Protocol

RCT of the efficacy and safety of an ICS/ LABA reliever therapy regimen in asthma

Short title: Novel START (Novel Symbicort Turbuhaler Asthma Reliever Therapy)

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Investigators

Richard Beasley, MRINZ, Wellington, New Zealand

Mark Weatherall, University of Otago Wellington, Wellington, New Zealand

Ian Pavord, University of Oxford, Oxford, United Kingdom

Alberto Papi, Università di Ferrara, Ferrara, Italy

Helen Reddel, Woolcock Institute of Medical Research, University of Sydney, Australia

Tim Harrison, University of Nottingham, Nottingham, United Kingdom

Guy B Marks, University of New South Wales, Sydney, Australia

Bob Hancox, Waikato Hospital, Hamilton, New Zealand

Global Sponsor: Medical Research Institute of New Zealand

Funder: AstraZeneca

Contact:

Professor Richard Beasley
Medical Research Institute of New Zealand
Private Bag 7902, Newtown
Wellington 6242, New Zealand
Telephone: +64-4-805 0230
Facsimile: +64-4-389 5707
Email: richard.beasley@mrinz.ac.nz

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Synopsis

Global Chief Investigator:
Professor Richard Beasley
Medical Research Institute of New Zealand
Private Bag 7902, Newtown
Wellington 6242, New Zealand
Telephone: +64-4-805 0230
Facsimile: +64-4-389 5707
Email: richard.beasley@mrinz.ac.nz

Study design

The Novel START (Novel Symbicort Turbuhaler Asthma Reliever Therapy) study is a 52-week, open label, parallel group, multicentre, phase III, randomised controlled trial to compare the efficacy and safety of three asthma treatment regimens:

1. Salbutamol metered dose inhaler (MDI) taken as required for relief of symptoms (SABA reliever therapy).
2. Budesonide/formoterol Turbuhaler taken as required for relief of symptoms (ICS/LABA reliever therapy).
3. Regular budesonide Turbuhaler plus salbutamol MDI taken as required for relief of symptoms (maintenance ICS and SABA reliever therapy).

Study sites

Participants will be recruited from sites in 9 regions in 4 countries (New Zealand, Australia, Italy and the United Kingdom).

Target population

675 patients with asthma currently treated with SABA monotherapy for symptom relief.

Objectives

Primary

1. To compare the efficacy of ICS/LABA reliever therapy with SABA reliever therapy and with maintenance ICS and SABA reliever therapy in adult patients using SABA monotherapy (i.e. without any other asthma medication).

Secondary

1. To compare the safety of ICS/LABA reliever therapy with SABA reliever therapy and with maintenance ICS and SABA reliever therapy in adult patients using SABA monotherapy (i.e. without any other asthma medication).

2. To determine whether baseline clinical characteristics such as reported beta agonist use, Th2 profile, smoking status or history of severe exacerbations predict preferential response to randomised treatments.
3. To examine patterns of inhaler use with the randomised regimens.
4. To examine patient attitudes to and experience with the treatment regimens.
5. To examine the cost effectiveness of each treatment regimen.

Study duration

Participants will be seen for the initial visit and at weeks 6, 12, 22, 32, 42 and 52.

Interventions

Participants will be randomised in equal proportions to one of three treatments:

(i) SABA reliever therapy; salbutamol MDI 100µg (Ventolin), 2 inhalations for relief of symptoms as required.

(ii) ICS/LABA reliever therapy; budesonide/formoterol Turbuhaler 200/6µg (Symbicort), one inhalation for relief of symptoms as required.

(iii) Maintenance ICS and SABA reliever therapy; budesonide Turbuhaler 200µg (Pulmicort), 1 inhalation twice daily and salbutamol MDI 100µg (Ventolin) 2 inhalations for relief of symptoms as required.

The original definition of the dose for Turbuhaler products has been the metered dose, which is the amount of powder filled into and released from the dosing unit. The definition adopted for Symbicort Turbuhaler is the delivered dose, which is defined as the amount of powder delivered from the exit of the mouthpiece. The delivered dose is thus the dose administered to the patient.

In most countries (including Italy) Symbicort Turbuhaler strengths are expressed as delivered dose (80µg/4.5µg, 160µg/4.5µg and 320µg /9µg) but in some countries (including New Zealand, Australia and United Kingdom) the products were given names that link back to the monoproducts metered dose strengths. The names Symbicort Turbuhaler 100µg/6µg per dose, Symbicort Turbuhaler 200µg/6µg per dose and Symbicort Turbuhaler 400µg/12µg per dose were given to maintain the coherence with the existing monoproducts already registered and expressed as metered dose. The objective was to avoid confusion for prescribers and patients, as this denomination facilitate the comparison with the monoproducts Pulmicort 100µg, 200µg and 400µg and Oxis 6µg and 12µg, which are expressed as metered dose. The delivered dose for these products are 80µg, 160µg and 320µg (80% of the metered dose) and 4.5µg and 9µg (75% of the metered dose), respectively, i.e. the same as the delivered doses for Symbicort Turbuhaler.

For this study, the metered dose naming convention will be used consistently for all participating countries.

Electronic Monitoring

All study inhalers will have electronic monitoring devices which record use, to enable identification of patterns of medication use.

Statistical methods

The primary analysis is comparison of the rate of exacerbations per patient per year by Poisson regression. This will be undertaken with an offset for the days of observation and a fixed effect for SABA use and number of prior severe exacerbations before recruitment.

The pre-specified treatment comparisons are:

1. ICS/LABA reliever therapy regimen compared to the SABA reliever therapy regimen

2. ICS/LABA reliever therapy regimen compared to the maintenance ICS and SABA reliever therapy regimen

Two sensitivity analyses will include potentially important predictors of response. Survival analysis with Kaplan-Meier plots and Cox's proportional hazards will be used to calculate the hazard ratio for time to first exacerbation.

For the secondary outcome variables based on medication use, counts of events will be analysed by Poisson regression with an offset for time of observation and correction for over-dispersion if necessary. Proportions of events will be analysed by calculation of relative risks or odds ratios and appropriate confidence intervals. Continuous variables, such as the ACQ-5 scores, and FEV_1 will be compared by t-tests and mixed linear models to account for repeated measurements and to examine patterns of change with time. If normal distribution assumptions are not met for continuous variables our plan is to seek data transformations or use the Mann-Whitney test. For the variables ICS dose and combined systemic corticosteroid load, the natural logarithm transformation will be used.

Pre-specified subgroup analyses will be used to evaluate if specific characteristics affect treatment response.

1. Abbreviations and definitions

ACQ	Asthma Control Questionnaire
ASK-12	Adherence Starts with Knowledge 12 questionnaire
ATS	American Thoracic Society
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
ED	Emergency Department
ERS	European Respiratory Society
FBC	Full Blood Count
FeNO	Fractional exhaled Nitric Oxide
FEV1	Forced Expiratory Volume over 1 second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
IMP	Investigational Medicinal Product
ICS	Inhaled Corticosteroid
LABA	Long Acting Beta Agonist
MDI	Metered Dose Inhaler
NZ	New Zealand
OTC	Over the counter
PRN	Pro re nata (as needed)
RCT	Randomised Controlled Trial
SABA	Short Acting Beta Agonist
SMART	Symbicort as Maintenance and Reliever Therapy

Exacerbation of Asthma:

An asthma exacerbation is defined by any of the following criteria:

a. Worsening asthma resulting in urgent medical review (primary care visit, ED visit or hospital admission) and/or
b. Worsening asthma resulting in the use of systemic corticosteroids, such as a course of oral prednisone for any duration and/or
c. Worsening asthma resulting in a high beta agonist use episode, defined as >16 actuations of salbutamol or >8 actuations of budesonide/ formoterol per 24 hour period as previously defined.[1] Note this data is collected from electronic monitors only, not participant report.

NOTE: For an exacerbation to be counted as a separate event, it must be preceded by at least 7 days[2] during which none of the above criteria are fulfilled

NOTE: Beta agonist use data from the day of a scheduled study visit is not to be used (so does not count towards defining a high beta agonist use episode). See Section 12.

Severe Asthma Exacerbation:

A severe asthma exacerbation is:[2]

a. The use of systemic corticosteroids for at least 3 days because of asthma, or
b. Hospitalisation or ED visit because of asthma, requiring systemic corticosteroids

High beta agonist use episode: >16 actuations of salbutamol in a 24 hour period or >8 actuations of budesonide/formoterol in a 24 hour period.

Marked beta agonist use episode: >24 actuations of salbutamol in a 24 hour period or >12 actuations of budesonide/formoterol in a 24 hour period.

Treatment failure:

Treatment failure is:

a. One severe exacerbation, or
b. Three exacerbations, or
c. Randomised treatment is modified by the participant's GP or other healthcare provider during the study, with the exception of:
    i. the addition of, or increase in maintenance ICS dose for ≤2 weeks in the setting of worsening asthma or an exacerbation
    ii. the addition of, or change in ICS/LABA regimen (e.g. SMART) for ≤2 weeks in the setting of worsening asthma or an exacerbation
    iii. the addition of SABA therapy for ≤2 weeks in the setting of worsening asthma or an exacerbation

Modifications are defined by an increase in the participants' randomised asthma inhaler regimen and/ or the addition of medications to aid asthma control including SABA, ICS/LABA, ICS, LABA, leukotriene receptor antagonists, mast cell stabilisers, theophylline and monoclonal antibody therapy.

Participants who obtain over the counter (OTC) SABA will be withdrawn from the study, however this will not be counted as a treatment failure.

24 hour period: From midnight to midnight, at local time to the investigator site.

Acute Care Visit: This refers to any contact the participant has with their usual healthcare provider/GP/ED/Afterhours service, in order to seek urgent or emergency care for their asthma.

Scheduled Study Visit: This refers to any of the 7 pre-defined study visits as outlined in Section 7.

Unscheduled Study Visit: This refers to any visit arranged in addition to the scheduled visits and takes place outside of scheduled visit windows. An unscheduled visit may be arranged for one of two purposes: for dispensing of additional study medication or for consideration of withdrawal of the participant from the study (see Section 8).

Local Chief Investigator: The Investigator responsible for the study in each country, as distinct from the Global Chief Investigator, who is responsible for the study globally.

Local Sponsor: A representative of the Global Sponsor in each country (NZ, Australia, UK, Italy) undertaking oversight of the study in that country, on behalf of the Global Sponsor. Responsibilities include reporting of relevant expedited safety reports, insurance cover for participant harm incurred as part of the study and obtaining ethical and regulatory approval within their country.

2. Rationale

Asthma is a major health problem globally.[3] Clinical research and management mainly focus on moderate to severe asthma however most adults with asthma have mild disease.[4] Globally little attention has focused on this 'silent majority' with intermittent and mild persistent asthma, who are often treated with a short-acting beta agonist (SABA) metered dose inhaler (MDI) as sole therapy for relief of symptoms. SABA treatment represents Step 1 management in international guidelines.[5] However, there is substantial morbidity in this population, for example in the OPTIMA study, 33% patients with intermittent or mild persistent asthma who were inhaled corticosteroid (ICS)-free at baseline and throughout the study (Group A) had severe exacerbations during the 12 month study period.[6]

While SABA therapy may provide symptom relief, there is inadequate evidence about the safety of treating so-called 'intermittent' asthma with SABA alone. Initiating asthma treatment with SABA alone may promote patient attitudes and behaviours that contribute to subsequent over-reliance on SABA, and which may lead to worse asthma outcomes long term.[7] Recognition of this adverse therapeutic profile and the demonstration of reduced risk of morbidity and mortality with ICS therapy[8] has led to past guideline recommendations to use regular ICS in patients using their SABA on more than two occasions in a week.[5] However, the 2014 GINA report[9] acknowledged the limited evidence base to support this specific level at which it is recommended to introduce ICS, and based on consensus, the lack of evidence for safety of SABA alone, and the benefits from ICS seen in the large START study[10] in which over 45% of patients would not have qualified for ICS and in a very small study in 'intermittent' asthma,[11] GINA expanded the indication for regular low dose ICS to include patients with symptoms on two occasions or more a month, one or more risk factors for exacerbations, or a severe exacerbation in the past 12 months. Nevertheless, surveys show neither doctors nor patients recognise the need for ICS therapy even at the previously recommended stage, and that many patients are reluctant to take ICS every day.[5,12,13] Poor adherence is not surprising as patients are required to take twice daily treatment regardless of whether they have symptoms. Recognition by primary care practitioners that such patients are unlikely to be adherent with regular ICS treatment is likely to contribute to the reluctance to prescribe ICS. These limitations have led to consideration of alternative regimens to that of SABA therapy for symptom relief.

Evidence suggests that a combination ICS/fast onset long-acting beta agonist (LABA) inhaler, used solely as reliever therapy, may be preferable to sole SABA reliever therapy use and represent an alternative to regular ICS with SABA reliever therapy in patients with intermittent or mild asthma.[14-16] Combination ICS/LABA reliever therapy has a major potential advantage over SABA monotherapy because it allows titration of ICS therapy according to need in patients who would otherwise not receive ICS therapy. This regimen also has major potential advantages over the introduction of regular ICS therapy. It may increase ICS use in otherwise poorly adherent patients who over-rely on their SABA. It also enables high dose ICS therapy to be delivered promptly by patients with worsening asthma. Evidence in support of the combination ICS/LABA reliever therapy regimen includes:

a. Symptom-based ICS/SABA combination inhaler is more effective in reducing exacerbations than SABA reliever therapy in patients with mild asthma.[17] The symptom driven as required use of combination ICS/SABA in a single inhaler has equivalent efficacy to regular ICS treatment in this population.[17]

b. Symptom-based use of ICS and SABA (in separate inhalers) has similar efficacy to a physician-based strategy of 6-weekly adjustment of maintenance ICS dose in addition to SABA reliever use, and greater efficacy during high risk periods of increased viral infections and allergen exposures.[18]

c. The SMART regimen, in which patients take the same combination ICS/fast onset LABA inhaler for both maintenance and reliever therapy, is more effective than either a SABA or LABA as reliever therapy, when taken with the same dose of ICS/fast onset LABA maintenance therapy.[1,19]

d. In patients with infrequent symptoms but elevated FeNO at baseline, symptom-based ICS/LABA combination inhaler causes reduced FeNO, an important biomarker of airway inflammation, compared with LABA reliever therapy, indicating better control of airway inflammation.[20]

e. Quadrupling ICS dose during exacerbations of asthma has a beneficial clinical effect.[21] Multiple doses of ICS administered at time intervals ≤30 minutes over 2 hours in severe exacerbations results in faster clinical improvement than systemic corticosteroids.[22]

f. When used as reliever therapy, a fast onset LABA results in greater efficacy than a SABA.[23, 24]

To investigate this management approach in patients with intermittent and mild persistent asthma treated with SABA monotherapy for symptom relief, we propose a randomised controlled trial (RCT).

