Protocol

Bronchodilation following repeated administration of budesonide/formoterol vs salbutamol in adult asthma: A randomised, open-label, cross-over study

Short title: Rescue Cumulative Dose Study

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Confidentiality Statement

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1. KEY TRIAL CONTACTS

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2. SYNOPSIS

Trial Title	Comparison of bronchodilation due to repeated administration of budesonide/formoterol vs salbutamol in adult asthma	
Internal ref. no. (or short title)	Rescue Cumulative Dose Study	
Clinical Phase	III B	
Trial Design	Randomised, controlled, cross-over single-centre trial	
Trial Participants	Participants aged 16-65 with asthma	
Planned Sample Size	44	
Treatment duration	Two visits 7 days to 4 weeks apart	
Follow up duration	nil	
Planned Trial Period	9 months	
	Objectives	Outcome Measures
Primary	To determine magnitude of bronchodilation at 180 mins	FEV_1 at 180 min
Secondary	To determine magnitude of bronchodilation over time To determine levels of airway inflammation over time To determine relief of breathlessness To determine changes in serum potassium following treatment To determine changes in blood eosinophil count following treatment	FEV_1 at baseline and at 30 min intervals for 4 hours, then hourly to 8 hours FeNO at baseline and at 30 min intervals for 4 hours, then hourly to 8 hours Modified Borg Dyspnoea Scale score at baseline and at 30 minute intervals for 4 hours, then hourly to 8 hours Serum potassium at baseline and at 3 and 8 hours Blood eosinophil level at baseline and at 3 and 8 hours.

	To determine changes in heart rate and QTc following treatment	QTc and heart rate at baseline and at 3 and 8 hours
Investigational Medicinal Product(s)	Budesonide/formoterol Salbutamol	
Formulation, Dose, Route of Administration	Budesonide/formoterol Turbuhaler 200µg/6µg per actuation Salbutamol 100µg per actuation via MDI 2.5mg via nebuliser Budesonide Turbuhaler 200 µg per actuation	

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CARM	Centre for Adverse Reactions Monitoring
eCRF	Electronic Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
ED	Emergency Department
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume at 1 second
GCP	Good Clinical Practice
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
HDEC	Health and Disability Ethics Committee
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
IMP	Investigational Medicinal Product
IRB	Independent Review Board
LABA	Long Acting Beta-Agonist
MDI	Metered Dose Inhaler
MRINZ	Medical Research Institute of New Zealand
PEF	Peak Expiratory Flow
PI	Principal Investigator
PIS	Participant Information Sheet
QTc	Corrected QT interval
SABA	Short Acting Beta-Agonist
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification

SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions

4. INTRODUCTION

4.1. Background and rationale

Comparison of the bronchodilator effects of the repeated administration of budesonide/formoterol with those of salbutamol as may occur in the community and Emergency Department (ED) setting, is crucial in determining its role as a 'rescue' medication in clinical practice.

One of the limitations to the use of Symbicort Turbuhaler (budesonide/formoterol) reliever therapy by adults with asthma is the perception that salbutamol is the preferred treatment for exacerbations, both in the community and in the hospital ED/ward setting. The entrenched use of salbutamol, both through an MDI ± spacer and by nebuliser, in these settings exists despite the evidence of similar bronchodilator efficacy of formoterol and salbutamol, in the dose ratio of 6µg:200µg respectively in the ED setting[1,2].

It is also known that repeat doses of ICS in the setting of acute severe asthma is associated with an improvement in lung function with a pooled weighted mean difference in PEF of 25, 35 and 46 L/min at 60, 120 and 180 min respectively.[3] Similar benefit is obtained with measures of FEV1 with a pooled weighted mean difference of 0.12, 0.16 and 0.24 L at 60, 120 and 180 min respectively. These differences are comparable with the clinically important differences in PEF and FEV1 of 19 L/min and 0.23 L respectively.[4]

The clinical significance of this bronchodilator efficacy is indicated by the observation that repeat doses of ICS in the setting of acute severe asthma reduce the risk of hospital admission (odds ratio 0.44 95% CI 0.31 to 0.62).[5] Furthermore, in patients treated with systemic steroids, repeat doses of ICS also reduce the risk of hospital admission (odds ratio 0.54 95% CI 0.36 to 0.81).[5]

Based on this evidence, it is likely that the administration of repeat doses of budesonide delivered from a combination budesonide/formoterol Turbuhaler would have greater efficacy than repeat doses of salbutamol when administered in the situation of acute severe asthma in the ED setting, both with and without concomitant systemic steroid use. This has been suggested from studies of the use of Symbicort as a reliever therapy, either with[6] or without[7], maintenance ICS/LABA therapy. This allows the treatment concept of 'rescue' as well as 'reliever' therapy when Symbicort is used in this way.

An alternative model to assess this clinical situation would be to compare the bronchodilator efficacy of repeat doses of budesonide/formoterol versus salbutamol in adults with severe airflow obstruction in an outpatient clinic situation. This would have the advantage of allowing for a cross-over study design, and prevent confounding due to beta agonist self-administration and/or systemic steroid treatment prior to the administration of the randomised treatments.

