration of budesonide over the dosing period.

The findings have two main clinical implications. The first, answering the main question addressed in this study, is that the use of budesonide/formoterol according to this cumulative dosing regimen does not result in superior bronchodilation compared to salbutamol and may in fact result in lesser bronchodilation over the first four hours, the time period over which clinical decisions regarding admission to hospital are made.

The second relates to the as-needed use of these medications as reliever therapy in the long-term treatment of asthma. The use of budesonide/formoterol 200/6µg one actuation as-needed reduces the risk of severe exacerbations compared with salbutamol 100µg x 2 (or equivalent terbutaline dose), when either taken alone or together with ICS/LABA maintenance therapy.[5–7, 25] The results of this study suggest that this greater efficacy with budesonide/formoterol is achieved despite a lesser acute although more prolonged bronchodilator response, suggesting that the ICS component of reliever therapy, titrated according to changes in symptoms, is the key component contribution to this efficacy. Arguably the clinical relevance of differences in bronchodilator efficacy in the community setting is a moot point, as the patient can simply take an additional dose if needed to relieve symptoms. The nature of as-required relief is that patients use as much as necessary, and the real-life use of these inhalers leads to different patterns of use. [3,4,30] However, it is pertinent to remember that asthma mortality epidemics [31-33] have been associated with high dose preparations of beta$_2$-agonist and that the relatively lower beta$_2$-agonist dose may have a potential safety advantage, as suggested by our findings.

In conclusion, these findings inform the comparative efficacy of repeated administration of budesonide/formoterol with salbutamol in the acute exacerbation setting, and provide insight into the greater efficacy of budesonide/formoterol reliever therapy in reducing severe exacerbation risk with long-term use.