3. Design and objectives

3.1. Design

The Novel START (Novel Symbicort Turbuhaler Asthma Reliever Therapy) study is a 52-week, open label, parallel group, multicentre, phase III, multinational RCT (see Appendix, Figure 1). The clinical trial will compare the efficacy and safety of three asthma treatment regimens: salbutamol metered dose inhaler (MDI) taken as required for relief of symptoms (SABA reliever therapy), budesonide/formoterol Turbuhaler taken as required for relief of symptoms (ICS/LABA reliever therapy), and regular budesonide Turbuhaler plus salbutamol MDI taken as required for relief of symptoms (maintenance ICS and SABA reliever therapy). Participants will be patients with asthma currently treated with SABA monotherapy for symptom relief.

3.2. Primary

1. To compare the efficacy of ICS/LABA reliever therapy with SABA reliever therapy and with maintenance ICS and SABA reliever therapy in adult patients using SABA monotherapy (i.e. without any other asthma medication).

3.3. Secondary

1. To compare the safety of ICS/LABA reliever therapy with SABA reliever therapy and with maintenance ICS and SABA reliever therapy in adult patients using SABA monotherapy (i.e. without any other asthma medication).
2. To determine whether baseline clinical characteristics such as reported beta agonist use, Th2 profile, smoking status or history of severe exacerbations predict preferential response to randomised treatments.
3. To examine patterns of inhaler use with the randomised regimens.
4. To examine patient attitudes to and experience with the treatment regimens.
5. To examine the cost effectiveness of each treatment regimen.

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4. Randomised treatments

4.1. Treatments/IMPs

4.1.1. Participants will be randomised in equal proportions to one of three treatments:

(i) SABA reliever therapy; salbutamol MDI 100µg, 2 inhalations for relief of symptoms as required.
(ii) ICS/LABA reliever therapy; budesonide/formoterol Turbuhaler 200/6µg, one inhalation for relief of symptoms as required.
(iii) Maintenance ICS and SABA reliever therapy; budesonide Turbuhaler 200µg, 1 inhalation twice daily and salbutamol MDI 100µg 2 inhalations for relief of symptoms as required.

The three treatments (salbutamol, budesonide/formoterol and budesonide) as listed above are IMPs, as per the definition provided in European Commission Directive 2001/20/EC, under article 2(d).

4.2. IMP labelling

The IMP will be labelled according to Good Manufacturing Practices, Annex 13. Manufacture of Investigational Medicinal Products. All IMPs will be labelled with a country specific study label, to account for local regulations and requirements.
The IMP will undergo release according to Good Manufacturing Practice, with a Qualified Person providing the final sign off prior to distribution to site.

4.3. IMP storage

The IMP will be stored according to the country specific label information, which is based on the data provided in the respective Summary of Product Characteristics documents.
The IMP should be stored securely, with access only given to Investigators and their delegated staff and in a suitable environment, including within the appropriate temperature range. If required, the storage of IMP may be delegated to a pharmacy. Temperature monitored storage is required for all IMP, from receipt at site until dispensing to participant.

4.4. IMP compliance

Compliance with IMP is an outcome of the study and will therefore be captured as part of the inhaler monitor data (see section 12). Compliance is only applicable to the Maintenance ICS and SABA reliever therapy arm, which involves a maintenance dose of 1 inhalation twice daily, of ICS. Salbutamol and ICS/LABA treatments are reliever medications, used PRN. Use of IMP will be analysed at the end of the study (see section 11).
Participants may be withdrawn for high use episodes (see Section 5.4), however all other non-compliance will not be a cause for withdrawal and will not be reported to the participant during the study.

4.5. IMP accountability

IMP will be dispensed at Visits 1-6 and collected at Visits 2-7, and dispensed and collected at unscheduled visits as applicable. A study medication log will be provided to Investigators to record all IMP dispensed and all IMP collected. This will also be recorded on the eCRF at each visit, for the purpose of remote accountability monitoring.
Destruction of used or unused inhalers will be performed after accountability and reconciliation has taken place.

4.6. Electronic Monitoring

All study inhalers will have electronic monitoring devices which record use, to enable identification of patterns of medication use (see section 12 for more information).

4.7. Concomitant medications

Concomitant medications will be recorded on a concomitant medication log and entered into the eCRF. Investigators should record all relevant medications used during the study, in addition to those the participant has been randomised to. For a list of medications that will result in withdrawal, see section 5.4. The Global Sponsor will review concomitant medications reported in the eCRF, for consistency (e.g. against adverse events) and as part of ongoing monitoring to ensure participants are withdrawn as per protocol.

4.8. Inhaler technique

4.8.1. At the first visit, participants will be educated on correct inhaler technique, with a demonstration and written instructions.

4.8.2. Inhaler technique will be assessed at study visits 1-6.

4.9. Asthma management plans

4.9.1. All participants will be given education on medication use and inhaler technique, and a written asthma self-management (“action”) plan relating to their randomised group. The management plans will be modified versions of the AstraZeneca “My Symbicort SMART Asthma Action Plan”[25] (see Appendix, Figures 2-7). The

purpose of these plans is to reinforce the randomised treatment regimens and provide written instructions on what actions the participants should take in the situation of worsening asthma. In particular this will explain when to seek GP review and emergency medical care in the situation of an exacerbation, and the maximum daily doses of budesonide/formoterol and salbutamol for the different regimens respectively. This approach also provides standardised assessment and recognition of exacerbations by participants in the clinical trial.

4.9.2. Participants will not be required to measure their peak flow or to fill in a record card every day as this would prompt the participants to take their medicines regularly and promote adherence. These effects would reduce the chance of seeing a difference between regular and reliever ICS regimens which occur in "real-world" scenarios. Those subjects who already monitor their peak flows on entry to the study will be advised to continue to do so with a management plan incorporating peak flow use. For the purpose of this study, a drop in peak flow to <60% of recent best will signify a deterioration in asthma control, requiring contact with a doctor.

4.10. Other inhalers

4.10.1. Participants will be advised not to share their allocated inhalers

4.10.2. Participants will be advised not to use other non-study inhalers or nebulisers, unless indicated by their doctor. If they do use non-study inhalers or nebulisers they will be asked to document this.

4.10.3. At the first study visit participants will have their regular inhalers collected by investigators.

4.11. Other written information

4.11.1. Each participant will be provided with a study card indicating that they are participating in the trial. This card will include the contact details for the investigators and the date and time of the next study visit, as well as space to document any courses of prednisone taken or acute medical visits (e.g. GP, ED or Afterhours Clinics).

4.11.2. Written information will be provided specific to study involvement. This will include the following instructions:

4.11.2.1. When to contact the investigators (see 8.3.1).
4.11.2.2. How to care for the monitors.

4.12. Participant feedback on monitor data and withdrawal criteria

4.12.1. Participants will be informed that they may be withdrawn from the study if the investigator is concerned about their safety.

4.12.2. Participants will not be informed that the investigator is counting their episodes of overuse for consideration of need to withdraw.

4.12.3. Participants will not be informed that the investigator has identified episodes of beta agonist overuse until three exacerbations have occurred, when the investigator will advise the participant of the need to withdraw from the study.

4.12.4. Participants will be informed they can withdraw from the study at any stage. Arrangements for patient follow-up will be as per local practice.

4.13. Rationale

The dose of budesonide is based on its established dose-response relationship in asthma,[26] and is consistent with consensus guidelines.[5] Budesonide 400µg/day achieves around 80-90% of the maximum obtainable efficacy for all major outcome measures including severe exacerbations.[26] In the initiation of ICS therapy budesonide 400µg/day or equivalent achieves maximum efficacy.[27] For this reason consensus guidelines recommend that ICS therapy is initiated with a dose of budesonide 400µg/day or equivalent.[5] The dose of budesonide/ formoterol 200/6µg one inhalation as required for symptom relief, is one of the doses recommended in the SMART regimen.[1, 19] Salbutamol taken 2 inhalations from the MDI for relief of symptoms represents the dose which is recommended for use.

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5. Participants

675 patients with a diagnosis of asthma will be recruited into the study.

5.1. Inclusion criteria

1. Adults aged 18 to 75 years.

2. Self-report of a doctor's diagnosis of asthma with:

    a. Self-reported use of a SABA on ≥2 occasions in the previous 4 weeks but on average ≤2 occasions per day in the previous 4 weeks, if there have been no severe exacerbations in the last 12 months, **or**

    b. Self-reported use of a SABA on average ≤2 occasions per day in the previous 4 weeks, if there has been a history of a severe exacerbation in the last 12 months.

3. Willing and able to give informed consent for participation in the trial.

4. In the Investigator's opinion, able and willing to comply with all trial requirements.

5. Willing to allow their General Practitioner and/ or consultant, if appropriate, to be notified of participation in the trial.

5.2. Exclusion criteria

1. Self-reported use of ICS, LABA, leukotriene receptor antagonist, theophylline, anticholinergic agent or cromone as regular maintenance therapy in the 3 months before potential study entry. Note nasal corticosteroid therapy is permitted.

2. Self-reported past admission to the Intensive Care Unit (ICU) with life-threatening asthma (patients at highest risk of adverse asthma outcomes).

3. Self-reported hospital admission for asthma in the 12 months before potential study entry (patients at highest risk of adverse asthma outcomes).

4. Self-reported treatment with oral prednisone in the six weeks before potential study entry, representing recent unstable asthma.

5. A home supply of prednisone for use in worsening asthma.

6. Self-reported diagnosis of COPD, bronchiectasis or interstitial lung disease.

7. Self-reported greater than 20 pack year smoking history, or onset of respiratory symptoms after the age of 40 years in current or ex-smokers with ≥10 pack year history.

8. Self-reported current pregnancy or breast feeding at the time of enrolment or planned pregnancy within the study period.

9. Self-reported congestive heart failure, unstable coronary artery disease, atrial fibrillation or other clinically significant cardiac disease.

10. Unwilling or unable to switch from current asthma treatment regimen.

11. Other illness(es) likely to compromise participant safety or impact on the feasibility of results, at the discretion of the investigator.

12. Self-report of participation in another research trial involving an investigational product, in the past 12 weeks.

13. An on treatment FEV_1 ≤50% of predicted at Visit 1 (predicted values must be calculated using the Global Lung Function Initiative equations[40]).

14. Any known or suspected contraindications to the Investigational Medicinal Products or excipients.

5.3. Participant enrolment

5.3.1. Potentially eligible participants will be allocated an enrolment number (sequential number at that site prefaced with the letter E). Sites will be responsible for documenting whether potentially eligible participants are excluded and why, on a screening log.

5.3.2. When a participant is randomised they will be given a randomisation number (sequential number at that site prefaced with the letter R and the designated site identifier).

5.3.3. Randomisation codes will be sequentially assigned as soon as participants are confirmed as eligible for randomisation.

5.3.4. Enrolment and randomisation numbers cannot be re-used.

5.4. Participant withdrawal criteria

5.4.1. Participants will be withdrawn from the study and discontinue randomised treatment if:

a. The participant was found to be incorrectly enrolled in the study (see Section 5.1 and 5.2).
b. Treatment failure:

i. The participant experienced a severe exacerbation (see definition 5.4.2), or

ii. The participant meets any of the exacerbation criteria on three separate occasions during the study period (see definition 5.4.3 and Section 5.5), or

iii. Randomised treatment is modified by the participant's GP or other healthcare provider during the study (see definition 5.4.4)

c. The participant obtains OTC SABA.

d. The participant decides to discontinue (withdrawal of informed consent).

e. The participant becomes pregnant.

f. Any safety reason as judged by the investigator

5.4.2. A severe asthma exacerbation is:[2]

a. The use of systemic corticosteroids for at least 3 days because of asthma, or
b. Hospitalisation or ED visit because of asthma, requiring systemic corticosteroids

5.4.3. An asthma exacerbation is defined by any of the following criteria:

a. Worsening asthma resulting in urgent medical review (primary care visit, ED visit or hospital admission) and/or
b. Worsening asthma resulting in the use of systemic corticosteroids, such as a course of oral prednisone for any duration and/or
c. Worsening asthma resulting in a high beta agonist use episode, defined as >16 actuations of salbutamol or >8 actuations of budesonide/ formoterol per 24 hour period as previously defined.[1] Note this data is collected from electronic monitors only, not participant report.

NOTE: For an exacerbation to be counted as a separate event, it must be preceded by at least 7 days[2] during which none of the above criteria are fulfilled.

NOTE: Beta agonist use data from the day of a scheduled study visit is not to be used (so does not count towards defining a high beta agonist use episode). Beta agonist use data meeting dose dumping criteria is not to be used. See Section 12.

5.4.4. Randomised treatment modification is:

When the randomised treatment is modified by the participant's GP or other healthcare provider during the study, with the exception of:

a. the addition of, or increase in maintenance ICS dose for ≤2 weeks in the setting of worsening asthma or an exacerbation
b. the addition of, or change in ICS/LABA regimen (e.g. SMART) for ≤2 weeks in the setting of worsening asthma or an exacerbation
c. the addition of SABA therapy for ≤2 weeks in the setting of worsening asthma or an exacerbation

Modifications are defined by an increase in the participants' randomised asthma inhaler regimen and/ or the addition of medications to aid asthma control including SABA, ICS/LABA, ICS, LABA, leukotriene receptor antagonists, mast cell stabilisers, theophylline and monoclonal antibody therapy.

Participants who obtain OTC SABA will be withdrawn from the study, however this will not be counted as a treatment failure.

5.5. Evaluation and counting three exacerbations

5.5.1. An overuse episode based on monitor data will be discounted if:
5.5.1.1. There is overuse on a single day that is also the day of a study visit
5.5.1.2. There is overuse that meets dose dumping criteria (see Section 12).

5.5.2. If an overuse episode is discounted:
5.5.2.1. This needs to be logged on the eCRF (see manual for details).
5.5.2.2. The Global Sponsor is to be informed as soon as practical.

5.5.3. For an exacerbation to be counted as a separate event, it must be preceded by at least 7 days[2] during which none of the criteria for an exacerbation are fulfilled (See Section 5.4.3).

5.6. Participant withdrawal procedure

5.6.1. Participants identified as needing withdrawal at a study visit:
5.6.1.1. The visit will be conducted as a Visit 7.
5.6.1.2. An exception to this is if the participant declines consent to continue the study visit.
5.6.1.3. In addition to Visit 7 procedures, reason for withdrawal must be documented. If possible, participants who decide to withdraw will be asked why.

5.6.2. Participants identified as needing to be withdrawn between study visits:
5.6.2.1. An unscheduled study visit should be booked as soon as practically possible (see Section 8.1).
5.6.2.2. If, at this visit the participant is identified as needing to be withdrawn, the visit will be conducted as a Visit 7.
5.6.2.3. In addition to Visit 7 procedures, reason for withdrawal must be documented. If possible, participants who decide to withdraw will be asked why.

5.6.3. At withdrawal from the study participants will be treated according to local medical practice.

6. Randomisation and blinding

6.1. Randomisation

6.1.1. Participants will be block randomised, block size nine.

6.1.2. Randomisation will be stratified by country.

6.1.3. A computer-generated randomisation number sequence will be created by the study statistician, independent of the investigators undertaking recruitment and subsequent visits.

6.1.4. The eCRF system will conceal the allocations and will release a participant's randomisation outcome at the time of randomisation. The randomisation schedule will be accessed only by the study statistician and the eCRF provider; study staff will not have access to the randomisation schedule.