The bronchodilator regimens under assessment would ideally be standardised to ensure it was based both on salbutamol self-administered by patients in the community prior to a hospital presentation, as well as the salbutamol regimen recommended for use in the ED. Based on New Zealand data of use in the community, a dose regimen of salbutamol 100µg x 2 by MDI every 30 minutes for two hours is proposed to replicate initial pre ED patient use.[8] This dose regimen is consistent with the New Zealand adult asthma guidelines recommendations for patients to take salbutamol MDI 100µg, 2 actuations at a time as required to relieve breathlessness during a severe exacerbation while seeking urgent medical help. This is equivalent to Symbicort Turbuhaler (budesonide/formoterol 200/6µg) one actuation every 30 minutes for

the two hour period. This dose regimen is consistent with the New Zealand adult asthma guidelines recommendations for patients following the SMART regimen to take Symbicort Turbuhaler (budesonide/formoterol 200/6µg) one actuation at a time as required to relieve breathlessness during a severe exacerbation while seeking urgent medical help.[9]

This repeated inhaler use would then be followed by nebulised salbutamol 2.5mg every 20 minutes for the next hour, as recommended by the New Zealand adult asthma guidelines[9] to replicate the administration of salbutamol to patients in the ED. Based on the 6:1 dose bronchodilator equivalence between nebuliser and MDI with spacer administration,[10] this is equivalent to 4 x 100µg salbutamol by MDI with each nebuliser administration. The equivalent Symbicort Turbuhaler (budesonide/formoterol 200/6µg) dose would be 2 actuations every 20 minutes for the one hour period. Participants would then receive a further salbutamol 2.5 mg dose 4 hours later, to replicate intermittent on demand use during the recovery period, with the equivalent Symbicort Turbuhaler (budesonide/formoterol 200/6µg) dose of 2 actuations at this time point.

The primary outcome variable would need to be a measure of lung function, as requirement for hospital admission is not applicable to an outpatient based study. The preferred lung function measure is FEV1, which is more sensitive to changes in airflow obstruction than PEF.[11] The preferred time point is 180 minutes, which has been shown in previous studies to demonstrate the greatest magnitude of effect of repeated doses of ICS in acute severe asthma.[3,5] Of note this acute non-genomic effect of ICS may resolve within 60 to 90 minutes of the last dose. However there is advantage to continue FEV1 measures for an 8 hour period to determine if an anti-inflammatory genomic effect can be detected within this period, as has been suggested after a single high dose of budesonide in patients with moderate symptomatic asthma.[12]

In addition to a measure of lung function, assessment of FeNO would inform on the time course of anti-inflammatory airways effects.[13] However, with the cross over design it is necessary to ensure there is an adequate washout period, and no carryover effect resulting from the ICS treatment. For this reason, the visit for the second randomised treatment will be 7 days to 4 weeks after the first visit, as the effects of budesonide on FeNO have resolved by this time.[14] In addition, at completion of the 8 hour measurement period patients randomised to the salbutamol arm will receive 12 actuations of budesonide 200µg via a Turbuhaler to ensure that they receive the same ICS dose on study days with no differential carry-over effects between randomised treatment arms.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures
Primary Objective To determine magnitude of bronchodilation post treatment	FEV_1 180 mins (adjusted for baseline FEV_1)
Secondary Objectives To determine magnitude of bronchodilation over time	FEV_1 at 30 min intervals for 4 hours, then hourly to 8 hours
To determine magnitude of airway inflammation over time	FeNO at 30 min intervals for 4 hours, then hourly to 8 hours
To determine relief of breathlessness	Modified Borg Dyspnoea Scale score prior to each spirometry measurement
To determine changes in serum potassium following treatment	Serum potassium at 3 and 8 hours via blood sampling.
To determine changes in blood eosinophil counts following treatment	Blood eosinophil level at 3 and 8 hours via blood sampling
To determine changes in heart rate and following treatment	ECG at 3 and 8 hours to measure heart rate
To determine changes in QTc following treatment	ECG at 3 and 8 hours to measure QTc

6. TRIAL DESIGN

This is an open-label, randomised controlled, cross-over, single centre trial. Participants will attend an initial screening visit at the MRINZ facility to determine eligibility. If eligible, each participant will then have two further dosing visits to receive one of the 2 randomised treatments in a random order. The two visits will be 7 days to 4 weeks apart.

The screening visit will last up to 1 hour and the two intervention visits will last up to 9 hours each. A summary of procedures that will be undertaken during all visits are outlined in Appendix 2.

7. PARTICIPANT IDENTIFICATION

7.1. Recruitment

Potential participants with a doctor's diagnosis of asthma will be identified from the existing MRINZ database, GP mailouts and contact made via telephone or email by a study investigator. Participants will also be identified by direct advertising (e.g.Student Job Search,social media etc.) If interested, participants will be sent out a Patient Information Sheet. Once an appropriate amount of time has been given for the participant to consider the information, they will be contacted again by a study investigator to discuss attending an initial screening visit. Participants will be encouraged to discuss the PIS and their involvement in the study with family, whānau and their healthcare provider.

7.2. Inclusion 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[15]
- Change in FEV_1 post 400µg salbutamol via MDI through a spacer >12% increase from baseline, and >200ml

7.3. Exclusion Criteria

- 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 LAMAs, 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[16]
- 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

- Any other condition which, at the investigator's discretion, is believed may present a safety risk or impact the feasibility of the study or the study results.