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COMPETING INTERESTS

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List of Figure Legends

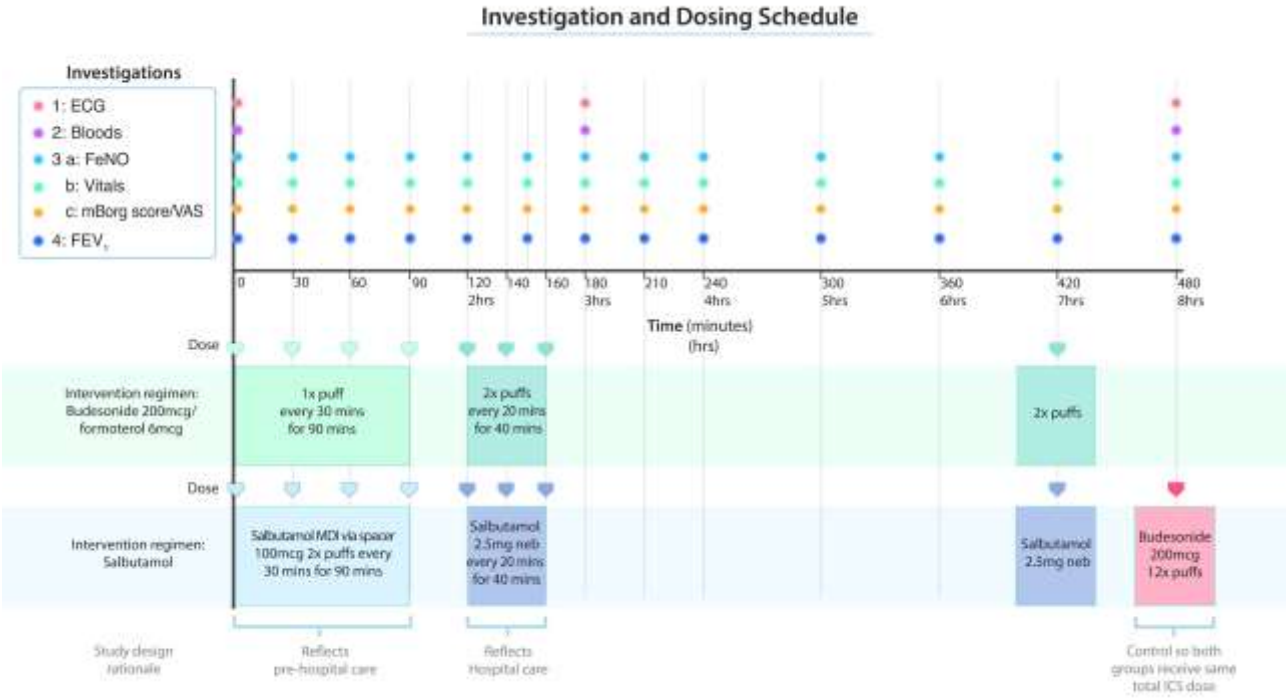

Figure 1: Investigation and dosing schedule

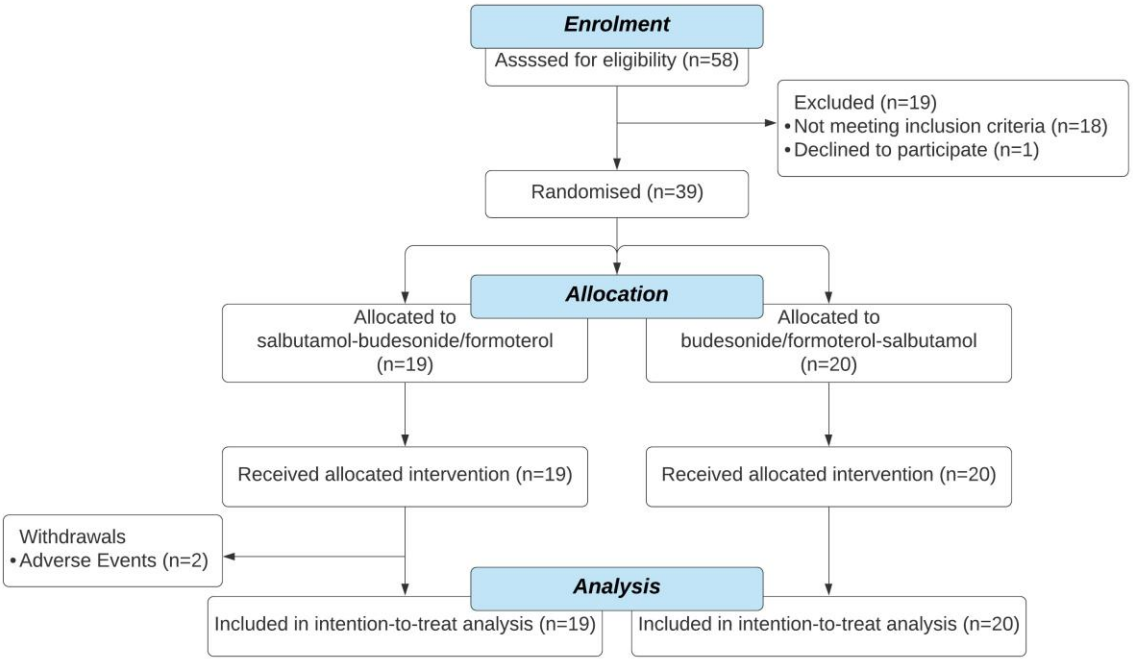

Figure 2: CONSORT Flow Diagram

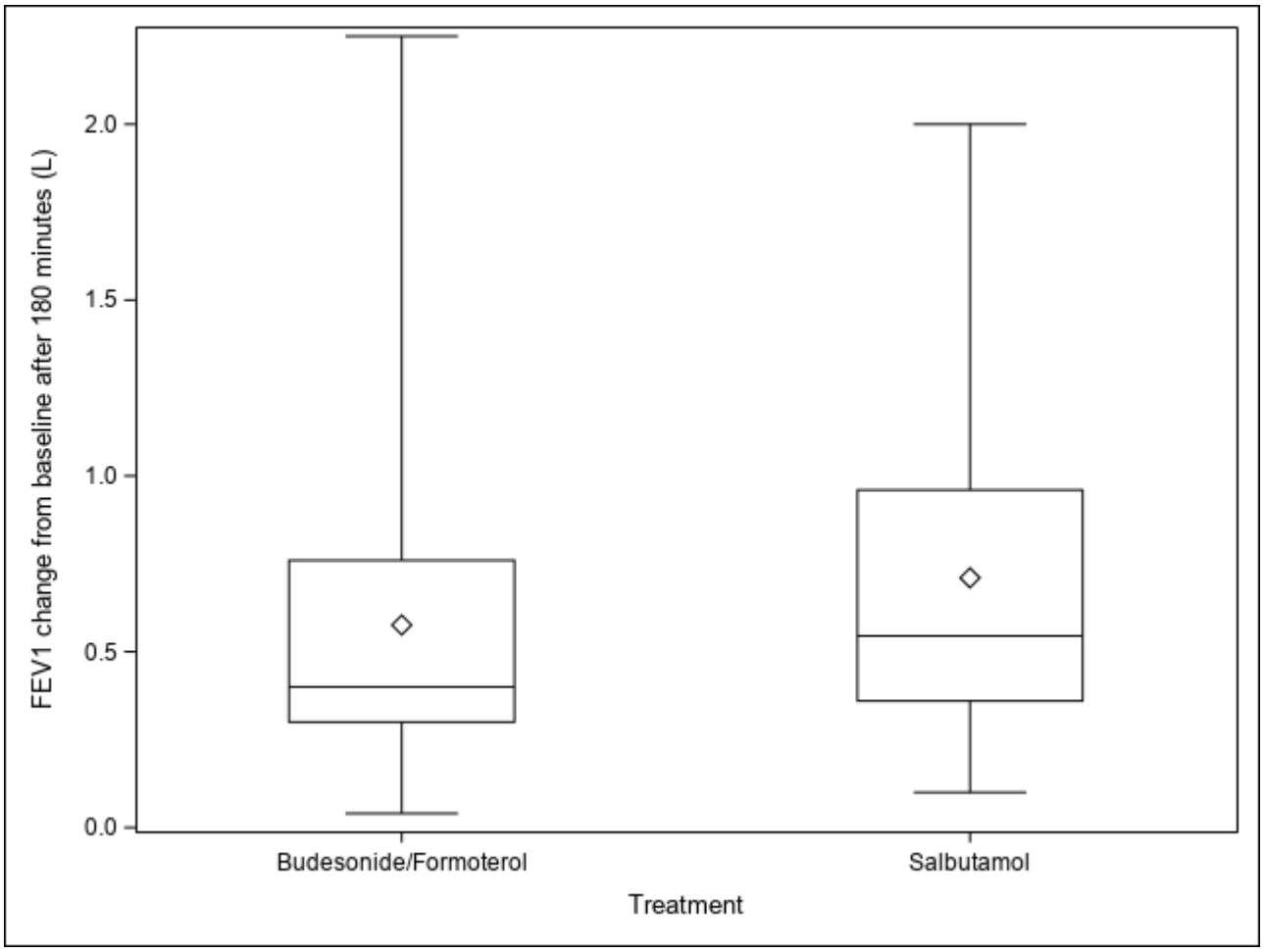

Figure 3: Boxplot of FEV_1 change from baseline after 180 minutes

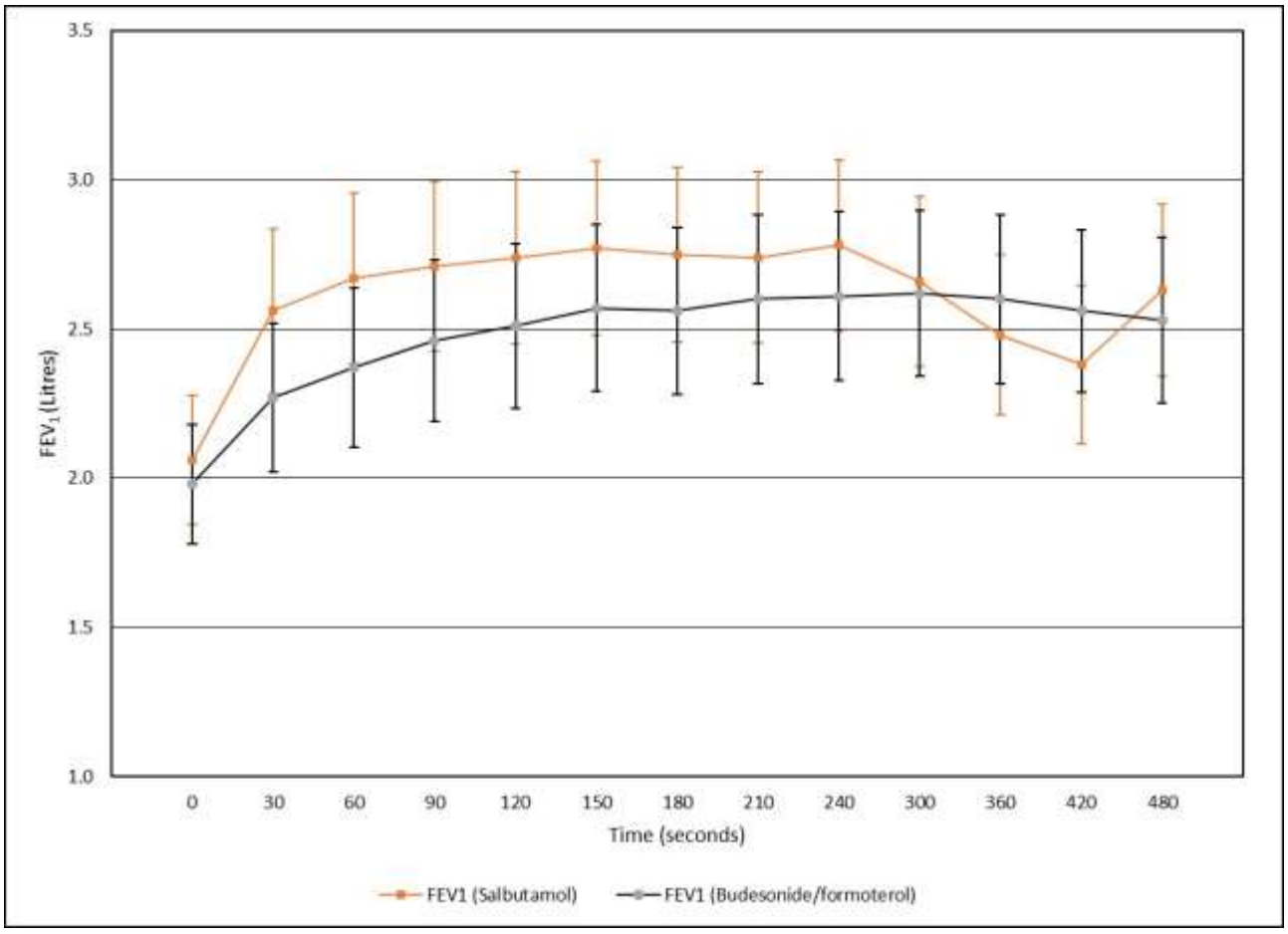

Figure 4: Time course of FEV_1 for Budesonide/Formoterol and Salbutamol

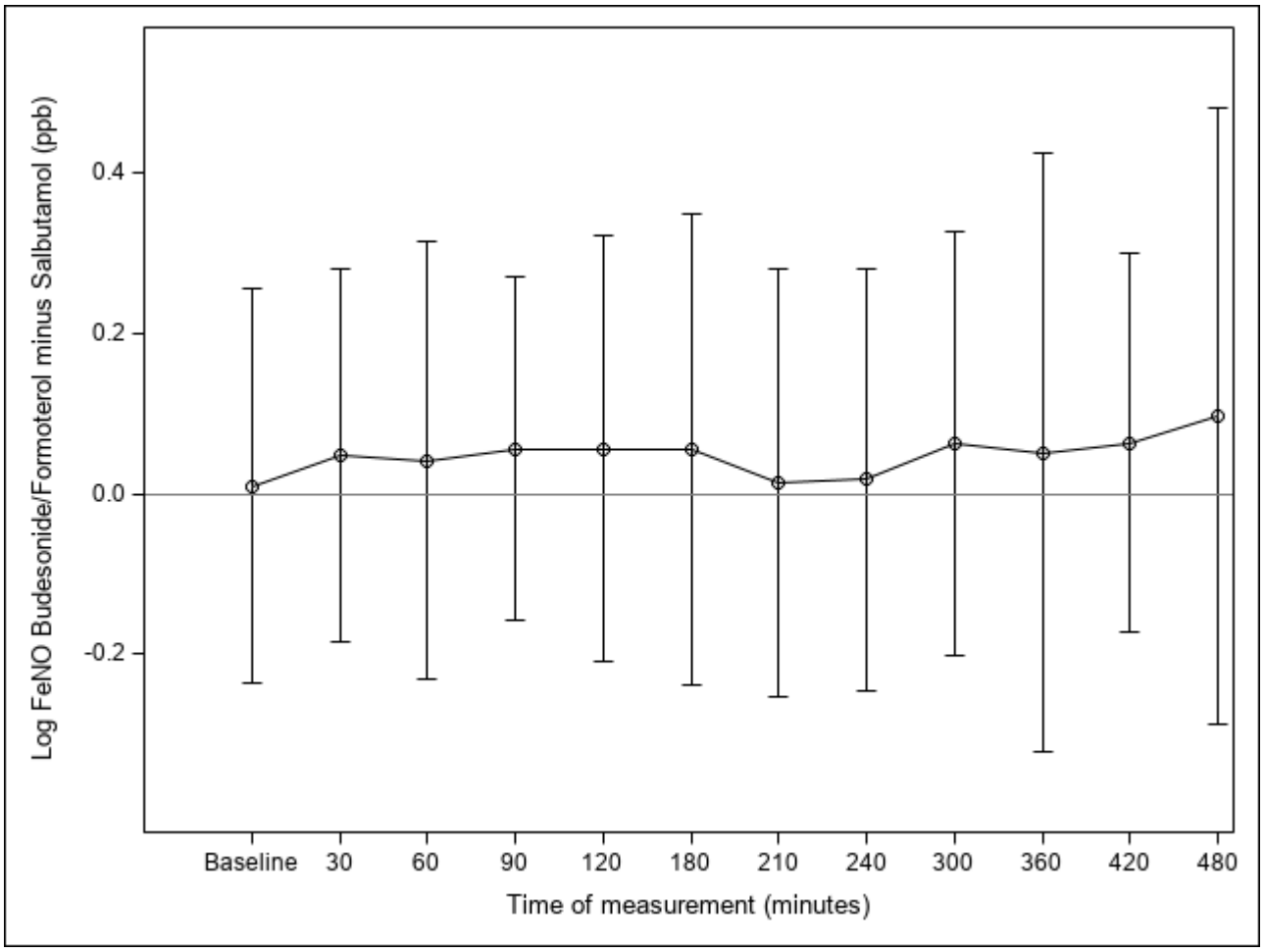

Figure 5: Time course for difference in Log FeNO over time, Budesonide/Formoterol minus Salbutamol