6.1.5. Detailed instructions regarding use of the eCRF system will be provided in a manual.

6.2. Blinding

6.2.1. A participant's treatment allocation will only be revealed to the researchers when that participant is randomised via the eCRF.

6.2.2. There is no blinding to allocated intervention in this study. Study investigators, study staff and participants will be aware of the treatment allocation. Blinding is not being performed, in order to maintain the potential 'real world' advantage of the ICS/LABA reliever therapy regimen, i.e. the use of a single medication and no requirement for regular inhaler use.

6.2.3. The study statistician will be blinded while performing the primary analysis of the primary outcome variable of asthma exacerbation [9.1.1], i.e. comparison of the rate of exacerbations per patient per year until completion of the study or withdrawal by Poisson regression with an offset for the days of observation.

7. Scheduled study visits

7.1. Visit overview

Visit Number	Consent & Enrolment	1	2	3	4	5	6	7	Unscheduled visit
Week	≤0*	0	6	12	22	32	42	52	As required
Day	≤0*	0	42	84	154	224	294	364	As required
Visit Window (Days)	n/a	n/a	±3	±3	±3	±3	±3	±3	n/a
Pre dispensing monitor check		X	X	X	X	X	X		
Written informed consent	X								
Inclusion/Exclusion criteria check	X	X*							
ACQ-5		X	X	X	X	X	X	X	
ASK-12		X						X	
GINA questions		X	X	X	X	X	X	X	
Medical history & demographics		X							
Weight and height		X							
FeNO[#]		X		X				X	
Spirometry		X	X	X	X	X	X	X	
Blood test for periostin		X							
Blood test for full blood count		X							
Randomisation		X							
Participant education		X	X	X	X	X	X		
Issue written asthma management plan and other written information		X							
Issue study inhalers with monitors attached		X	X	X	X	X	X		
Inform GP of study enrolment		X							
Review: - Exacerbations - AEs - SAEs^ -Medication changes - Overuse episodes -Issues with equipment use			X	X	X	X	X	X	X
Returned electronic monitors: - Check for damage - Upload from monitor via USB cable			X	X	X	X	X	X	X
Exercise inhaler use questions								X	
If participant is to be withdrawn, documentation of cause and notification to GP and MRINZ			X	X	X	X	X	X	X
Inform GP and MRINZ of study completion								X	

*Performed if consent and enrolment done on a different day to Visit 1, n/a: not applicable, [#] Performed prior to spirometry
^ Investigator to inform Global Sponsor within 24 hours of becoming aware of an SAE (for further detail see Section 13)

7.2. End of study

7.2.1. The end of the study is defined as the date of database lock, subsequent to the last visit of the last participant undergoing the study.

7.2.2. The Global Sponsor will stop the study prematurely if any safety concerns are apparent, either arising from this study, or if the Global Sponsor is informed of any safety issues arising outside of this study, including but not limited to safety concerns regarding the study medications. Sites will be informed of early termination of the study due to safety concerns, as soon as possible.

7.2.3. In the case of safety concerns arising during the study, the Sponsor and Investigators may deviate from the protocol only in cases where appropriate urgent safety measures are warranted to protect the trial participants against any immediate hazard to their health or safety. The Global Sponsor must be informed of any cases where the protocol is not adhered to and the reasons for non-adherence, as soon as possible. Non-adherence will be reported to the appropriate ethics committees and regulatory authorities in line with local requirements.

7.3. Visit windows

7.3.1. Study visits are to be scheduled to occur within +/- 3 days of their due date (see section 7.1); however if this is not possible for some reason or they have to be held early or postponed the visit window may be extended at the investigator's discretion.

7.3.2. Subjects may also arrange to attend an additional unscheduled appointment at any time if their medications are running low or they are concerned about inhaler or monitor function (Section 8.2).

7.3.3. If a subject fails to attend their scheduled study appointments at the study clinics they will be contacted by telephone and arrangements made to reschedule the missed appointment.

7.4. Written informed consent

7.4.1. Is to take place according to GCP guidelines, prior to any study specific procedures.

7.5. Inclusion/exclusion criteria check

7.5.1. Please see Section 5 for criteria.

7.6. ACQ-5[28] & ASK-12[29]

7.6.1. Will be administered prior to history taking or spirometry.

7.6.2. The questionnaires will be in paper format. The participant should read and fill them in without intervention by the investigator. Where this is not possible the investigator may read and/or record answers for them, however it must be documented that this took place.

7.7. GINA questions[9]

7.7.1. Will be verbally asked following ACQ-5 and ASK-12.

7.7.2. A yes or no answer is required. The questions will be phrased as: “In the past 4 weeks, have you had:

- 7.7.2.1. Daytime asthma symptoms more than twice per week?
- 7.7.2.2. Any night wakening due to asthma?
- 7.7.2.3. Reliever needed for symptoms more than twice per week?
- 7.7.2.4. Any activity limitation due to asthma?”

7.8. Medical history and demographics

7.8.1. Date of birth, age and sex.

7.8.2. Smoking history:

- 7.8.2.1. Current, ex or never
- 7.8.2.2. Pack years

7.8.3. Asthma history:

- 7.8.3.1. Age of diagnosis
- 7.8.3.2. Whether the participant currently uses an asthma action plan, and whether it is with or without peak flow measurement
- 7.8.3.3. Number of courses of prednisone in the last year, and number of days per course
- 7.8.3.4. Number of ED visits for asthma in the last year
- 7.8.3.5. Number of hospital admissions for asthma ever
- 7.8.3.6. Number of severe exacerbations for asthma in the last year
- 7.8.3.7. Whether the participant has ever previously been prescribed ICS inhalers, and if so when last used.

7.8.4. Other medical conditions and medications

7.8.5. Sinusitis history

7.8.6. Highest education level

7.9. Weight and height

7.9.1. Will be measured without shoes on and using site equipment.

7.10. FeNO

7.10.1. Performed as a single test at each study visit as per ATS/ERS criteria[30] and manufacturer instructions prior to any spirometry.

7.11. Spirometry

7.11.1. FEV_1 and FVC will be performed according to ATS/ERS criteria[31] using a hand-held spirometer. For further detail see the study manual.

7.11.2. Study participants will not be required to with-hold from using their inhalers prior to the study appointments and spirometry testing.

7.11.3. Reversibility testing will not be performed at any visit.

7.11.4. Spirometry must be conducted prior to randomisation at Visit 1, in order to assess exclusion criterion 13, to ensure that a patient's FEV_1 is >50% of predicted. The predicted values must be calculated according to the Global Lung Function Initiative equations[40].

7.12. Blood test for full blood count and periostin

7.12.1. FBC sample at Visit 1 (week 0).

7.12.2. Periostin sample will be taken at visit 1 (week 0).

7.12.3. Please see study manual for processing instructions.

7.13. Randomisation and participant study medication allocation

7.13.1. For details on randomisation please see Section 6.

7.13.2. The eCRF system will allocate a unique randomisation number to each participant. Investigators will allocate study medication to each participant based on their randomisation outcome. The Investigator will record the randomisation number on each dispensed inhaler.

7.13.3. If a participant withdraws from the study their randomisation number cannot be re-used.

7.13.4. If a participant is randomised and subsequently found not to meet the inclusion or inclusion criteria (Sections 5.1 and 5.2) or is allocated incorrect study medication, contact needs to be made with the Global Sponsor as soon as practical.

7.14. Participant education and participant management plans

7.14.1. <u>Visit 1 only:</u>

7.14.1.1. <u>Inhaler technique</u>

7.14.1.1.1. Participants will be given instructions based on written information sheets.

7.14.1.2. <u>Participants will be given a written action plan</u>:

7.14.1.2.1. Specific to their regimen (see Section 4)
7.14.1.2.2. If participants use a peak flow meter and are able to provide the Investigator with their usual best peak flow value, this will be documented and incorporated in to their management plan.
7.14.1.2.3. Participants will be neither encouraged nor discouraged from using their reliever inhaler before exercise to prevent exercise induced asthma

7.14.1.3. Prevention of other inhaled medication use:

7.14.1.3.1. Participants will be asked to bring their current inhalers in to visit 1 to be collected by investigators.
7.14.1.3.2. Participants will be advised not to use other non-study inhalers or nebulisers, unless indicated by their doctor. If they do use non-study inhalers or nebulisers they will be asked to document the date, time and dose.
7.14.1.3.3. Participants will be advised not to share their study allocated inhalers.

7.14.1.4. Participants will be informed:

7.14.1.4.1. Monitors:
7.14.1.4.1.1. Measure the date and time of actuations to enable assessment of patterns of use
7.14.1.4.1.2. Can record if they have been removed/tampered with
7.14.1.4.1.3. Are not to be removed, tampered with or gotten wet

7.14.1.4.2. Safety:
7.14.1.4.2.1. While participants will be informed that if there is any concern about their safety during the study the investigator may withdraw them, they will not be informed of the specific cut-offs for withdrawal in case this alters behaviour, including inhaler use, seeking medical review or initiation of prednisone.

7.14.2. Visits 1-6:

7.14.2.1. Inhaler technique:

7.14.2.1.1. Will be taught and checked. Participants will be given instructions based on written information sheets.

7.14.2.2. Participants will be reminded

7.14.2.2.1. The instructions of the asthma 'action' plan. Note that data uploaded from the monitors is not to be discussed with the participant or used to guide discussion around compliance with the asthma 'action' plan.
7.14.2.2.2. Monitors can record if they have been removed/tampered with. They are not to be removed, tampered with or gotten wet.
7.14.2.2.3. They are to take all dispensed inhalers (including used or empty inhalers) to their next study visit.

7.14.2.3. Participants will be advised to contact the investigator if:

7.14.2.3.1. They seek medical help for worsening asthma (e.g. go to their GP or hospital) or start systemic corticosteroids, such as a course of prednisone.
7.14.2.3.2. Their GP or usual healthcare provider makes any changes to their randomised treatment
7.14.2.3.3. They are concerned they will run out of inhaler medications prior to the next study visit.

7.14.2.3.4. They are concerned the allocated monitors or inhalers are not operating correctly
7.14.2.3.5. They wish to withdraw from the study

7.15. Dispense monitors with pre-dispensing monitor check

7.15.1. Visit 1: Monitors must be tested after randomisation and prior to dispensing

7.15.2. Visit 2-6: Monitors must be tested prior to visit on day of visit

7.15.3. Please see Section 12 for detail on how to perform check.

7.16. Review

7.16.1. For AEs and SAEs, with associated documentation (AE/SAE reporting as required, see Section 13)

7.16.2. Specific enquiry and documentation required for assessment of asthma exacerbations including:

Any medical review (GP/ED/hospitalisation)

Any systemic corticosteroids such as oral prednisone taken

Whether any other medications were used for asthma (other than those allocated as part of the randomised study regimen),

Any change in medication (update medication log)

Any concerns with equipment use (including monitors and inhalers)

7.17. Returned inhalers and monitors

7.17.1. Perform collection check (see Section 12)

7.17.2. Upload of data via USB cable

7.17.3. Check for overuse episodes. There must be more than 7 days between the onset of the index and subsequent overuse episodes for them to be counted as separate events. This check must be carried out by investigators at the local site and should be completed within 5 working days of the study visit.

7.17.3.1. If the participant denies an episode of overuse, the uploaded data is considered the valid record of medication use, unless it meets dose dumping criteria (see Section 12).
7.17.3.2. Inhaler use on the day of the study visit will be discounted in order to avoid erroneous data triggered by an upcoming study visit/dose dumping and to discount the validation actuations performed by the investigator from being included in the analysis.
7.17.3.3. Data that meets dose dumping criteria will be discounted (see Section 12).

7.17.4. Monitors will be checked for actuations and undergo the collection check (see Section 12). If there are no actuations recorded and the monitor passes a pre-dispensing check, it may be reissued with the same medication canister to the

participant at the visit. Inhaler medication returned at the study visits will be removed from the electronic monitor and stored until Global Sponsor confirms it may be destroyed.

7.18. GP communication and study completion

7.18.1. If the participant has a GP, they must be informed when the participant is enrolled into the study and after completion of the study.

7.18.2. At completion of study participants will be treated according to local medical practice. IMP will not be made available at the end of the study.

7.19. Exercise inhaler use questions

7.19.1. At Visit 7 participants will verbally be asked:

7.19.1.1. Whether in the last 2 weeks they had used their reliever inhaler before exercise to prevent exercise induced asthma

7.19.1.2. If yes, how many times in the past 2 weeks.

7.20. Qualitative exit interviews

7.20.1. Between visit 6 and 7, or as soon as possible after Visit 7 or withdrawal, qualitative exit interviews will be conducted by telephone with a subset of participants using a semi-structured interview guide, to enhance understanding of the study findings and patterns of medication use and the impact of treatment on patient beliefs.

7.20.2. Purposeful sampling will be used to provide a representative sample of up to 120 subjects who participated in the trial, in terms of treatment (i.e. randomisation group) and personal demographics (e.g. age and gender) and country. Subjects recruited in Italy will not be part of the sample and will not perform exit interviews.

7.20.3. Participants from each trial group will continue to be recruited for the qualitative study until data saturation has been reached.

7.20.4. For further detail see the qualitative exit interview study manual.

7.20.5. The qualitative interviews will be undertaken under the supervision of Professor Helen Reddel.

8. Unscheduled study visits

8.1. Unscheduled visit for consideration of withdrawal

8.1.1. Should an investigator become aware that a participant wishes to withdraw or may require withdrawal from the study between study visits they will request attendance at an unscheduled visit.

8.1.2. This is to take place as soon as practically possible

8.1.3. Unscheduled visits will not take the place of the participant's usual medical care

8.1.4. Participants will be asked to bring all dispensed inhalers and monitors to the visit.

8.1.5. The following steps will be taken:

8.1.5.1. Review

8.1.5.1.1. For AEs and SAEs, with associated documentation (medical condition log and AE/SAE reporting as required, see Section 13)

8.1.5.1.2. Specific enquiry and documentation required for assessment of asthma exacerbations including:
Any medical review (GP/ED/hospitalisation)
Any systemic corticosteroids such as oral prednisone taken
Any non-study inhaled drugs taken
Any change in medication (update medication log)
Any concerns with equipment use (including monitors and inhalers)

8.1.5.2. Returned inhalers and monitors

8.1.5.2.1. Perform collection check (see Section 12)

8.1.5.2.2. Upload of data via USB cable

8.1.5.2.3. Check for overuse episodes: there must be at least 7 days between the onset of the index and subsequent overuse episodes for them to be counted as separate events.

8.1.5.2.4. Inhaler use on the day of the study visit will be discounted in order to avoid erroneous data triggered by an upcoming study visit/dose dumping and to discount the validation actuations performed by the investigator from being included in the analysis.

8.1.5.2.5. Data that meets dose dumping criteria will be discounted (see Section 12).

8.1.6. If the participant is withdrawn:

8.1.6.1. The visit will become a Visit 7 (final visit).

8.1.6.2. An exception to this is if the participant declines consent to continue the study visit.

8.1.6.3. In addition to Visit 7 procedures, reason for withdrawal must be documented. If possible, participants who decide to withdraw will be asked why.