8. TRIAL PROCEDURES

8.1. Informed Consent

The participant must personally complete the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: why the trial is being conducted, procedures to be performed by participants, total duration of the study, participant benefits of being involved; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated e-signature and dated e-signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Principal Investigator. An iPad and stylus will be used to record the e-signatures which will be stored in the secure REDCap database. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the trial site. Should the e-consent form not be functioning, written informed consent will be obtained using a hard copy of the consent form.

8.2. Screening and Eligibility Assessment

Potential participants will attend the MRINZ facility at Wellington Regional Hospital for a screening visit at which the PIS will be discussed and written informed consent will be completed. At this visit eligibility will be assessed. If a potential participant is deemed ineligible, then a reason for this will be recorded.

The following information will additionally be collected after obtaining their consent:

8.2.1. Medical History and Demographics

The information collected will include the following:

- Date of birth, age, ethnicity, sex.
- Height and weight
- Contact details
- Smoking history: smoking status (ex, current, never), pack years. Ex-smoker is defined as not having had tobacco containing products in the preceding 30 days.
- Age at asthma diagnosis

- Asthma history
- Cardiovascular history
- Current medications for asthma
- History of respiratory tract infections in the last 4 weeks
- Need for oral corticosteroid in the last 6 weeks
- Other medical conditions and medications
- Allergies
- Females with child bearing potential only: pregnancy status

8.2.2. Weight and height

Height and weight will be measured without shoes and wearing light indoor clothing calibrated using site equipment.

8.2.3. Vital Signs

Participants will have their oxygen saturation and heart rate measured by pulse oximetry, and respiratory rate and blood pressure measured. Vital signs may be taken in the seated position, but should be performed consistently in the same manner for each participant throughout the study. Subject position during vital signs should be recorded. Subjects should be in a rested and calm state for at least 5 minutes before taking vital sign measurements.

8.2.4. Spirometry

FEV1 and forced vital capacity (FVC) will be performed according to ATS/ERS 2005[17] criteria using Care Fusion MasterScope non-heated pneumotach spirometer running software V5.32.0

Reversibility testing will be conducted: Salbutamol 400micrograms will be administered using an MDI with a spacer. Repeat spirometry will be conducted after 15 minutes but before 30 minutes after administration of the final dose of Salbutamol.

8.2.5. ECG

One interpretable 12-lead ECG recording (e.g., without artifacts) will be obtained at screening using Cardiosoft v6.7 software manufactured by GE Medical Systems.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital ECG machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the subject has been resting in a supine position for at least 10 minutes.

Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the subject's permanent study file at the site. Digital recordings will be stored at the site.

8.2.6. Blood Sampling

Blood sampling will be conducted by trained MRINZ staff. Samples for the following laboratory tests will be sent to the local laboratory for analysis as per laboratory protocol:

1. Serum potassium levels
2. Blood eosinophil levels
3. Serum beta-HCG (for women only)

8.3. Randomisation

Following the screening process, eligible participants who have given written consent to be enrolled in the study will be randomised 1:1 to one of the following treatment arms:

a) Salbutamol arm (N = 22): Participants receive Salbutamol first, followed by Symbicort after a washout period
b) Budesonide/formoterol arm (N = 22): Participants receive Symbicort first, followed by Salbutamol after a washout period

The randomisation method will involve a computer-generated sequence supplied by the study statistician, independent of the investigators. The sequence will be uploaded into the Research Electronic Data Capture (REDCap) system by an individual who is otherwise uninvolved in study processes. REDCap will conceal the allocations and will release a participant's randomisation outcome at the time of randomisation. Only authorised MRINZ personnel responsible for the electronic randomisation system administration will have access to the randomisation schedule. The participant's GP will be notified regarding their enrolment in the study.

8.3.1. Procedures for handling incorrectly enrolled or randomized subjects

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the Sponsor immediately, and a discussion should occur between the Sponsor and the Investigator regarding whether to continue or discontinue the patient from treatment. The Sponsor must ensure all decisions are appropriately documented.

8.4. TREATMENT ARMS

The dosing schedules are illustrated in Appendix 1.

8.4.1. Symbicort arm

Budesonide/formoterol 200µg/6µg per actuation from the Turbuhaler, 1 actuation at 30 minute intervals for 4 doses over 90 minutes, followed by 2 actuations on 3 occasions at 20 minute intervals for 1 hour, followed by 2 actuations at 7 hours.

8.4.2. Salbutamol arm

Salbutamol 100µg per actuation from the MDI and spacer inhaled in a single maximal breath[18,19], 2 actuations at 30 minute intervals for 4 doses over 90 minutes, followed by salbutamol 2.5mg via nebuliser on 3 occasions at 20 minute intervals for 1 hour, followed by salbutamol 2.5mg via nebuliser at 7 hours. Prior to leaving the study site, this group will receive 12 actuations of Budesonide 200µg via Turbuhaler.

8.5. Intervention One

The participant will be randomised to one of two treatment arms (Salbutamol arm or Symbicort arm). The dosing visit will be approximately 9 hours long. The date of Intervention One can be up to 4 weeks from the date of screening visit. If a participant develops a respiratory tract infection or worsening of their asthma, the date of Intervention One may be postponed for a minimum of two weeks up to a maximum of six weeks from the date of the screening visit. It is acceptable for the intervention visit to be conducted beyond the 4 week window (from the screening visit) only in these cases.

The timing of procedures will be done at various time points as outlined in Appendix 1.