ONLINE SUPPLEMENT

REPEATED DOSE BUDESONIDE/FORMOTEROL COMPARED TO SALBUTAMOL IN ADULT ASTHMA: A RANDOMISED CROSS-OVER TRIAL

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Contents

1. Inclusion and Exclusion Criteria

Table 1: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Self reported doctor diagnosis of asthma • Age 16 to 65 years • SABA monotherapy or SABA with regular ICS therapy, or regular or as needed ICS/LABA treatment • FEV1 40 to 70% (inclusive) predicted as per GLI 2012 criteria[1] • FEV_1 reversibility ≥12% and ≥200 mL, 15 to 30 minutes after 400µg salbutamol via a spacer	• Other significant respiratory disorder • Other significant cardiovascular disorder such as history of arrhythmia including atrial fibrillation and supraventricular tachycardia • Current or recent respiratory tract infection in last 4 weeks • Current use of other asthma medications including Long Acting Muscarinic Antagonists, theophylline, oral corticosteroids, biologics, sodium cromoglycate or nedocromil sodium • Asthma exacerbation requiring oral steroids in last 6 weeks • Current smoker or ex-smoker with >10 pack year history • QT_{CF} > 430ms for men and > 450ms for women[2] • Pregnant, or planning a pregnancy, or breast feeding • Allergy to investigational products, including previous adverse effects following administration of similar doses to those used in the study • Current use of beta-blockers

2. Details on testing procedures

Spirometry [Care Fusion MasterScope non-heated pneumotach spirometer running software V5.32.0] and FeNO [NIOX VERO] were measured according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines[3, 4] with Caucasian reference equations for ethnicity. The Modified Borg Scale score[5, 6] rated from "0: Nothing at all" to "10: Maximal" was used to assess breathlessness. 12-lead electrochardiograms (ECG) [Cardiosoft v6.7, GE Healthcare] were used to measure heart rate and QT_{CF} (Corrected QT interval using Fridericia's formula).