8.1.6.4. The Global Sponsor must be informed of the withdrawal as soon as is practical, via the eCRF system.

8.1.7. <u>If the participant is not withdrawn:</u>

8.1.7.1. All inhalers and monitors that the participant brought to the visit will be returned to them.

8.1.7.2. The participant will continue on their randomised regimen and attend their next scheduled visit.

8.2. Unscheduled visit for dispensing of trial medication or review of equipment

8.2.1. This may occur if a participant reports that:

8.2.1.1. They are concerned they will run out of inhaler medication prior to the next study visit.

8.2.1.2. They are concerned the allocated monitors or inhalers are not operating correctly

8.2.2. This is to take place as soon as practically possible

8.2.3. The following steps will be taken:

8.2.3.1. <u>Review</u>

8.2.3.1.1. For AEs and SAEs, with associated documentation (medical condition log and AE/SAE reporting as required, see Section 13).

8.2.3.1.2. Specific enquiry and documentation required for assessment of asthma exacerbations including:
Any medical review (GP/ED/hospitalisation)
Any systemic corticosteroids such as oral prednisone taken
Any non-study inhaled drugs taken
Any change in medication (update medication log)
Any concerns with equipment use (including monitors and inhalers)

8.2.3.2. <u>Returned inhalers and monitors</u>

8.2.3.2.1. Perform collection check (see Section 12)

8.2.3.2.2. Upload of data via USB cable

8.2.3.2.3. Check for overuse episodes: there must be more than 7 days between the onset of the index and subsequent overuse episodes for them to be counted as separate events.

8.2.3.2.4. Inhaler use on the day of the study visit will be discounted in order to avoid erroneous data triggered by an upcoming study visit/dose dumping and to discount the validation actuations performed by the investigator from being included in the analysis.

8.2.3.3. Dispense new set of monitors with pre-dispensing check

8.2.3.3.1. Please see Section 12 for detail on how to perform check.

8.2.3.4. If the participant is withdrawn:

8.2.3.4.1. The visit will become a Visit 7 (final visit).

8.2.3.4.2. An exception to this is if the participant declines consent to continue the study visit.

8.2.3.4.3. In addition to Visit 7 procedures, reason for withdrawal must be documented. If possible, participants who decide to withdraw will be asked why.

8.2.3.4.4. The Global Sponsor must be informed of the withdrawal as soon as is practical, via the eCRF system.

8.3. Participant contact between visits

8.3.1. Participants are advised to contact the investigator if:

8.3.1.1. They seek medical help for their asthma (e.g. go to their GP or hospital) or start systemic corticosteroids such as oral prednisone.

8.3.1.2. Their GP or usual healthcare provider makes any changes to their randomised treatment

8.3.1.3. They are concerned they will run out of inhaler medication prior to the next study visit.

8.3.1.4. They are concerned the allocated monitors or inhalers are not operating correctly

8.3.1.5. They wish to withdraw from the study

8.3.1.6. Investigator's will contact the participant if:

8.3.1.6.1. The participant forgets to bring their inhalers/monitors to a visit (in which case every effort should be made to have them returned to the investigator as soon as possible (e.g. via a self-addressed courier bag)).

8.3.1.7. If the investigator becomes aware the participant may meet withdrawal criteria between visits:

8.3.1.7.1. They should organise an unscheduled visit for consideration of withdrawal as soon as possible.

9. Study outcome measures

9.1. Primary outcome

9.1.1. Asthma exacerbation rate expressed as number of exacerbations per patient per year. An asthma exacerbation is defined as:

9.1.1.1. Worsening asthma resulting in urgent medical review (primary care visit, ED visit or hospital admission) and/or

9.1.1.2. Worsening asthma resulting in use of systemic corticosteroids, such as a course of prednisone for any duration and/or

9.1.1.3. Worsening asthma resulting in a high beta agonist use episode, defined as >16 actuations of salbutamol or >8 actuations of budesonide/formoterol per 24 hour period as previously defined.[1]

These thresholds are based on the limits of beta agonist use requiring medical review defined by self-management plans, supported by the short term bronchodilator equivalence of 6µg formoterol to 200µg salbutamol with repeat dosing in acute asthma,[32, 33] and the use of two MDI inhalations of salbutamol and one Turbuhaler inhalation of budesonide/formoterol as required for relief of symptoms. High beta agonist use, systemic corticosteroid treatment, or urgent medical review separated more than 7 days are treated as separate exacerbations. The use of high beta agonist use episodes ensures that the identification of an exacerbation is not dependent on whether or not a participant seeks medical review, which may be influenced by randomised treatments.

9.2. Secondary outcomes

9.2.1. Clinical outcomes

9.2.1.1. The proportion of exacerbations defined by each of the above criteria (9.1.1.1-9.1.1.3)

9.2.1.2. The proportion of participants with at least one exacerbation

9.2.1.3. Time to first exacerbation of asthma

9.2.1.4. Proportion of participants withdrawn due to “treatment failure”:

9.2.1.4.1. One severe exacerbation, or
9.2.1.4.2. Three exacerbations, or

9.2.1.4.3. If randomised treatment is modified by the participant's GP or other healthcare provider (see Section 5.4.4 for detail).

9.2.1.5. The proportion of "treatment failures" defined by each of the above criteria (9.2.1.4.1-9.2.1.4.3)

9.2.1.6. Rate of severe exacerbations defined by the ATS/ERS criteria[2]

9.2.1.6.1. The use of systemic corticosteroids for at least 3 days, or
9.2.1.6.2. Hospitalisation or ED visit because of asthma, requiring systemic corticosteroids

9.2.1.7. Time to withdrawal due to severe exacerbation

9.2.1.8. The proportion of severe exacerbations defined by each of the above criteria (9.2.1.6.1, 9.2.1.6.2)

9.2.1.9. Asthma Control Questionnaire (ACQ-5 score)[28]

9.2.1.10. GINA question category[9] (well, partly or un-controlled)

9.2.1.11. On-treatment FEV_1, i.e. without withholding of bronchodilator medication

9.2.1.12. On-treatment FEV_1 percentage predicted, i.e. without withholding of bronchodilator medication

9.2.1.13. FeNO (a measure of airways inflammation)[30]

9.2.2. Medication use

9.2.2.1. Mean ICS dose per day (budesonide µg/day);

9.2.2.2. Periods without ICS use:

9.2.2.2.1. Proportion of participants with at least 1 day of no ICS actuations
9.2.2.2.2. Number of days of no ICS use
9.2.2.2.3. Number of ≥7 consecutive day periods of no ICS use
9.2.2.2.4. Number of ≥14 consecutive day periods of no ICS use
9.2.2.2.5. Longest duration of no ICS use (days)

9.2.2.3. Total oral corticosteroid dose

9.2.2.4. Number of courses of oral corticosteroid per year

9.2.2.5. Total systemic corticosteroid exposure*

* Composite systemic corticosteroid exposure/year in which the total ICS dose/year, converted to oral prednisone-equivalent dose for systemic effects on adrenal function,[34] is added to the oral prednisone dose per year, as previously defined (budesonide 5000µg inhaled equivalent to prednisone 10mg oral).[1] For other systemic corticosteroids, conversion to prednisone-equivalent doses will be undertaken by reference to the British National Formulary (Appendix).

9.2.2.6. High beta agonist use:

9.2.2.6.1. Proportion of participants with at least one episode of high use
9.2.2.6.2. Number of days of high use
9.2.2.6.3. Number of days of high use in participants with at least one day of high use
9.2.2.6.4. Number of days of high use without medical review within 48 hours, 7 days and 14 days in participants with at least one high use episode
9.2.2.6.5. Proportion of high use episodes without medical review within 48 hours, 7 days and 14 days.

9.2.2.7. Marked beta agonist overuse, defined as >24 actuations of salbutamol or >12 actuations of budesonide/formoterol per 24 hour period, as previously defined.[1]

9.2.2.7.1. Proportion of participants with at least one episode of marked overuse
9.2.2.7.2. Number of days of marked overuse
9.2.2.7.3. Number of days of marked use in participants with at least one day of marked overuse
9.2.2.7.4. Number of days of marked overuse without medical review within 48 hours, 7 days and 14 days in participants with at least one marked overuse episode
9.2.2.7.5. Proportion of marked overuse episodes without medical review within 48 hours, 7 days and 14 days.

9.2.2.8. Maximum number of beta agonist actuations in a 24 hour period.

9.2.2.9. Use of study medications in the 14 days prior to severe exacerbations, as previously defined,[35] with graphical presentation of the median (interquartile range) daily medication use for the randomised groups, and the medication use for the individual participants within each randomised group.

9.2.2.10. Inhaler use for exercise induced asthma

9.2.2.10.1. Proportion of participants who self-report use of reliever inhaler before exercise to prevent exercise induced asthma in the past 2 weeks
9.2.2.10.2. If yes, number of times in the past 2 weeks.

9.2.3. Adverse events

9.2.3.1. Adverse events.

9.2.3.2. Serious adverse events.

9.2.4. Cost-effectiveness

9.2.4.1. The medical costs (medications, emergency medical and ED visits, hospital admissions), and non-medical costs (days off work/study/school). The cost-effectiveness data collected will allow extrapolation to future pricing models.

9.2.5. Patient attitudes

9.2.5.1. ASK-12 questionnaire.[29]

9.2.5.2. Qualitative interview results.

10. Sample size calculation

The primary outcome variable is the rate of asthma exacerbations expressed as the number of exacerbations per patient per year. A sample size of 180 in each treatment arm has 80% power, alpha 5%, to detect a decrease in the rate of exacerbations from 1.2 to 0.9 per patient per year, representing a relative risk of exacerbation of 0.75. Allowing for a 20% drop-out rate, this requires randomisation of 225 participants in each treatment group.

The rate of exacerbations per patient per year of 1.2 nominated for the control group is conservative. It is derived from two pivotal RCTs in which patients were randomised to placebo maintenance and SABA reliever therapy. In the OPTIMA study, patients randomised to this regime had 0.77 severe exacerbations per year, 71% of which were identified by the managing physician as requiring systemic corticosteroids, and not by the peak flow criteria.[16] We have previously reported that there were 17.8 days of high beta agonist use per 12 months (using the same criteria as in this proposed study) in a high risk population in whom there were 0.97 severe exacerbations per 12 months.[1] In the BEST study in patients with mild asthma[17] the annualised rate of exacerbations on salbutamol reliever therapy alone was 1.63 per patient per year, utilising a composite measure which was less severe than that proposed in this study, although did not include electronic monitoring of inhaler use and was in a population with very well controlled asthma after treatment with ICS on entry into the study.

The nominated treatment effect of 0.75 for the relative risk of exacerbations is conservative. It is derived from the treatment effect seen in the BEST trial comparing ICS/SABA as required compared to SABA as required, in which a relative risk of exacerbations of 0.5 was observed.[17] Furthermore, the reduction in exacerbations with ICS/LABA reliever therapy is expected to be greater than that due to ICS/SABA reliever[19] on which the power calculations are based.[17]

Sample size re-estimation at the blinded interim analysis point

We plan a re-estimation of the required sample size for the trial at the interim analysis point. The currently planned blinded interim analysis, after recruitment of 400 participants, aims to detect a safety signal that might require a Data Safety and Monitoring Committee review. We plan to also use the opportunity to re-estimate the sample size based on the rate of events in each of the arms of the study. The current sample size is based on a rate in the control arm of 1.2 events per participant per year with 80% power, to detect a rate of 0.9 events per participant per year, a relative rate of 0.75. If the event rate in the arm of the study that has the largest event rate is less than 1.2 events per participant per year then the sample size requirements will be larger than currently planned. The sample size will be estimated by simulation from appropriate Poisson distributions.

11. Statistical analysis

Primary outcome variable analysis:

This will be an 'intention to treat' superiority analysis. The primary analysis of the primary outcome variable of asthma exacerbation [9.1.1] is comparison of the rate of exacerbations per patient per year until completion of the study or withdrawal from the study. This will be by Poisson regression with an offset for the time of observation. Over-dispersion will be evaluated prior to analysis and a corrected analysis applied if necessary.[1]

The pre-specified treatment comparisons are:

1. ICS/LABA reliever therapy regimen compared to the SABA reliever therapy regimen

2. ICS/LABA reliever therapy regimen compared to the maintenance ICS and SABA reliever therapy regimen

Two sensitivity analyses will be performed:

Sensitivity analysis 1:

Poisson regression as described in a model including the following co-variates:

SABA use (measured as the average number of occasions per week of self-reported SABA use in 4 weeks prior to enrolment) and the number of prior severe exacerbations in the 12 months before recruitment.

The pre-specified strategy is to treat SABA use as a continuous variable however if distribution is very highly skewed e.g. nearly all participants using SABA less than twice a week, then a cut point will be used.

Sensitivity analysis 2:

Poisson regression as described in a model including the following co-variates:

SABA use and number of prior severe exacerbations (as for Sensitivity analysis 1), but also including age, sex, smoking status, baseline ACQ-5 score, FeNO, blood eosinophil count, and serum periostin level.

If the outcome data are sparse it may not be possible to include all of the confounding variables for the second sensitivity analysis.