8.5.1. Pregnancy Testing

A urinary pregnancy test will be carried out for women only.

8.5.2. FeNO

FeNO will be measured on NiOX Vero, made by Circassia in Sweden in accordance with guidelines published by the ATS 2005[20]. FeNO will be measured at baseline and at 30 min intervals for 4 hours, then at hourly intervals until 8 hours, prior to spirometry measurements. An average from three FeNO measurements will be taken.

Participants will be instructed not to consume food or beverages for at least 1 hour prior to their FeNO measurement. An exception will be made for FeNO measurements at 300mins and 420 minutes, where participants will be given a standardized low nitrate lunch (immediately after investigations at 240 minutes) and afternoon tea (immediately after investigations at 360 minutes). Participants will be advised to avoid consumption of nitrate-rich foods (such as processed meats [bacon, lunch meat, hot

dogs, sausage etc.], spinach, green beans, broccoli, and cauliflower) for at least 8 hours prior to FeNO measurement.

8.5.3. Spirometry:

Spirometry will be conducted at baseline and then at 30 min intervals for 4 hours, then at hourly intervals until 8 hours using a hand-held spirometer.

8.5.4. Inspiratory Flow Training

Participants will be trained using the In-check dial G16 (Clement Clark International) device by trained MRINZ staff to ensure optimal inspiratory flow rates are achieved when using inhalers. The training will occur prior to treatment.

Symbicort arm: Acceptable inspiratory flow rate - 30-60 L/min[21]

8.5.5. ECG

One interpretable 12-lead ECG recording (e.g., without artifacts) will be obtained at baseline and at 3 and 8 hours to measure heart rate and QTc. Single ECG recordings may be obtained at unscheduled time points as clinically indicated.

If at a particular post dose timepoint the mean QTcF is >500 ms and/or 60 ms longer than the baseline value, another triplicate ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive triplicate ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator.

8.5.6. Blood Sampling

Blood sampling will be undertaken at baseline, 3 and 8 hours and will be conducted by trained MRINZ staff. Samples for the following laboratory tests will be sent to the local laboratory for analysis:

1. Serum potassium levels
2. Blood eosinophil levels

8.5.7. Vital signs

Participants will have their SpO_2, heart rate, respiratory rate and blood pressure measured up to 10 minutes prior to each dose, at 3 hours and then hourly to 8 hours.

8.5.8. Patient reported outcomes

Participants will be asked to report their perceived breathlessness on the modified Borg Dyspnoea Scale score (Appendix 3) before every time-point at which spirometry is undertaken.

The modified Borg Dyspnoea Scale score[22,23] is rated from "0: Nothing at all" to "10: Maximal" and participants will be asked to choose one score at each time point.

8.6. Intervention Two

Intervention Two will be 7 days to 4 weeks after Intervention One. At this visit, each participant will be allocated the treatment they did not receive during Intervention One. For example, if a participant was randomised to the salbutamol arm during Intervention One, they will be allocated to the Symbicort arm during Intervention Two and vice versa. Inspiratory training, spirometry, FeNO measurements, ECG monitoring, measurement of vital signs, patient related outcomes and blood sampling will be done at identical points to Intervention One and as outlined in Appendix 1.

If a participant develops a respiratory tract infection or worsening of their asthma, the date of Intervention Two may be postponed for a minimum of two weeks up to a maximum of six weeks from the date of Intervention One. It is acceptable for the Intervention Two visit to be conducted beyond the 4 week window (from the Intervention One visit) only in these cases.

The participant's GP will be notified regarding their completion of the study after Intervention Two.

8.7. Subsequent Visits

There will be no follow-up visits.

8.8. Sample Handling

After obtaining verbal consent from the participant, peripheral blood samples will be taken by trained staff using a vacutainer system and aseptic technique. Blood samples will be taken during screening, at baseline, 3 hours and 8 hours during each Intervention visit and sent immediately to the Wellington Southern Community Laboratories (SCL) to determine beta-HCG (screening visit and female participants only), serum potassium and blood eosinophil levels. Blood samples and request forms will be labelled with the participant study ID number, date of birth, date of sampling, subject sex and the signature of the staff member who collected the sample. Blood sampling will be undertaken as per MRINZ Standard Operating Procedure by trained staff and blood samples will be processed and discarded by the laboratory in accordance with the Wellington SCL standard procedures.

8.9. Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time. A participant that decides to discontinue will always be asked about the reason(s) and the presence of any adverse events but are not required to provide a reason for their decision to withdraw.In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the trial or determined in retrospect)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements

- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- An exacerbation of asthma
- Requirement for medications that would make a participant ineligible as listed in Section 9.5
- Withdrawal of Consent

Participants who withdraw will not be replaced. The reason for withdrawal if given by the participant will be recorded in the eCRF. If withdrawal from or discontinuation of the study is due to an adverse event, the Investigator will arrange follow-up visits and/or telephone calls until the adverse event has resolved or stabilised. The participant will be encouraged to participate in this follow-up, however it is recognised that this is not mandated after withdrawal of consent. The data of all eligible participants will be included in the data analysis.