The Visual Analogue Score (VAS) was initially used, in addition to the mBORG score to measure breathlessness but was removed following randomisation of nine participants. The investigators noted that participants were having difficulty comparing current levels of breathlessness to the level of breathlessness prior to administration of medication, especially given the eight-hour day.

3. Statistical Methods

Data descriptions use mean, standard deviation (SD), median and 25^{th} to 75^{th} percentile as the inter-quartile range (IQR) and minimum (Min) to maximum (Max); for continuous variables and counts and proportions expressed as percentages for categorical variables. On the box-plots the symbol is the mean the horizontal lines are the 25^{th}, 50^{th} (median) and 75^{th} percentiles and the whiskers are from the minimum to maximum values.

For the primary analysis of the FEV_1 after 180 minutes a mixed linear model was used with fixed effects for the baseline FEV_1, order of treatments, and treatment; and a random effect based on the participant with an unstructured variance-covariance matrix. For the sensitivity analyses a full mixed linear model was used with all the measurement times and estimates of within measurement times for the treatment difference. In these models (also used for logarithm FeNO and the Borg score) the interaction term tests if the difference between treatments is different for the different measurement time. If the interaction term is not statistically significant this means the treatment difference is the same at all measurement times. For the primary outcome variable and time, an interaction term explored if the treatment difference was different depending on ICS use at baseline and an analysis was also carried out with participant protocol violation data excluded (online supplement, page 9).

The analysis of serum potassium, blood eosinophil count, heart rate, and QTc_F used the same models as for the logarithm FeNO and Borg score. FeNO had a strongly skewed distribution and was analysed on the logarithm transformed scale. The exponent of the difference in logarithms is interpreted as the ratio of geometric means. McNemar's test for paired contingency tables and an appropriate estimate of the difference in paired proportions was used to assess for the difference in proportion of participants with adverse events. SAS version 9.4 was used except for the analysis of adverse events where version 12.4 was used.

4. Log FeNO

Table 2: Log FeNO at each timepoint for salbutamol regimen and budesonide/formoterol regimen