Secondary outcome variable analyses:

The pre-specified treatment comparisons for the secondary outcomes will be as for the primary outcome:

1. ICS/LABA reliever therapy regimen compared to the SABA reliever therapy regimen

2. ICS/LABA reliever therapy regimen compared to the maintenance ICS and SABA reliever therapy regimen

The following methods will be used:

Poisson regression with an offset for number of days in the study:

- Rates of severe exacerbation by the ATS/ERS criteria [9.2.1.6]
- Number of days of no ICS use [9.2.2.2.2]
- Number of days of high use [9.2.2.6.2]
- Number of days of high use in participants with at least one day of high use [9.2.2.6.3]
- Number of days of high use without medical review within 48 hours, 7 days and 14 days, in participants with at least one high use episode [9.2.2.6.4]
- Number of days of marked over use [9.2.2.7.2]
- Number of days of marked overuse in participants with at least one day of marked overuse [9.2.2.7.3]
- Number of days of marked overuse without medical review within 48 hours, 7 days and 14 days, in participants with at least one marked overuse episode [9.2.2.7.4]
- Number of courses of oral corticosteroid per year [9.2.2.4]

Descriptive data:

- Use of study medications in the 14 days prior to severe exacerbations [9.2.2.9]

Survival analysis with Kaplan-Meier plots and Cox's proportional hazards used to estimate the hazard ratios for association with treatment:

- Time to first exacerbation [9.2.1.3]
- Time to withdrawal due to severe exacerbation [9.2.1.7]

Simple t-tests by time of measurement and mixed linear models for repeated measures by time:

- ACQ-5 score [9.2.1.9]
- FEV_1 [9.2.1.11]
- FEV_1 percentage predicted [9.2.1.12]
- FeNO, likely 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 [9.2.1.13]
- Total oral corticosteroid use, likely on the logarithm transformed scale based on our previous experience with the skewed distribution of this variable and that normality assumptions were better met on this scale [9.2.2.3]. This variable may need to analysed by a Mann-Whitney test and Hodges-Lehmann estimator of location shift should many participants receive no oral corticosteroid
- Total systemic corticosteroid exposure use per year likely on the logarithm transformed scale [9.2.2.5]
- Simple estimation of costs [9.2.4.1]
- ASK-12 questionnaire [9.2.5.1]

General linear model (ANCOVA) with an offset for number of days in the study:

- Mean ICS dose per day [9.2.2.1]

Comparison of proportions by logistic regression:

- The proportion of exacerbations defined by each criteria [9.2.1.1, (9.1.1.1-9.1.1.3)]
- The proportion of participants with at least one exacerbation [9.2.1.2]
- The proportion of participants withdrawn due to "treatment failure" [9.2.1.4]

- The proportion of "treatment failures" defined by each criteria [9.2.1.5, (9.2.1.4.1-9.2.1.4.3)]
- The proportion of severe exacerbations defined by each criteria [9.2.1.8 (9.2.1.6.1, 9.2.1.6.2)]
- The proportion of participants with at least one day of no ICS use [9.2.2.2.1]
- The proportion of participants with at least one episode of high use [9.2.2.6.1]
- The proportion of high use episodes without medical review within 48 hours, 7 days or 14 days [9.2.2.6.5]
- The proportion of participants with at least one episode of marked overuse [9.2.2.7.1]
- The proportion of marked overuse episodes without medical review within 48 hours, 7 days or 14 days [9.2.2.7.5]
- The proportion of participants who self-report use of reliever inhaler before exercise to prevent exercise induced asthma in the past two weeks [9.2.2.10.1]

Other:

- GINA question category [9.2.1.10] and ASK-12 category [9.2.5.1] will be analysed by ordinal regression with an appropriate generalised linear mixed model and a time by treatment interaction
- For the longest duration of no ICS use (days) [9.2.2.2.5], the maximum number of beta agonist actuations in a 24 hour period [9.2.2.8], number of times a reliever inhaler was used before exercise to prevent exercise induced asthma in the past 2 weeks [9.2.2.10.2], the data distribution will be examined for the likely most appropriate analysis strategy. If these are best treated as a count variable then Poisson regression will be used.
- The dataset will also be used to test the hypothesis that prolonged periods of non-ICS use (≥7 consecutive days, ≥14 consecutive days) [9.2.2.2.3, 9.2.2.2.4] have different associations with the probability of poor asthma control (end of study ACQ-5 score ≥1.5) or a severe exacerbation. Logistic regression with a non-ICS use-treatment interaction term will be used for severe exacerbations; ANCOVA, with a similar interaction term will be used for the ACQ-5 score.
- Adverse events will be summarised by the number and percentage of participants with at least 1 adverse event [9.2.3.1]
- Serious adverse events will be summarised by the number and percentage of participants with at least 1 serious adverse event [9.2.3.2]

Sub-group analysis

Sub-group analyses will be performed for the three outcome variables: rate of exacerbations, rate of severe exacerbations, and ACQ-5. In these analyses the differential effect of treatment on outcome will be explored with each of the following baseline moderating variables: SABA use (measured as the average number of occasions per week of self-reported SABA use in the four weeks before enrolment), whether there has been a severe exacerbation in the year prior to enrolment, age, sex, smoking status, baseline ACQ-5 score, FEV_1 % predicted, FeNO, blood eosinophil count, serum periostin level and Th2 status (a Th2 score based on tertiles for each baseline measure of blood eosinophil count, FeNO, serum periostin).

Whether there is evidence of a sub-group effect will be tested by fitting interaction terms between treatment and the possible moderating variables for each of the three selected outcome variables. For the rate of exacerbations and rate of severe exacerbations we plan to use Poisson regression, with an offset for the time of observation. Dependent on the data distribution for the severe exacerbations this may be better modelled as logistic

regression if there are very few severe adverse events. ACQ-5 will be modelled with ANCOVA.[36]

Electronic monitoring analysis

Absolute values and percentages will be presented for:

- Total number of monitors dispensed, and with which medication
- Number of monitors that failed pre study checks
    - Why (extra actuations, missed actuations, battery, failure to upload data, other)
- Number of monitors that failed within study checks
    - Why (extra actuations, missed actuations, battery, failure to upload data, other)
- Ability to upload data from failed monitors by Adherium Ltd
- Number of monitors lost/thrown away by participants
- Overall number of monitors supplying complete data without loss or failed within study checks

12. Electronic monitoring

12.1. Monitor kits

12.1.1. Participants will be allocated electronic monitors by the Investigator, in accordance with Section 12 and a separate study manual.

12.1.2. Electronic monitors (Adherium) with unique ID numbers are to be attached to each inhaler to record the date and time of every actuation, and to allow a detailed assessment of the patterns of use of the randomised treatments.

12.1.3. Should an Investigator incorrectly allocate an electronic monitor to a participant, contact must be made with the Global Sponsor as soon as possible.

12.2. Monitors

12.2.1. Will record the date and time of inhaler actuations

12.2.2. Will have individual ID numbers and will remain participant-specific during the course of the study.

12.2.3. Will upload data via USB at the study visit via software provided by Adherium.

12.2.4. The participants will be told that they are using a modified inhaler that has been produced specifically for this study to count the precise number and timing of doses used during the study period. This will provide a reason for the need to avoid using other inhalers. Participants will be told that the purpose of the study is to compare the benefits of the three treatment regimens and to determine whether the patterns of use influence outcome.

12.3. SmartInhalerLive website

12.3.1. The occurrence of episodes of beta agonist use in excess of predetermined limits designated by the self-management plan ('high beta agonist use episodes' – see definition and Section 5) will be checked via data uploaded from the monitor at study visits.

12.3.2. Electronic data on days of study visits will be discounted by the investigator checking the website, because dose-dumping may occur at this time as well as validation testing of inhalers.

12.3.3. Data that meets dose dumping criteria[37] will be discounted by the investigator checking the website. Dose dumping is defined as greater than or equal to 100 actuations in a three hour period.

12.4. Pre-site, pre-dispensing and collection checks

12.4.1. The following comprehensive trial quality control programme will be implemented in which all monitors and involves testing prior to dispensing and during the full study period, as performed in our previous RCT.[38,39]

Initial-site check:

12.4.1.1. This will be completed by individual study sites prior to dispensing monitors for the first time. The following steps will be undertaken:

12.4.1.1.1. Monitor will be woken from sleep mode by connecting the device via supplied USB cable to the Smartinhaler Connection Centre software.
12.4.1.1.2. Perform a log upload (following which the monitor clock will automatically be set to local time as set on the computer to which it is connected). Remove the monitor from the USB cord.
12.4.1.1.3. Perform battery check, as per Adherium instruction manual. If the light does not glow green the monitor will be classed as having failed screening. Discontinue the pre-site check and see Section 12.4.2.2.
12.4.1.1.4. Attach the monitor to the inhaler, as per Adherium instruction manual.
12.4.1.1.5. Perform two actuations, separated by 10-20 seconds, followed at least 15 minutes later by two further actuations separated by 10-20 seconds, all actuation times are to be manually recorded.
12.4.1.1.6. Data upload via supplied USB cable to the Smartinhaler Connection Centre software.
12.4.1.1.7. Review of data on the SmartinhalerLive website.
12.4.1.1.8. Any monitors with missing or spurious actions will be classed as having failed screening. Discrepancy between the time recorded and the data on the SmartinhalerLive website should be less than or equal to 5 minutes.

12.4.1.2. Failed Monitors:

12.4.1.2.1. Will be returned to the Global Sponsor for review as soon as practical

12.4.1.2.2. Will be replaced with another monitor, which will need to be assigned to the participant on the SmartinhalerLive website (see manual for instructions) and undergo the initial site and pre-dispensing monitor checks.[38,39]

12.4.2. Pre-dispensing check:

12.4.2.1. To be performed the day of the study visit. This does not need to be performed if an initial site check has been performed on the same day.

12.4.2.2. Battery check: If battery light does not flash green the monitor is deemed to have failed the check.

12.4.2.3. Actuation check:

12.4.2.3.1. Two actuations performed, with the time and date recorded.
12.4.2.3.2. USB upload of data to the SmartInhalerLive website.
12.4.2.3.3. Check for consistency of time and date between that recorded by investigator and that displayed on SmartInhalerLive website.
12.4.2.3.4. Any monitors with missing or spurious actions will be classed as having failed screening. Discrepancy between the time recorded and the data on the SmartinhalerLive website should be less than or equal to 5 minutes.

12.4.2.4. Failed Monitors:

12.4.2.4.1. Will be returned to the Global Sponsor for review as soon as practical.
12.4.2.4.2. Will be replaced with another monitor, which will need to be assigned to the participant on the SmartinhalerLive website (see manual for instructions) and undergo the initial site and pre-dispensing monitor checks.

12.4.3. Collection check:

12.4.3.1. Monitor check:

12.4.3.1.1. Battery check (red, orange or green).
12.4.3.1.2. Any sign of damage.
12.4.3.1.3. If monitor passes check (displays green on battery check and has no signs of damage) then after USB upload the monitor will be stored for re-use by the participant at subsequent visits.
12.4.3.1.4. If monitor fails check then after USB upload it will be sent back to the Global Sponsor as soon as is practical.

13. Safety monitoring, adverse events and serious adverse events

High risk participants will be ineligible if they have had a previous ICU admission for asthma or a hospital admission in the last 12 months, or SABA use on more than two occasions per day on average in the 4 weeks prior to enrolment (this may result in 4 actuations if the participant routinely uses 2 actuations of their SABA MDI on each occasion). All participants will receive a written asthma action plan. Participants will be required to contact the investigators if they seek urgent medical help for their asthma, start prednisone, if any changes are made to their randomised treatment, if they are concerned they will run out of study medication before their next scheduled visit, if they are concerned about equipment malfunction or if they wish to withdraw from the study (see Section 8.3). Investigators will upload data from the monitors at each scheduled study visit. This will be used to check for episodes of beta agonist use that meet the criteria for withdrawal. Any participant with three exacerbations or a severe exacerbation due to asthma will be withdrawn from the study.

13.1. Adverse events (AEs)

An adverse event is any untoward medical occurrence in a study subject temporally associated with participation in the trial and the administration of study medication, whether or not considered related to the medicine. An adverse event can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of the study treatment. A worsening of a pre-existing medical condition other than asthma will be considered an adverse event. For detail on worsening of asthma see Section 13.3.

Adverse event data will be collected from Visit 2 until Visit 7, or the last visit at which the participant attends, and analysed with efficacy data at the end of the study. If an adverse event is ongoing at Visit 7, this will be followed up as required by the Investigator, but will not require recording in the eCRF. The Global Sponsor may request further follow-up data on adverse events, if necessary.

Participants will be asked to grade adverse events and the maximum severity will be recorded in the eCRF, according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated).
- Moderate (discomfort sufficient to cause interference with normal activities).
- Severe (incapacitating, with inability to perform normal activities).

It is noted that there is a distinction between serious and severe AEs. Severity is a measure of intensity, as outlined above, whereas seriousness is defined by the criteria in Section 13.2.

An assessment of causality and expectedness will be performed by the Investigator submitting the adverse event report. Causality will be based on the Investigator's judgement and will result in a decision of related, or not related, to IMP.
Causality will be assessed based on:

- Related: The temporal relationship of the AE or SAE to IMP administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.

- Unrelated: The temporal relationship of the AE or SAE to IMP administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide sufficient explanation for the AE/SAE.

Expectedness will be assessed against the Summary of Product Characteristics for each IMP.

13.2. Serious adverse events (SAEs)

For the purposes of this study the following events will be considered to be SAEs and require expedited reporting:

- Death.
- Life-threatening event.
- Permanently disabling or incapacitating event.
- Inpatient Hospitalisation or prolongation of hospitalisation. Hospitalisation for the purposes of SAE reporting is defined as an admission to hospital and does not include a presentation to the Emergency Department followed by discharge without admission or an admission for elective reasons.
- Consists of a congenital anomaly or birth defect.
- Any event considered serious by the study investigator.

Females pregnant, breastfeeding or planning pregnancy at the time of recruitment will be excluded from participating in the trial. Should a female subject enrolled on the study become pregnant during the course of the trial she should inform investigators at her earliest opportunity and be withdrawn from the study. Current clinical practice allows for the use of budesonide or combination budesonide/formoterol during pregnancy, as the benefits to both mother and child of adequate asthma control outweigh the theoretical risks of treatment. The subject will be asked to contact the researchers after the birth of the baby and any congenital anomaly or birth defect will be considered to be an SAE.

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 Global Sponsor within 24 hours of Investigators becoming aware of the event. Any follow up information required by the Global 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 medically indicated, but this will not require recording in the eCRF. The Global Sponsor may request further follow-up data on SAEs, if necessary.

If the eCRF is not available, an SAE report should be faxed to the Global Sponsor within 24 hours, to +64 4 389 5707.

The Global Sponsor will receive notification of SAE submission via the eCRF and will review SAEs on an ongoing basis, within 1 working calendar day (based on NZ time) of submission by the Investigator. An assessment will be made by the Global Sponsor as to the causality and expectedness of the event, based on the Investigator's report and the relevant Summary of Product Characteristics.

13.3. Expedited adverse event reporting

Adverse Events or Adverse Drug Reactions shall be reported to relevant health authorities in accordance with applicable laws, and to any overseeing Ethics Committee in accordance with its policies.

For events that require expedited reporting and that are fatal or life threatening, reporting will be no later than 7 calendar days from Global Sponsor awareness, and within 8 calendar days for any further additional relevant information. For all other events requiring expedited reporting, the initial report will be performed within 15 days.
The Local Sponsor and/ or the Local Chief Investigator (as required), will submit and report to the ethics and regulatory bodies in each country, on behalf of the Global Sponsor. The Global Sponsor will liaise with each Local Chief Investigator and Local Sponsor (as applicable) to ensure that all expedited reporting requirements can be met, as per the specific timelines in the country of origin of the event.

The Global Sponsor will provide all reported Adverse Events, Serious Adverse Events, Adverse Reactions, Serious Adverse Reactions and Suspected Unexpected Serious Adverse Reactions for the country of the Local Sponsor, on request. If required, the Local Sponsor may also request all of the safety events (worldwide) submitted to the Global Sponsor as part of the study.

AstraZeneca shall be notified of all Adverse Events or Adverse Drug Reactions subject to expedited reporting at the same time the reports are sent to any health authority.

13.4. Asthma exacerbations

If a study participant has an exacerbation during the study or they have a worsening of their asthma control, they will be asked to contact their General Practitioner for assessment and management or visit an Accident and Emergency Department/Clinic in their area. It will be reinforced to the study participants that they will receive standard medical care (from their GP, after hours or ED) for their asthma during the course of the study.

- Subjects randomised to the ICS maintenance plus SABA reliever therapy regimen or SABA only regimen will be advised that should they take more than 16 inhalations of salbutamol over any 24 hour period they should see their doctor or attend ED the same day.

- Subjects randomised to the ICS/LABA reliever therapy regimen will be advised that should they take more than 8 inhalations of budesonide/formoterol over any 24 hours period they should see their doctor or attend ED the same day.

As per the self-management plans, if participants usually measure their own peak flow at home they should continue to do this and seek medical review should this drop to below 60% of best measurement.