8.10. Definition of End of Trial

The end of the trial is the date and time of completion of the last visit by the final participant.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1. IMP Description

The products used in this study are as below:

- SYMBICORT 200/6 TURBUHALER® (budesonide/formoterol fumarate dihydrate) is a dry powder inhalation device. One inhalation contains 200 micrograms budesonide and 6 micrograms formoterol fumarate dihydrate. Symbicort Turbuhaler contains lactose and may contain milk protein residue, this acts as a “carrier”. The amount added does not usually cause problems in lactose-intolerant people therefore, this will not be a contraindication to use.

- SALBUTAMOL 100 MDI is a pressurised metered dose inhaler which delivers 100 micrograms of Salbutamol sulphate per actuation, suspended in the CFC-free propellant HFA134a

- Salbutamol nebules 2.5mg/2.5mL are a plastic ampoule presentation containing a sterile, aqueous colourless solution of salbutamol sulphate in normal saline. The concentration of salbutamol is 0.1% (1mg salbutamol sulphate in 1mL). Each nebule contains 2.5mL of solution equivalent to 2.5mg salbutamol. Salbutamol nebules will be used with a nebuliser under the direction of a study investigator.

- BUDESONIDE Turbuhaler is a dry powder inhaler. One inhalation contains 200 micrograms budesonide.

9.2. Storage of IMP

The salbutamol pMDI, Symbicort Turbuhalers,budesonide Turbuhalers and salbutamol nebules will be stored at room temperature between 15ºC and 30ºC in the temperature controlled 24/7 monitored pharmacy cupboard. This room will only be accessed by authorized staff.

Each participant will be allocated a Symbicort Turbuhaler, salbutamol pMDI and budesonide Turbuhaler which will be labelled with their study ID number and participant initials. It will be discarded when that participant completes the study.

9.3. Compliance with Trial Treatment

All treatment will be administered by an investigator and observed by a medically trained investigator.

9.4. Accountability of the Trial Treatment

The funder will provide the Symbicort Turbuhalers and budesonide turbuhaler. Salbutamol MDI and nebules will be sourced from the local pharmacy.

9.5. Concomitant Medication

Participants will be asked to withhold their SABA, LABA and ultra-LABA for 6 hours, 24 hours and 48 hours respectively prior to each Intervention visit.

The use of the following medications either at screening or at either Intervention visit will render the participant ineligible.

- Oral corticosteroids in the 6 weeks prior to the screening or intervention visits
- Long-acting muscarinic receptor antagonists in the 4 weeks prior to the screening or intervention visits
- Theophylline in the 4 weeks prior to the screening or intervention visits
- Biologics in the 4 weeks prior to the screening or intervention visits
- Sodium cromoglycate in the 4 weeks prior to the screening or intervention visits
- Nedocromil sodium in the 4 weeks prior to the screening or intervention visits
- Beta-blockers in the 4 weeks prior to the screening or intervention visits

9.6. Post-trial Treatment

There will be no post-trial treatment or provision of the IMP beyond the trial period.

10. SAFETY REPORTING

10.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: results in death is life-threatening requires inpatient hospitalisation or prolongation of existing hospitalisation results in persistent or significant disability/incapacity consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product

	in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".

10.2. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

10.3. Procedures for Recording Adverse Events

All AEs occurring during the trial that are observed by the Investigator or reported by the participant, will be recorded on the eCRF, whether or not attributed to trial medication.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of an AE will be graded according to the Common Terminology Criteria for Adverse Events[24] (CTCAE) as described below.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

AEs considered related to the trial medication as judged by a medically qualified investigator will be followed either until resolution, or the event is considered stable.

If a participant endures an adverse event but is able to continue with the study, they will receive subsequent doses as per the randomised schedule and undergo the relevant measurements as per the protocol.

It will be left to the Investigator's clinical judgment or the Sponsor to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

10.4. Reporting Procedures for Serious Adverse Events

Serious Adverse Events will be recorded in the eCRF from the date of consent until the last study visit a participant attends, and reported to the Sponsor within 24 hours of Investigators becoming aware of the event. Any follow up information required by the Sponsor must be reported as soon as the Investigator becomes aware of new information. If an SAE is ongoing at the last contact visit, the Investigator should follow this up until resolution. The Sponsor will report to the CARM (Centre for Adverse Reactions

Monitoring) within the required time period, of all serious adverse reactions in accordance with current reporting requirements.

10.5. Expectedness

Expectedness will be determined according to the Medsafe Data Sheet for each IMP respectively.

10.6. SUSAR Reporting

All SUSARs will be reported by the Sponsor to CARM (Centre for Adverse Reactions Monitoring) and to the HDEC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

10.7. Reporting of serious adverse events to Company (AstraZeneca)

The Sponsor is responsible for informing Company of the SAE. All SAEs have to be reported to Company, whether or not considered causally related to the investigational product. All SAEs are to be submitted to the AstraZeneca Product Safety mailbox, AEMailboxClinicalTrialTCS@astrazeneca.com. Serious adverse events that do not require expedited reporting to the HDEC still need to be reported to Company. All SAEs that are related will be reported to the Company no later than 24 hours after the Sponsor is first aware of the reaction.