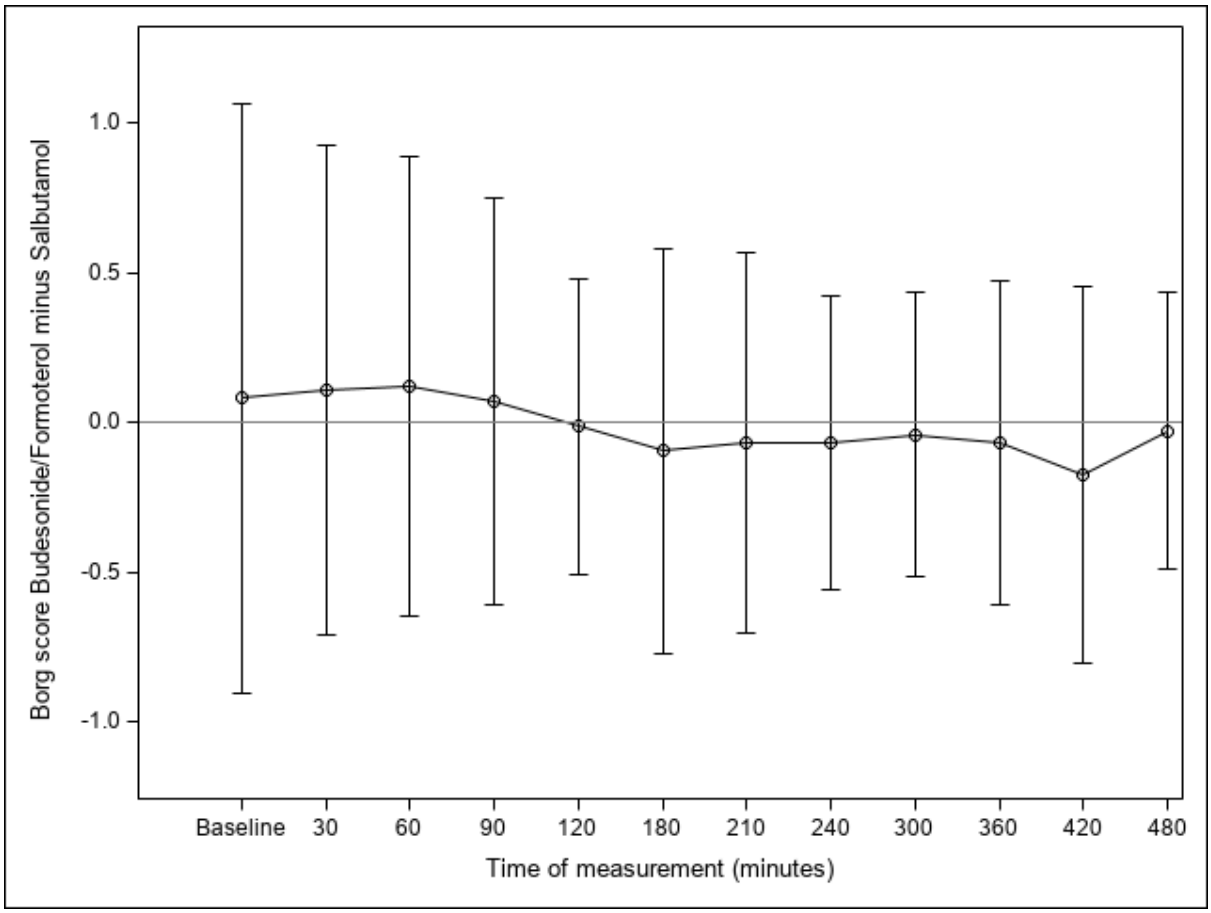
Time Point (minutes)	Mean (SD) for salbutamol regimen	Mean (SD) for budesonide/formoterol regimen
0	3.4 (0.85)	3.34 (0.77)
30	3.42 (0.92)	3.38 (0.83)
60	3.44 (0.93)	3.4 (0.86)
90	3.44 (0.91)	3.42 (0.85)
120	3.45 (0.94)	3.43 (0.86)
150	3.42 (0.93)	3.39 (0.87)
180	3.39 (0.85)	3.43 (0.84)
210	3.39 (0.87)	3.39 (0.86)
240	3.38 (0.89)	3.37 (0.85)
300	3.35 (0.86)	3.39 (0.86)
360	3.38 (0.88)	3.41 (0.86)
420	3.34 (0.84)	3.39 (0.84)
480	3.3 (0.9)	3.38 (0.8)

5. Modified Borg Dyspnoea Scale Score

Table 3: mBorg Dyspnoea Scale score at each timepoint for salbutamol regimen and budesonide/formoterol regimen

Time Point (minutes)	Mean (SD) for salbutamol regimen	Mean (SD) for budesonide/formoterol regimen
0	1.9 (1.32)	1.91 (1.19)
30	1.01 (0.96)	1.16 (0.91)
60	0.69 (0.77)	0.85 (0.86)
90	0.54 (0.64)	0.64 (0.82)
120	0.5 (0.55)	0.51 (0.61)
150	0.35 (0.53)	0.38 (0.48)
180	0.43 (0.82)	0.35 (0.45)
210	0.38 (0.67)	0.32 (0.46)
240	0.33 (0.52)	0.27 (0.38)
300	0.39 (0.57)	0.36 (0.59)
360	0.43 (0.5)	0.36 (0.56)
420	0.54 (0.63)	0.36 (0.54)
480	0.34 (0.47)	0.32 (0.43)

Figure 1: Time course for difference in modified Borg dyspnoea scale score over time, budesonide/formoterol minus salbutamol



6. Serum Potassium

Table 4: Serum potassium levels at each measured timepoint for salbutamol regimen and budesonide/formoterol regimen

Time Point (minutes)	Mean (SD) for salbutamol regimen	Mean (SD) for budesonide/formoterol regimen
0	4.52 (0.37)	4.49 (0.37)
180	3.95 (0.37)	4.21 (0.38)
480	4.13 (0.29)	4.27 (0.31)