The comparative efficacy of the medication regimens on asthma control is an objective of this study. Asthma exacerbations that do not meet the criteria for being considered an SAE will be reported as adverse events and the data concerning these events will be collected as measures of study outcomes. Should a participant report a worsening of asthma that does not meet the criteria for an exacerbation (e.g. feeling more wheezy than usual, worse ACQ score), this will be considered part of the fluctuating course of asthma, and not to be an AE.

13.5. Data safety monitoring committee (DSMC)

A DSMC will be established, which is independent from the study team. The DSMC will review all serious adverse events and the results of the interim safety statistical analysis undertaken when 400 patients have been randomised. We anticipate a very low rate of SAE, less than 2% based on our previous RCT in participants with more severe asthma. We have therefore based this interim assessment based on this anticipated rate of eight participants with a SAE when 400 have been recruited. If all these participants came from one arm of the study; the estimated rate of SAE in this arm of the study would be 8/133 (6%) with an exact 98.8% confidence limit of 2.0 to 13.2%. The 98.8% confidence interval is based on a calculated interim P value for performing a single safety review of the study (using the 1d98 Program), of 0.006 (using a one-sided O'Brien-Fleming boundary) and one interim analysis, and an overall P value for SAE proportions of 0.05. If the proportion of SAE overall 400 participants exceeds 8/400 then the DSMC will consider an analysis with masked treatment code for the safety variable amongst the treatment arms, review of the SAE, and if one of the treatment arms has a rate of SAE above 2% consider whether the study should be terminated.

The study management team will compile summaries of all protocol deviations, serious breaches, Serious Adverse Events and withdrawals for pooled data, for the DSMC, on a monthly basis. The DSMC will have the capacity to request an analysis with masked treatment code for any variable amongst the treatment arms. DSMC meetings will take place every 6 months, or sooner if indicated.

Unblinded data can be made available at the DSMCs request.

13.6. Monitoring

The Global Sponsor will monitor the study in accordance with current approved protocol, Good Clinical Practice guidelines, relevant regulation, standard operating procedures and the Study Monitoring Plan. A Global Sponsor representative, the Clinical Trial Monitor, will have regular contact with the sites and will act as the first point of contact during the study. The Clinical Trial Monitor and Global Chief Investigator will perform an on-site monitoring visit (SMV) at specified intervals to include the following:

- Site performance assessment, to confirm recruitment rates, protocol adherence and study drug accountability.
- Perform source data verification activities (verify the key pre-specified data entered into eCRF against the source data for each subject, as per the Study Monitoring Plan).
- Provide advice/ support as necessary for the site.

Remote monitoring of data will also take place, to ensure any logical inconsistencies or missing data can be resolved prior to the SMV, and throughout the study. The eCRF will also provide inbuilt validation checks to ensure consistent and correct data are entered.

A close-out visit will also be performed once the study has completed, to formally close out each site and to ensure any ongoing responsibilities are met.

13.7. 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 Global Sponsor must be contacted within 1 working day. In collaboration with the Investigator and the Local Sponsor, the serious breach will be reviewed by the Global Sponsor and, if appropriate, the Local Sponsor will report it to their relevant ethics committee, regulatory authority, and local governance body (as applicable) within seven calendar days.

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14. Electronic data capture

An eCRF will be used to randomise subjects into the study, dispense and track medications and enable data entry for each patient. After they have received training, study staff will be given appropriate access to the eCRF system and will complete subject study data entry on an ongoing and timely basis within the system. The eCRF system will be separate from the site specific collection of individual subject medication use (via the electronic monitors), which will take place as outlined in Section 12.

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15. Site training

Site Initiation Visits (SIV) combined with Investigator Meetings will be held in NZ, Australia, Italy and the UK to provide information and training for the Principal Investigator and Research Coordinator from each site. SIVs will take place at each site.

SIVs will be performed by the Clinical Trial Monitor and Global Chief Investigator. These will ensure the site is ready to begin recruiting for the study and that all necessary approvals (ethics/regulatory/research office etc) are in place prior to the first patient enrolment, and to provide training on the eCRF and Electronic Monitors, as well as study specific procedures e.g. spirometry. The appropriate manuals and guidelines will also be issued to sites in order that they are able to perform the study as per protocol. Any additional training for study procedures will be performed as necessary.

16. Ethics

16.1. Ethical considerations

All patients will be randomised to either the same treatment step (SABA reliever therapy) or a higher step of treatment incorporating ICS therapy (ICS/LABA reliever therapy or ICS maintenance and SABA reliever therapy) during the study. Participants deemed to be at 'high risk' will be excluded, on the basis of a previous ICU admission, a hospital admission in the last year, or SABA use on average >2 occasions per day in the 4 week period prior to recruitment. Participants will be followed closely during the study with provision of asthma self-management plans, and those who experience three exacerbations or one severe exacerbation during the study period will be withdrawn. As a result, we are confident that all patients randomised in the study will be at substantially lower risk during the study than if they had not been enrolled.

16.2. Ethics and regulatory review

An Ethics Committee at each study site (or country where multiple sites exist) will approve the final study protocol and the final version of the Informed Consent Form and any other written information and/or materials to be provided to study participants. The Principal Investigator at each site will ensure that an Ethics Committee has approved all study documents, as applicable, and distribute to their study site staff.

The opinion of the Ethics Committee should be given in writing. The Principal Investigator should submit the written approval to the Local Sponsor before enrolment of any patient into the study. The Local Sponsor will forward on approvals to the Global Sponsor, on request.

The Ethics Committee should approve all advertising used to recruit patients for the study.

The Local Sponsor should approve any modifications to the Informed Consent Form that are needed.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, will be approved by the national regulatory authority or a notification to the national regulatory authority will be undertaken, according to local regulations.

16.3. Ethics and regulatory reporting

The Local Chief Investigator shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the responsible ethics committee, and Local Sponsor. In addition, an End of Trial notification and final report will be submitted to the responsible regulatory body, ethics committee and the Local Sponsor.

Local reporting requirements will be fulfilled by the Local Chief Investigator, including submission of any required reports to their host institution.

In order to meet the above requirements, the Global Sponsor will collaborate with the Local Chief Investigator/ Local Sponsor to ensure the necessary information is made available for reporting.

The Global Sponsor will provide the Local Chief Investigator with safety updates/reports according to local requirements, including safety information relating to any serious and unexpected adverse drug reactions from this study.

The Local Chief Investigator will submit safety reports to the responsible regulatory body, ethics committee, host institution and Local Sponsor, as required.

All reports will be submitted to the Global Sponsor, on request.

16.4. Participant confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a randomisation ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials, date of birth and ethnicity will be added, as part of demographic information. All documents will be stored securely and only accessible by study staff and authorised personnel. Each site will comply with local data protection laws when recording and locally storing information for the study.

De-identified data recorded in the eCRF will be securely stored on servers in Australia.

De-identified data recorded by the electronic monitors will be securely stored on servers in the USA and New Zealand

Periostin samples will be analysed, and the data stored in the USA, at:
Covance Central Laboratory
8211 SciCor Drive
Indianapolis, IN 46214
USA

The Global Sponsor will obtain all study data and securely store it in New Zealand.

In all cases, where data or samples leave the study site, they will be de-identified, with identifiable information such as participant name removed, and replaced with the randomisation ID.

The Global Sponsor will have access to the identifiable source data at site, for on-site monitoring purposes, to ensure the study is being run in compliance with GCP and the protocol.

17. Finance and insurance

17.1. Funding

The study is being funded by AstraZeneca. The funding agreement is made between AstraZeneca and MRINZ, as Global Sponsor. MRINZ will enter into contracts with study sites and will provide funding in the form of start-up fees, paid on execution of a contract, and per-participant payments, paid for each completed visit (including data completion for that visit).

17.2. Participant reimbursement

Participants will be given reasonable reimbursement for travel and inconvenience costs, according to local practice and in accordance with local ethical approval.

17.3. Insurance

Insurance will be obtained by each Local Sponsor, as applicable to their country requirements. The Sponsor will ensure that each Local Sponsor has appropriate insurance in place to cover any participant suffering harm as a result of their involvement in the research, according to local regulations, prior to recruitment starting at any site within that country.

18. 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 1 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.

19. References

1. Patel M, et al. Efficacy and safety of maintenance and reliever combination budesonide–formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. Lancet Respiratory Medicine 2013;1:32-42.

2. Reddel HK, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.

3. Masoli M, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469-78.

4. Rabe KF, et al. Worldwide severity and control of asthma in children and adults: the global Asthma Insights and Reality surveys. J Allergy Clin Immunol 2004;114:40-7.

5. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma, 2011. (Accessed 11/03/15, 2015, at http://www.ginasthma.org/uploads/users/files/GINA_Report2011_May4.pdf.)

6. O'Byrne PM, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma. The OPTIMA randomized trial. Am J Respir Crit Care Med 2001;164:1392-7.

7. Beasley R, et al. Beta-agonists: what is the evidence that their use increases the risk of asthma morbidity and mortality? J Allergy Clin Immunol 1999;104:S18-30.

8. Masoli M, et al. Inhaled corticosteroid therapy in the management of asthma in adults. In: JT L, ed. The pharmacotherapy of Asthma. New York: Taylor & Francis Group; 2006:83-115.

9. Global Strategy for asthma management and prevention. Global Initiative for Asthma, 2014. (Accessed May 2014, 2014, at www.ginasthma.org.)

10. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003;361:1071-6

11. Boulet LP, et al. Benefits of low-dose inhaled fluticasone on airway response and inflammation in mild asthma. Respir Med 2009;103:1554-63.

12. Williams LK, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol 2004;114:1288-93.

13. Menckebert TT, et al. Beliefs about medicines predict refill adherence to inhaled corticosteroids. J Psychosom Res 2008;64:47-54.

14. Papi A, et al. Rescue treatment in asthma: more than as-needed bronchodilation. Chest 2009;135:1628-33.

15. Barnes PJ, et al. Scientific rationale for using a single inhaler for asthma control. Eur Respir J 2007;29:587-95.

16. Beasley R, et al. Combination corticosteroid/beta-agonist inhaler as reliever therapy: a solution for intermittent and mild asthma? J Allergy Clin Immunol 2014;133:39-41.

17. Papi A, et al. Rescue use of beclomethasone and albuterol in as a single inhaler for mild asthma. N Engl J Med 2007;356:2040-52.

18. Calhoun W, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. JAMA 2012;308:987-97.

19. Rabe KF, et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006;368:744-53.

20. Haahtela T, et al. Formoterol as needed with or without budesonide in patients with intermittent asthma and raised NO levels in exhaled air: a SOMA study. Eur Respir J 2006;28:748-55.

21. Oborne J, et al. Quadrupling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial. Am J Respir Crit Care Med 2009;180:598-602.

22. Rodrigo GJ. Rapid effects of inhaled corticosteroids in acute asthma: an evidence-based evaluation. Chest 2006;130:1301-11.

23. Tattersfield AE, et al. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. Lancet 2001;357:257-61.

24. Pauwels RA, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. Eur Respir J 2003;22:787-94.

25. Symbicort SMART Asthma Action Plan (Turbuhaler). (National Asthma Council Australia). http://www.nationalasthma.org.au/health-professionals/asthma-action-plans/asthma-action-plan-library#ssaap [Accessed April 2015].

26. Masoli M, et al. Dose-responsive relationship of inhaled budesonide in adult asthma: a meta-analysis. Eur Respir J 2004;23:552-8.

27. Powell H, Gibson PG. High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children (Review). Cochrane Database of Systematic Reviews 2008.

28. Juniper EF, et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.

29. Matza LS, et al. Derivation and validation of the ASK-12 adherence barrier survey. Ann Pharmacother 2009;43:1621-30.

30. ATS/ERS. ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide. American J Respir Crit Care Med 2005;171:912-930.

31. Miller MR, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.

32. Balanag VM, et al. Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. Pulm Pharmacol Ther 2006;19:139-47.

33. Rubinfeld AR, et al. Formoterol Turbuhaler as reliever medication in patients with acute asthma. Eur Respir J 2006;27:735-41.

34. Aaronson D, et al. Effects of budesonide by means of the Turbuhaler on the hypothalmic-pituitary-adrenal axis in asthmatic subjects: a dose-response study. J Allergy Clin Immunol 1998;101:312-9.

35. Patel M, et al. The use of β_2-agonist therapy before hospital attendance for severe asthma exacerbations: a *post-hoc* analysis. Prim Care Respir Med 2015;25:14099; doi:10.1038/npjpcrm.2014.99.

36. Pilcher J, et al. Combination budesonide/formoterol inhaler as maintenance and reliever therapy in Maori with asthma. Respirology 2014;19:842-51.

37. Rand CS, et al. Metered-Dose Inhaler Adherence in Trial1-3. Am Rev Respir Dis 1992;146:1559-64.

38. Patel M, et al. Six-month in vitro validation of a metered-dose inhaler electronic monitoring device: Implications for asthma clinical trial use. J Allergy Clin Immunol 2013;130:1420-2.

39. Patel M, et al. Use of metered-dose inhaler electronic monitoring in a real-world asthma randomized controlled trial. J Allergy Clin Immunol: In Practice 2013;1:83-91.