10.8. Overdose

An overdose of formoterol would likely lead to effects that are typical for beta2-agonists: tremor, headache, palpitations, and tachycardia. Hypotension, metabolic acidosis, hypokalemia and hyperglycemia may also occur. Supportive and symptomatic treatment may be indicated. A dose of 90 micrograms formoterol administered during 3 hours in patients with acute bronchial obstruction raised no safety concerns.[25]

Acute overdose with Budesonide, even in excessive doses, is not expected to be a clinical problem.[26]

The most common signs and symptoms of overdose with salbutamol are transient beta2-agonist pharmacologically mediated events. Lactic acidosis has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy.[27]

If an overdose occurs in the course of the study, then the Investigator will inform the Sponsor immediately, or no later than 24 hours of when the investigator becomes aware of it. The Sponsor will work with the Investigator to ensure that all relevant information is provided in the eCRF. An overdose is considered to be the administration of either salbutamol, budesonide or Symbicort at a dose higher than that specified in the dosing schedules.

10.9. Pregnancy

All pregnancies and outcomes of pregnancy should be reported to Sponsor and the Company.

10.9.1. Maternal exposure

If a subject becomes pregnant during the course of the study, she will be removed from the study and all study drugs will be discontinued immediately. Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. The outcome of all pregnancies (spontaneous miscarriage, termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs during the course of the study, then the Investigator informs the Sponsor within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The Sponsor works with the Investigator to ensure that all relevant information is captured within the eCRF within 1 or 5 calendar days for SAEs and within 30 days for all other pregnancies. SAEs will be reported to CARM if applicable.

The same timelines apply when outcome information is available.

10.9.2. Paternal exposure

The study does not require abstinence or use of contraception for male partners. As neither the investigational product nor comparative drugs are contraindicated in pregnancy, we will not be eliciting the pregnancy status of participants' partners.

10.10. Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) led by Consultant Physician, Dr.Shirtcliffe will be formed to review all SAEs on an expedited basis, and undertake a review of enrolments, withdrawals, and adverse events according to a DSMC charter to ensure adequate study safety, and minimal risk to participants. The DSMC may recommend to the study sponsor that the study should be stopped, however the final decision will rest with the study sponsor.

11. STATISTICS

11.1. Description of Statistical Methods

For the primary outcome variable of FEV_1 at 180minutes a mixed linear model will be used with the baseline FEV_1, treatment allocation, and treatment order as fixed effects; and participant treated as a random effect to take into account the cross-over design. For the FEV_1 at other measurement times a mixed linear model will be used for each of the variables with baseline values as continuous co-variates, and further fixed effects for randomised order, randomised treatment, and time, as well as a time by treatment interaction term. A random intercept term will be used to take into account the repeated measures for each participant. A similar statistical method will be utilised for analysing the secondary

variables: modified Borg Dyspnoea Scale score, heart rate and QT_C, blood eosinophil and potassium levels.

Data for FeNO will be analysed on the logarithm transformed scale based on our previous experience with the skew distribution of this variable and that normality assumptions were better met on the logarithm transformed scale, interpreted as the ratio of geometric means. Further details regarding analyses methods can be found in the Statistical Analysis Plan.

11.2. The Number of Participants

Based on the past research where a mean difference of 0.23L was detected in a cross-over study with N=24, the estimated paired SD for this study is 0.43L.[28] A sample size of 39 has 90% power to detect a difference of 0.23L with a two-sided alpha of 0.05. Although sample size is based on a one-sample t-test the analysis will be a mixed linear model with baseline measurements as continuous co-variates and this will likely to have increased statistical power to detect differences compared to a paired t-test of change from baseline FEV1. Assuming a drop out rate of 10%, then a total of 44 patients would be required. A cumulative total Salbutamol dose of 2400µg by MDI equivalent achieves close to the maximum obtainable improvement in lung function in stable asthma.[29–31]

As the inclusion criteria and dosage regimens used are not exactly the same as the previous study on which the power calculations have been based, after 15 participants have been studied, the SD will be estimated to confirm the assumed SD (0.43L) is accurate. The 15 participants gives 14 degrees of freedom to estimate a 95% CI for the SD. The maximum limit of the number of participants included in the study following the interim analyses is 88.

11.3. The Level of Statistical Significance

The level of significance is $P \leq 0.05$.

11.4. Criteria for the Termination of the Trial

Early termination may occur at the discretion of the Investigators for any reason that is believed may present a safety risk.

- Sponsor: If the Sponsor terminates or suspends a trial, the Sponsor should promptly inform the HDEC and provide the HDEC a detailed written explanation for the termination or suspension.

- Health and Disability Ethics Committee (HDEC): If the HDEC terminates or suspends its approval/favourable opinion of a trial, HDEC will provide a detailed written explanation for the termination or suspension.

11.5. Procedure for Accounting for Missing, Unused and Spurious Data

The mixed linear model proposed for the main analysis uses all available data and no form of imputation will be used for missing data which will be assumed to be missing at random.

11.6. Inclusion in Analysis

All participants who are randomised will be included in the analysis.

11.7. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical plan will be described and justified in the final report.

12. DATA MANAGEMENT

12.1. Source Data

Source documents are where data are first recorded, and from which participants' eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the eCRF), MRINZ electronic participant database (including e-consent forms), clinical and office charts, laboratory and pharmacy records, diaries, radiographs, and correspondence. eCRF entries will be considered source data if the eCRF is the site of the original recording (e.g. there is no other written or electronic record of data)..