7. Blood Eosinophils

Table 5: Blood eosinophil levels at each measured timepoint for salbutamol regimen and budesonide/formoterol regimen

Time Point (minutes)	Mean (SD) for salbutamol regimen	Mean (SD) for budesonide/formoterol regimen
0	0.34 (0.22)	0.37 (0.34)
180	0.22 (0.15)	0.3 (0.25)
480	0.22 (0.15)	0.2 (0.18)

8. Heart Rate

Table 6: Heart rate at each measured timepoint for salbutamol regimen and budesonide/formoterol regimen

Time Point (minutes)	Mean (SD) for salbutamol regimen	Mean (SD) for budesonide/formoterol regimen
0	69.7 (11.8)	71 (10.5)
180	75.9 (11.8)	66.6 (11.5)
480	74.1 (11.1)	70.8 (12.8)

9. QT_{CF} Interval

Table 7: QT_{CF} interval at each measured timepoint for salbutamol regimen and

Time Point (minutes)	Mean (SD) for salbutamol regimen	Mean (SD) for budesonide/formoterol regimen
0	415.05 (18.1)	418.76 (20.29)
180	433.51 (20.16)	431.22 (20.8)
480	427.66 (17.46)	425.51 (20.18)

budesonide/formoterol regimen

10. Adverse Events

Table 8: Adverse event profile

Adverse Event	Between regimens	Salbutamol (screening*)	Salbutamol	Budesonide/ formoterol	Total
Agitation			2		2
Bony lump	1				1
Chest pain			1		1
Cough	1				1
Diarrhoea	1				1
ECG T wave abnormalities			1		1
Facial flushing			1		1
Headache			8	5	13
Hypokalaemia			1		1
Lightheaded-ness			11	2	13
Nausea			1		1
Palpitations			2		2
Prolonged QT interval			1		1
Psoriasis flare up	1				1
Respiratory Tract Infection	4				4
Right Hand Laceration	1				1
Streptococcal pharyngitis	1				1
Tremor		1	24	8	33
Total	**10**	**1**	**53**	**15**	**79**
* Salbutamol 400µg via spacer was used to assess for reversibility during screening					

11. Interaction with prior ICS use

There was no evidence that there was an interaction (sub-group effect) between prior use of ICS and treatment; P=0.96.The estimates of treatment effect for the primary outcome variable by ICS treatment status are shown below.

Table 9: Estimates of treatment effect for the primary outcome variable by ICS treatment

	Budesonide/Formoterol minus Salbutamol Difference (95% CI)	**P**
No prior ICS use	-0.13 (-0.42 to 0.17)	0.35
Prior ICS use	-0.12 (-0.26 to 0.02)	0.083

12. Removal of participants with protocol violation

There were two protocol violations that could have potentially affected the primary outcome. These were related to the two participants that were withdrawn during the first intervention regimen due to adverse events (QT_{CF} prolongation and T wave abnormalities) following administration of salbutamol. There was no important change in the main outcome estimate with the participant data with protocol violations removed.

Table 10: Main outcome estimate with removal of protocol violations

	Difference (95% CI)	**P**
Budesonide/Formoterol minus Salbutamol	-0.12 (-0.26 to 0.01)	0.076

13. Comparison of baseline FEV_1 at Intervention 1 and 2

The interaction between period and treatment was not statistically significant, consistent with the difference between periods being the same for both treatments. The Period-Treatment interaction estimates are shown for illustration only.

Table 11: Data description

FEV_1	**Mean (SD)**	**Median (IQR)**	**Min to Max**
First Intervention N=39	2.00 (0.60)	1.92 (1.52 to 2.46)	0.70 to 3.29
Second Intervention N=37	2.04 (0.66)	1.99 (1.65 to 2.35)	0.71 to 4.12

Table 12: Mixed linear model comparisons with estimates of period difference by treatment

FEV_1	**Difference (95% CI)**	**P**
Second minus First, Salbutamol	0.02 (-0.39 to 0.43)	0.92
Second minus First, Budesonide/formoterol	0.06 (-0.37 to 0.48)	0.79

14. References

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