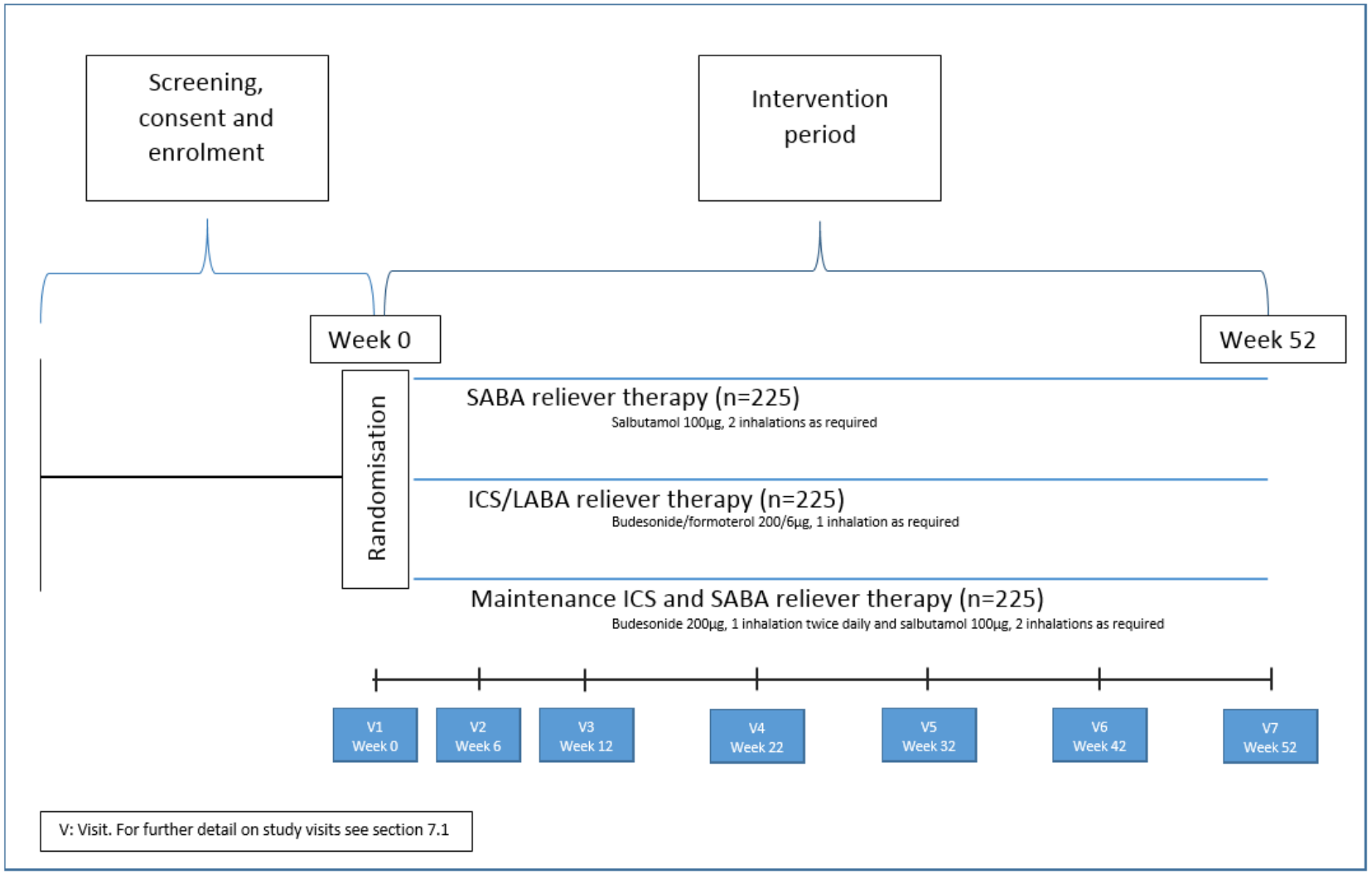
40. Quanjer et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40(6):1324–43; DOI: 10.1183/09031936.00080312

Appendix 1

RCT of the efficacy and safety of an ICS/ LABA reliever therapy regimen in asthma

Short title: Novel START (Novel Symbicort Turbuhaler Asthma Reliever Therapy)

Figure 1: Study design



Asthma management plans

All participants will be given education on medication use and inhaler technique, and a written asthma self-management ("action") plan relating to their randomised group. The self-management plans are based on the prototype plans which have been shown to reduce morbidity and requirement for acute medical treatment in adult asthma, and represent modified versions of the AstraZeneca "My Symbicort SMART Asthma Action Plan" (Figures 2-7). The asthma self-management system of care involves the integration of self-assessment and self-management, and incorporates written guidelines for both the long term treatment of asthma and the treatment of severe attacks.

The purpose of these plans is to reinforce the randomised treatment regimens and provide written instructions as to how patients recognise worsening asthma, and what actions the participants should take in the situation of an exacerbation. In particular the plans will explain when to seek GP review and emergency medical care in the situation of an exacerbation. This approach, based primarily on symptom severity and frequency of use of beta agonist reliever therapy, also provides standardised assessment and recognition of exacerbations by participants in the clinical trial.

Participants will not be required to measure their peak flow or to fill in a record card every day as this would prompt the participants to take their medicines regularly and promote adherence. These effects would reduce the chance of seeing a difference between regular and reliever ICS regimens which occur in "real-world" scenarios. Those subjects who already monitor their peak flows on entry to the study will be advised to continue to do so with a management plan incorporating peak flow use. For the purpose of this study, a drop in peak flow to <60% of recent best will signify an asthma exacerbation that requires medical review.

The plans included below, as an example, are the New Zealand Master versions. Each country will have a specific version to accommodate local differences in language, medication names and participant medical care during the study, based on the NZ Master .

Figure 3: SABA self-management plan front

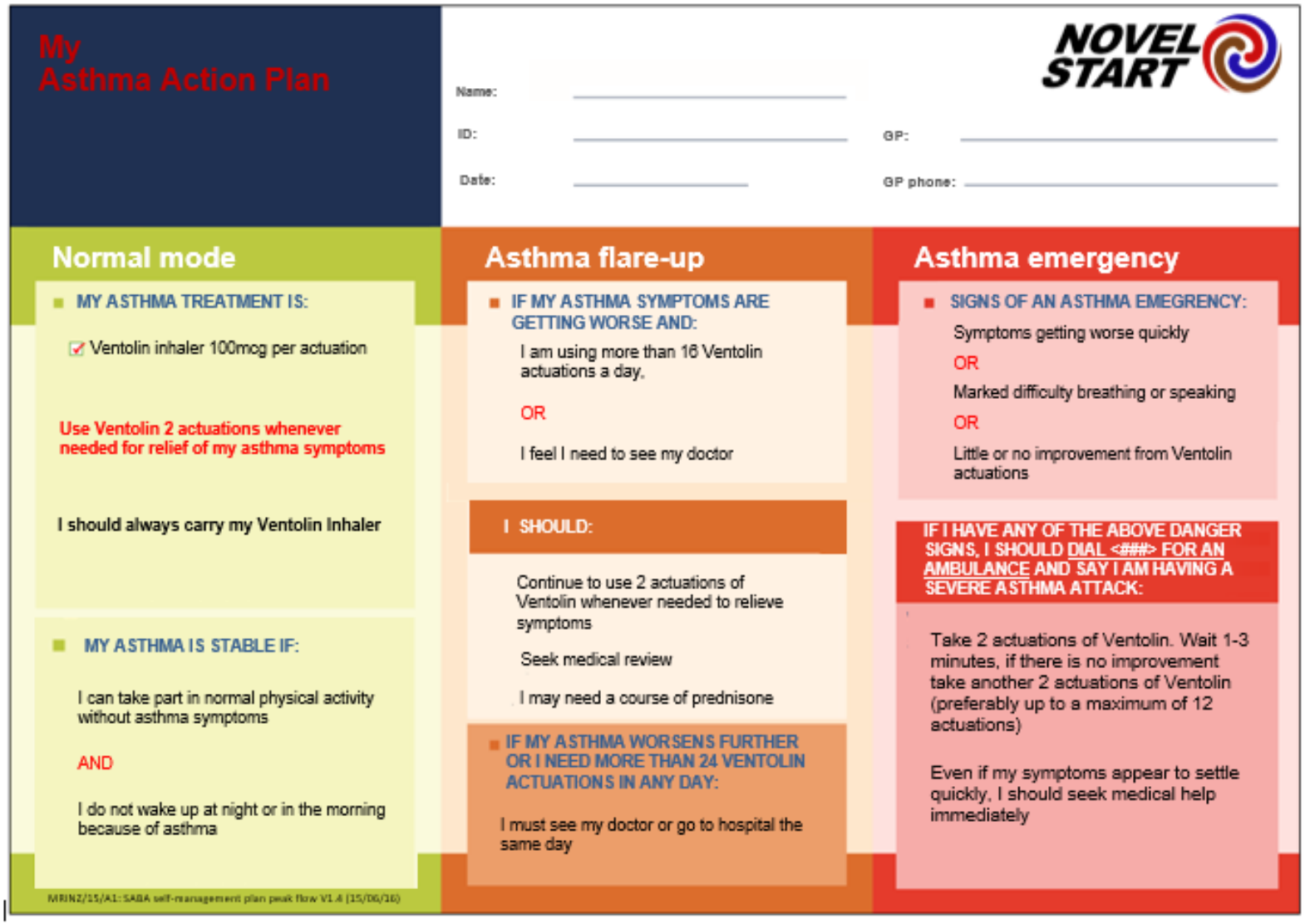


Figure 4: SABA self-management plan reverse

NEXT APPOINTMENT DATE

Visit 2: _____
Visit 3: _____
Visit 4: _____
Visit 5: _____
Visit 6: _____
Visit 7: _____

INVESTIGATOR CONTACT DETAILS

Name _____
Phone number _____
Email _____

For medical help contact your own GP, after hours service or hospital, to get treated quickly in accordance with standard practice.
Do NOT contact the investigator for medical help

HOW TO USE VENTOLIN INHALER

1. **SHAKE**
   Remove cover. Hold UPRIGHT and shake well
2. **EXHALE**
   Breathe out, away from mouthpiece. Form a tight seal over mouthpiece with lips
3. **INHALE**
   Breathe in slowly and deeply while activating your inhaler by pressing down on canister, with your thumb under the canister
4. **REPEAT**
   Wait around 30 seconds then repeat the steps above for the second inhalation

REMEMBER

Do not activate (test fire) your inhaler in air
1 inhalation = 1 activation of your inhaler

ASTHMA FLARE UPS

Have you visited your GP/ED or been admitted to hospital due to asthma?
If YES, please fill table below. If NO, please leave table blank.

Date	Type of visit	Prednisone given?		Prednisone dose	How long for?	Start date	Stop date	Comments
e.g.15/01/16	e.g. GP/ED	Yes	No	e.g. 40mg	e.g. 4 days	e.g. 15/01/16	e.g. 19/01/16	e.g. Admitted

OTHER MEDICATION

Have you started any new medication (other than prednisone - see above) OR have you had any changes to existing medication? If YES, please fill table below. If NO, please leave table blank

Medication started/ changed	Dose	How many times a day?	How long for?	Date started/ changed	Date stopped	Comments (e.g. reason for medication)
E.g. Amoxicillin	e.g. 500mg	e.g. Three	e.g. 5 days	e.g. 15/01/16	e.g. 20/01/16	e.g. Reason for medication. Sore throat

Figure 5: SABA self-management plan with peak flow front

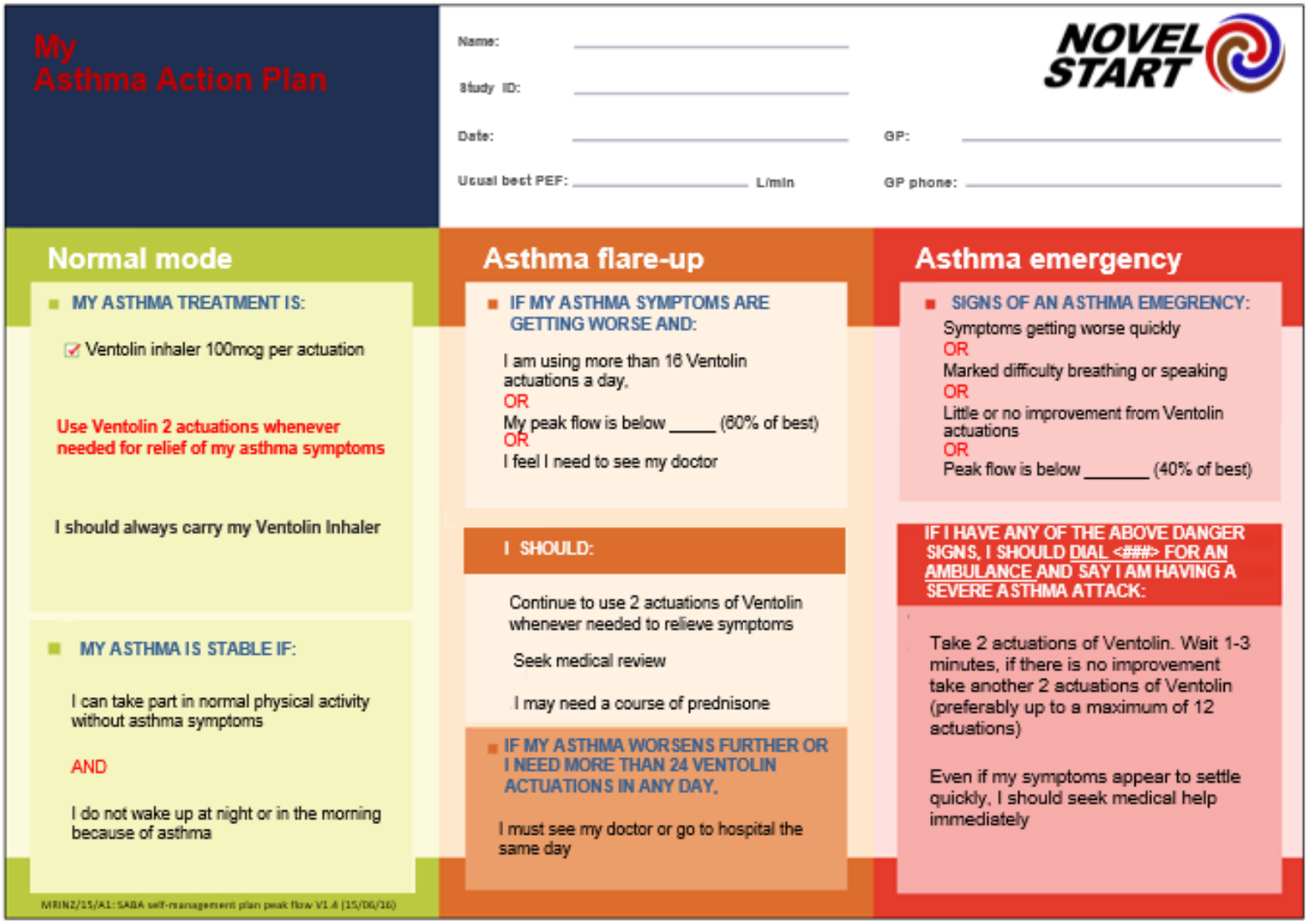


Figure 6: SABA self-management plan with peak flow reverse

NEXT APPOINTMENT DATE

Visit 2: _____
Visit 3: _____
Visit 4: _____
Visit 5: _____
Visit 6: _____
Visit 7: _____

INVESTIGATOR CONTACT DETAILS

Name _____
Phone number _____
Email _____

For medical help contact your own GP, after hours service or hospital, to get treated quickly in accordance with standard practice.
Do NOT contact the investigator for medical help

HOW TO USE VENTOLIN INHALER

1. **SHAKE**
   Remove cover. Hold UPRIGHT and shake well
2. **EXHALE**
   Breathe out, away from mouthpiece. Form a tight seal over mouthpiece with lips
3. **INHALE**
   Breathe in slowly and deeply while activating your inhaler by pressing down on canister, with your thumb under the canister
4. **REPEAT**
   Wait around 30 seconds then repeat the steps above for the second inhalation

REMEMBER

***Do not** activate (test fire) your inhaler in air*
1 inhalation = 1 activation of your inhaler

ASTHMA FLARE UPS

Have you visited your GP/ED or been admitted to hospital due to asthma?
If YES, please fill table below. If NO, please leave table blank.

Date	Type of visit	Prednisone given?		Prednisone dose	How long for?	Start date	Stop date	Comments
e.g.15/01/16	*e.g. GP/ED*	*Yes*	*No*	*e.g. 40mg*	*e.g. 4 days*	*e.g. 15/01/16*	*e.g. 19/01/16*	*e.g. Admitted*

OTHER MEDICATION

Have you started any new medication (other than prednisone - see above) OR have you had any changes to existing medication? If YES, please fill table below. If NO, please leave table blank

Medication started/ changed	Dose	How many times a day?	How long for?	Date started/ changed	Date stopped	Comments (e.g. reason for medication)
E.g. Amoxicillin	*e.g. 500mg*	*e.g. Three*	*e.g. 5 days*	*e.g. 15/01/16*	*e.g. 20/01/16*	*e.g. Reason for medication. Sore throat*

Figure 7: ICS/LABA self-management plan front

Figure 8: ICS/LABA self-management plan reverse

NEXT APPOINTMENT DATE

Visit 2: _____

Visit 3: _____

Visit 4: _____

Visit 5: _____

Visit 6: _____

Visit 7: _____

INVESTIGATOR CONTACT DETAILS

Name _____

Phone number _____

Email _____

For medical help contact your own GP, after hours service or hospital, to get treated quickly in accordance with standard practice.
Do NOT contact the investigator for medical help.