12.2. Access to Data

Only authorised study staff will be permitted access to the password protected REDCap database where study specific data will be stored. Paper documents will be stored in a locked site with restricted access at the MRINZ facility. On all trial-specific documents, other than the signed consent form and the letter to the GP, the participant will be referred to by the unique participant code, not by name. Access will be granted to authorised representatives from MRINZ and the regulatory authorities to permit trial-related monitoring, audits and reports. Participants enrolled in the trial will have an alert displayed on their electronic hospital records (Concerto) to inform healthcare providers of their enrolment in the study.

12.1. Data Sharing

Study data sets may be shared with other researchers who are not participating in this study according to a Data Sharing Plan. Under no circumstances will uniquely identifying information or identified data be shared. Any requests for de-identified data-sharing will be reviewed in accordance with MRINZ's policy on clinical trial data sharing.

12.2. Data Recording and Record Keeping

Data will be entered from or as source documentation using electronic data capture tools hosted and supported by the MRINZ. REDCap is a secure, HIPAA (United States Health Insurance Portability and Accountability Act 1996) compliant web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages, including de-identified data sets; and 4) procedures for importing data from external sources.

Informed signed consent will be captured with an electronic signature on REDCap, which will be obtained using a stylus and iPad.

Participants will be identified by a unique study ID in any data export from the eCRF database. The name and any other identifying detail will not be included

Study documents including eCRFs will be stored on site at MRINZ, or offsite under MRINZ control for 15 years after the completion of the trial to comply with GCP standards.

13. QUALITY ASSURANCE PROCEDURES

13.1. Training of study site personnel

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will maintain a record of all individuals involved in the study and the training they have received.

13.2. Monitoring

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. Regular monitoring will be performed according to GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following the study monitoring plan, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14. SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the Investigator the serious breach will be reviewed by the Sponsor and, if appropriate, report it to the responsible ethics committee, regulatory authority, and local governance body (as applicable) within seven calendar days.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

15.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

15.3. Approvals

The study does not require submission to Medsafe (via the Standing Committee on Therapeutic Trials), as the IMPs are approved products in New Zealand, being investigated in a slightly different population of patients, therefore the study is not under the scope of Medsafe review or the need for approval under Section 30 of the Medicines Act 1981.

Ethical Submission will be made to one of the Health and Disability Ethics Committees of New Zealand. The opinion of the Ethics Committee will be given in writing. Locality approval must be granted at each site before any participants are recruited, as per Ethics Committee guidelines. The Ethics Committee should approve all advertising used to recruit patients for the study.

Approval for the study will also be sought from the Regional Advisory Group – Māori (RAG-M), and such approval will be given prior to locality being activated.

The Sponsor should approve any modifications to the Participant Information Sheet and Consent Form/s that are needed, including submission to the Ethics Committee as necessary.

The co-ordinating investigator will submit all substantial amendments to the original approved documents to the HDEC.

15.4. Reporting

The Principal Investigator shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the responsible Ethics Committee. In addition, an End of Trial Notification and Final Report will be submitted to the responsible Ethics Committee.

15.5. Participant Confidentiality

The study staff will ensure that the participant's anonymity is maintained. Participant identifiable data will be entered into the MRINZ electronic participant database (including e-consent forms). The database is password protected and only accessible by authorized staff members.

De-identified information from the electronic database will be included in the eCRF. The eCRF will contain the unique participant number. It is the intention of the study site to capture as much participant-related information directly into an eCRF (electronic case report form) on REDCap, and to use this eCRF as source documentation. The eCRF is an encrypted secure system that is protected by unique username and password requirements for log-in, which are only provided to trained study staff

15.6. Expenses and Benefits

Participants will be eligible for reimbursement for their time and travel costs in attending study visits.

15.7. Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of AstraZeneca and the Sponsor.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the responsible Ethics Committee. If a protocol amendment requires a change to the Informed Consent Form, Sponsor and the responsible Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

16. FINANCE AND INSURANCE

16.1. Funding

The trial will be funded by a research grant from AstraZeneca. The funding agreement is made between AstraZeneca and MRINZ.

16.2. Insurance

This study is not being conducted for the benefit of a drug manufacturer or distributor and therefore insurance to cover participant injury due to participation in the study is not required. Participants may claim under the Accident Compensation Act 2001 for injury sustained during the study, if appropriate.

17. PUBLICATION POLICY

The study findings will be published by MRINZ, in a scientific peer reviewed journal, according to the International Committee of Medical Journal Editors recommendations. The Investigators listed on page one will be listed as authors, in recognition of their contribution to the design, implementation and oversight of the study.

Results of the study will be sent to participants on request (once available) and will be made available on a publicly available trial registry website, recognised by the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) as a Primary Registry.

18. REFERENCES

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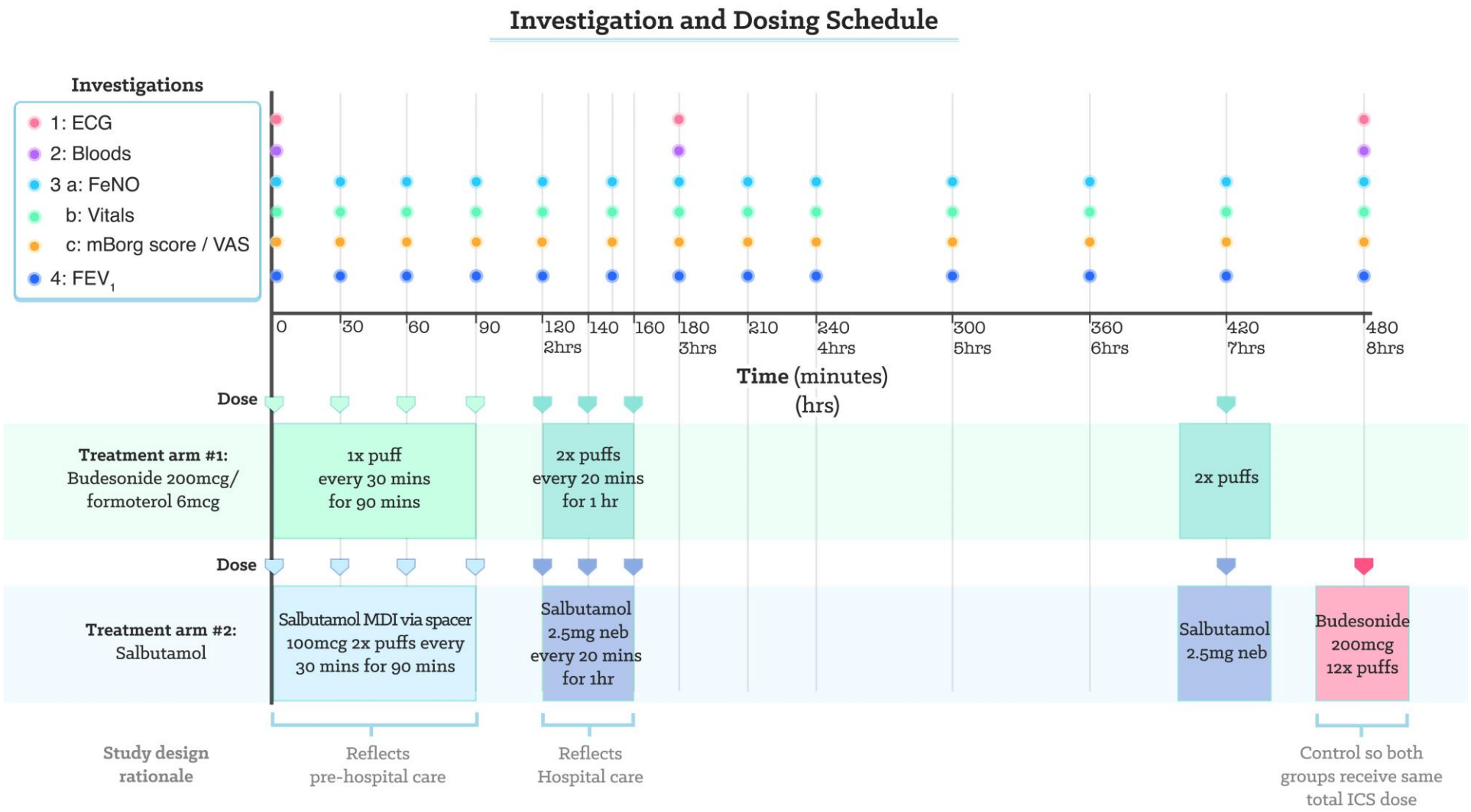
19. APPENDICES

19.1. Appendix 1: Dosing and investigation schedule



19.2. Appendix 2: Schedule of Procedures

Visit	Screening	Intervention One Visit	Intervention Two Visit
Day	<0	0	7 days to 4 weeks
Procedure			
Written informed consent	X		
Demographics	X		
Medical/Surgical history	X		
Inclusion/Exclusion criteria	X	X	X
Weight and height measurements	X		
Vital signs	X	X	X
FeNO		X	X
Spirometry	X	X	X
Reversibility Testing	X		
12 lead ECG	X	X	X
Blood sampling for K+ and eosinophils	X	X	X
Blood sampling for serum beta-HCG	X		
Randomisation		X	
Inform GP of study enrolment	X		
Treatment administration		X	X
Urinary Pregnancy Testing		X	X
Inspiratory Flow Training		X	X
Modified Borg Dyspnoea Scale score		X	X
Review: - Exacerbations - AEs - SAEs - Medication changes		X	X
Inform GP of completion of study			X

19.3. Appendix 3: Modified Borg Dyspnoea Scale Score

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

19.4. Appendix 4: Dose Limiting Adverse Events

The following is a guide on dose limiting AEs that may result from the administration of Symbicort[25], budesonide[26] or salbutamol[27]. The clinical judgement of a medically qualified investigator takes precedence over this guidance.

Adverse Event	Dose Limiting signs/symptoms/reasons
Tremor	Patient unwilling/unable to continue
Headache	Patient unwilling/unable to continue
Hypokalaemia	ECG changes[32,33]: Decreased T wave amplitude T wave inversion ST segment depression Prominent U Wave Prolongation of QT(U) Interval Ventricular tachycardia Torsades de pointes
Tachycardia	Symptomatic Patient unwilling/unable to continue
Asthma aggravated	Patient unwilling/unable to continue Symptomatic
Bradycardia	Symptomatic Patient unwilling/unable to continue
Chest pain	Presence of chest pain
Dizziness	Unresolving dizziness Patient unwilling/unable to continue
Hypertension	Patient unwilling/unable to continue
Pruritus	Patient unwilling/unable to continue
Irritation in throat	Patient unwilling/unable to continue
Hoarseness	Patient unwilling/unable to continue
Coughing	Patient unwilling/unable to continue