HOW TO USE SYMBICORT TURBUHALER

TWIST

Unscrew and lift off cover. Hold UPRIGHT and twist base in one direction and then twist base in opposite direction, listening for a CLICK

INHALE

Breathe out, away from mouthpiece. Form a tight seal over mouthpiece with lips and breathe in strongly and deeply

REMEMBER

Follow the steps above every time you need to use your Turbuhaler
1 click = 1 inhalation
***Do not** twist your Turbuhaler base unless you need to use it*

ASTHMA FLARE UPS

Have you visited your GP/ED or been admitted to hospital due to asthma?
If YES, please fill table below. If NO, please leave table blank.

Date	Type of visit	Prednisone given?		Prednisone dose	How long for?	Start date	Stop date	Comments
e.g.15/01/16	*e.g. GP/ED*	*Yes*	*No*	*e.g. 40mg*	*e.g. 4 days*	*e.g. 15/01/16*	*e.g. 19/01/16*	*e.g. Admitted*

OTHER MEDICATION

Have you started any new medication (other than prednisone - see above) OR have you had any changes to existing medication? If YES, please fill table below. If NO, please leave table blank

Medication started/ changed	Dose	How many times a day?	How long for?	Date started/ changed	Date stopped	Comments (e.g. reason for medication)
E.g. Amoxicillin	*e.g. 500mg*	*e.g. Three*	*e.g. 5 days*	*e.g. 15/01/16*	*e.g. 20/01/16*	*e.g. Reason for medication. Sore throat*

Figure 9: ICS/LABA self-management plan with peak flow front

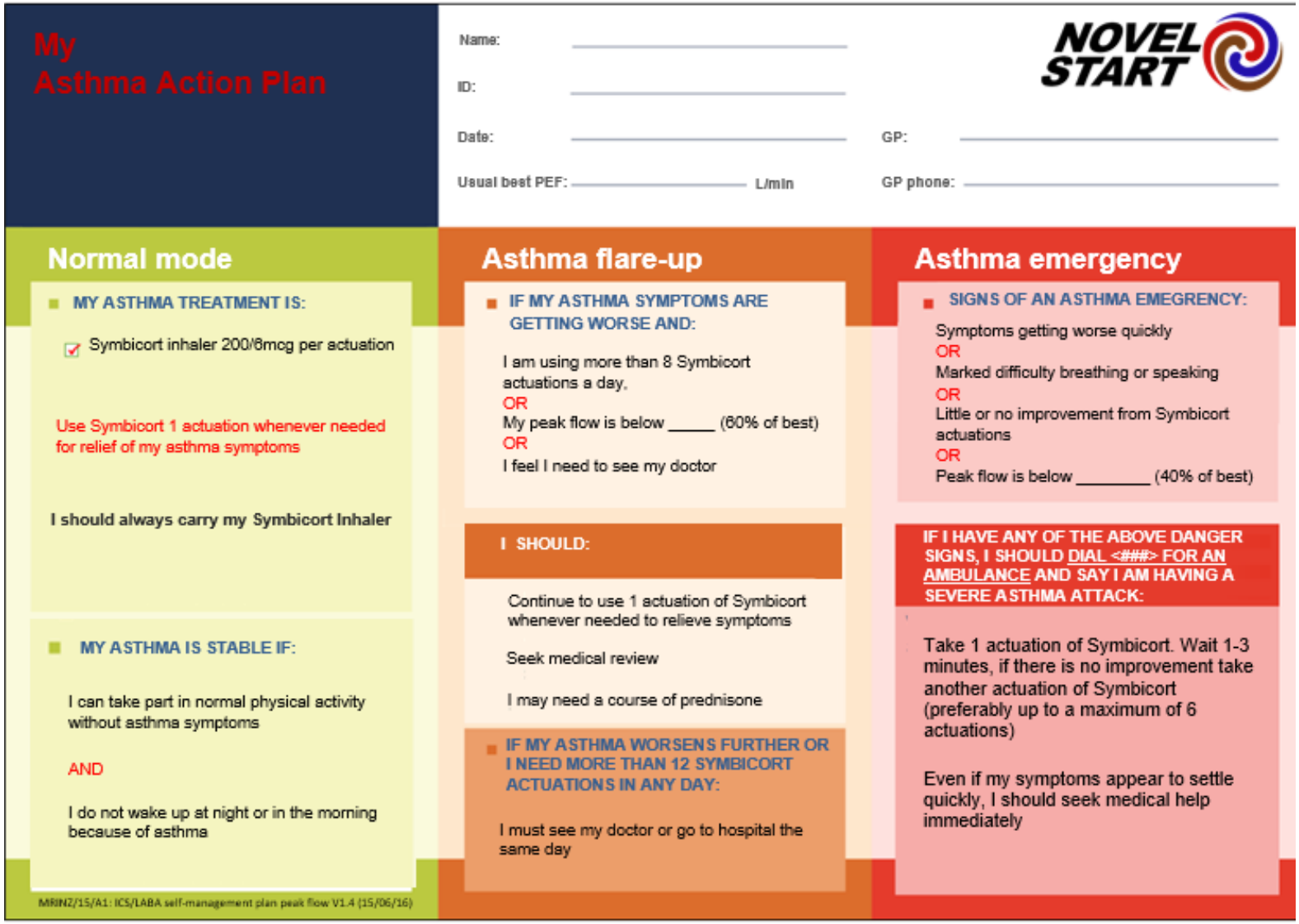


Figure 10: ICS/LABA self-management plan with peak flow reverse

NEXT APPOINTMENT DATE

Visit 2: _____

Visit 3: _____

Visit 4: _____

Visit 5: _____

Visit 6: _____

Visit 7: _____

INVESTIGATOR CONTACT DETAILS

Name _____

Phone number _____

Email _____

For medical help contact your own GP, after hours service or hospital, to get treated quickly in accordance with standard practice.
Do NOT contact the investigator for medical help.

HOW TO USE SYMBICORT TURBUHALER

TWIST

Unscrew and lift off cover. Hold UPRIGHT and twist base in one direction and then twist base in opposite direction, listening for a CLICK

INHALE

Breathe out, away from mouthpiece. Form a tight seal over mouthpiece with lips and breathe in strongly and deeply

REMEMBER

Follow the steps above every time you need to use your Turbuhaler
1 click = 1 inhalation
***Do not** twist your Turbuhaler base unless you need to use it*

ASTHMA FLARE UPS

Have you visited your GP/ED or been admitted to hospital due to asthma?
If YES, please fill table below. If NO, please leave table blank.

Date *e.g.15/01/16*	Type of visit *e.g. GP/ED*	Prednisone given?		Prednisone dose *e.g. 40mg*	How long for? *e.g. 4 days*	Start date *e.g. 15/01/16*	Stop date *e.g. 19/01/16*	Comments *e.g. Admitted*
		Yes	*No*					

OTHER MEDICATION

Have you started any new medication (other than prednisone - see above) OR have you had any changes to existing medication? If YES, please fill table below. If NO, please leave table blank

Medication started/ changed *E.g. Amoxicillin*	Dose *e.g. 500mg*	How many times a day? *e.g. Three*	How long for? *e.g. 5 days*	Date started/ changed *e.g. 15/01/16*	Date stopped *e.g. 20/01/16*	Comments (e.g. reason for medication) *e.g. Reason for medication. Sore throat*

Figure 11: ICS and SABA self-management plan front

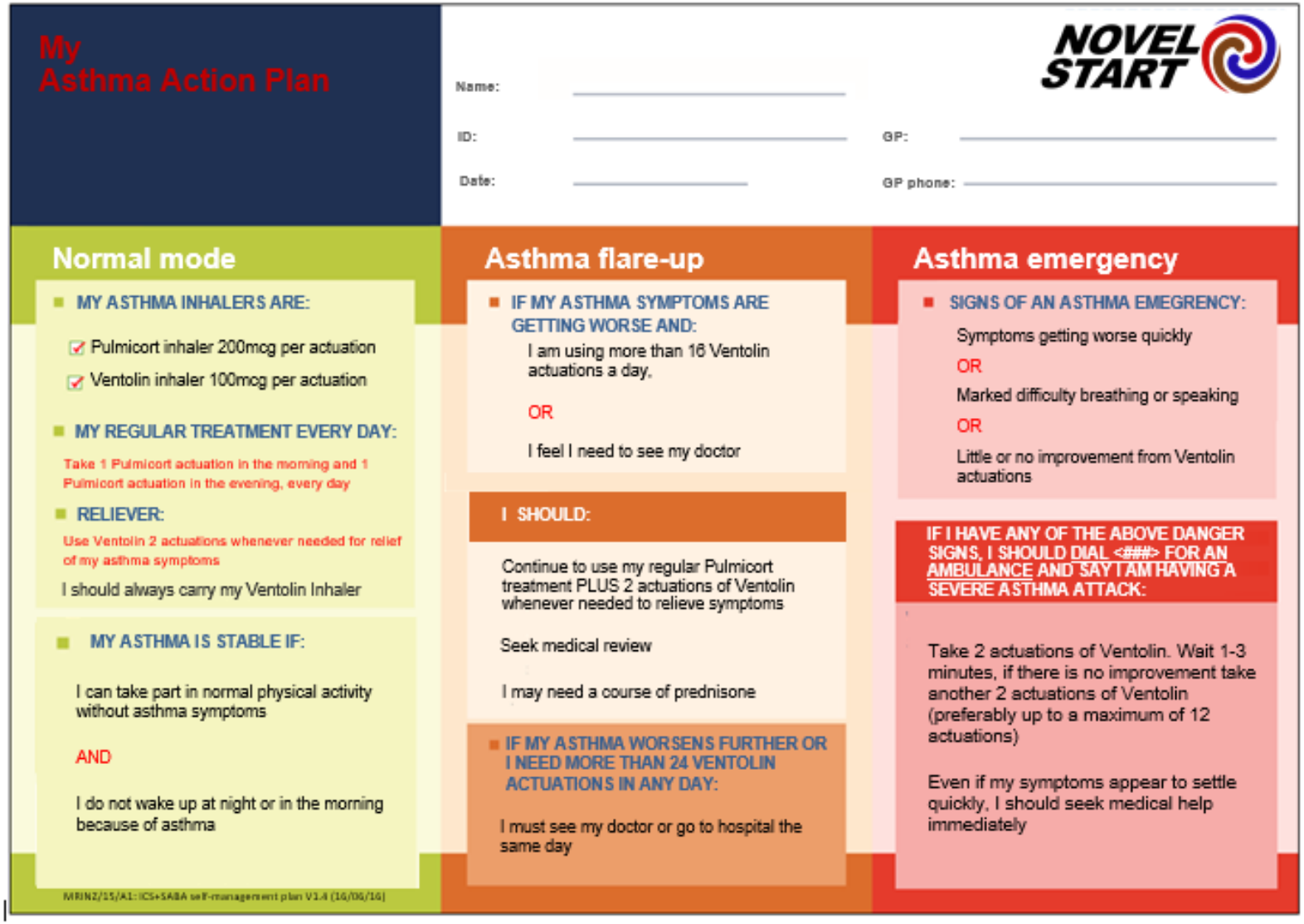


Figure 12: ICS and SABA self-management reverse

NEXT APPOINTMENT DATE

Visit 2: _____
Visit 3: _____
Visit 4: _____
Visit 5: _____
Visit 6: _____
Visit 7: _____

INVESTIGATOR CONTACT DETAILS

Name _____
Phone number _____
Email _____

For medical help contact your own GP, after hours service or hospital, to get treated quickly in accordance with standard practice.
Do NOT contact the investigator for medical help.

HOW TO USE PULMICORT TURBUHALER

TWIST
Unscrew and lift off cover. Hold UPRIGHT and twist base in one direction and then twist base in opposite direction, listening for a CLICK

INHALE
Breathe out, away from mouthpiece. Form a tight seal over mouthpiece with lips and breathe in deeply

REMEMBER
Follow the steps above every time you need to use your Turbuhaler
1 click = 1 inhalation
***Do not** twist your Turbuhaler base unless you need to use it*

HOW TO USE VENTOLIN INHALER

1. **SHAKE**
   Remove cover. Hold UPRIGHT and shake well
2. **EXHALE**
   Breathe out, away from mouthpiece. Form a tight seal over mouthpiece with lips
3. **INHALE**
   Breathe in slowly and deeply while activating your inhaler by pressing down on canister, with your thumb under the canister
4. **REPEAT**
   Wait around 30 seconds then repeat the steps above for the second inhalation

REMEMBER
***Do not** activate (test fire) your inhaler in air*
1 inhalation = 1 activation of your inhaler

ASTHMA FLARE UPS

Have you visited your GP/ED or been admitted to hospital due to asthma?
If YES, please fill table below. If NO, please leave table blank.

Date	Type of visit	Prednisone given?		Prednisone dose	How long for?	Start date	Stop date	Comments
e.g.15/01/16	*e.g. GP/ED*	*Yes*	*No*	*e.g. 40mg*	*e.g. 4 days*	*e.g. 15/01/16*	*e.g. 19/01/16*	*e.g. Admitted*

OTHER MEDICATION

Have you started any new medication (other than prednisone - see above) OR have you had any changes to existing medication? If YES, please fill table below. If NO, please leave table blank

Medication started/ changed	Dose	How many times a day?	How long for?	Date started/ changed	Date stopped	Comments (e.g. reason for medication)
E.g. Amoxicillin	*e.g. 1g*	*e.g. Three times a day*	*e.g. 5 days*	*e.g. 15/01/16*	*e.g. 20/01/16*	*e.g. Reason for medication. Sore throat*

MRINZ/15/A1: ICS SABA Peak Flow Management Plan V1.4 (15/06/16)

Figure 13: ICS and SABA self-management plan with peak flow front

Figure 14: ICS and SABA self-management plan with peak flow reverse

NEXT APPOINTMENT DATE

Visit 2: _____
Visit 3: _____
Visit 4: _____
Visit 5: _____
Visit 6: _____
Visit 7: _____

INVESTIGATOR CONTACT DETAILS

Name _____
Phone number _____
Email _____

For medical help contact your own GP, after hours service or hospital, to get treated quickly in accordance with standard practice.
Do NOT contact the investigator for medical help.

HOW TO USE PULMICORT TURBUHALER

TWIST
Unscrew and lift off cover. Hold UPRIGHT and twist base in one direction and then twist base in opposite direction, listening for a CLICK

INHALE
Breathe out, away from mouthpiece. Form a tight seal over mouthpiece with lips and breathe in deeply

REMEMBER
Follow the steps above every time you need to use your Turbuhaler
1 click = 1 inhalation
***Do not** twist your Turbuhaler base unless you need to use it*

HOW TO USE VENTOLIN INHALER

1. **SHAKE**
   Remove cover. Hold UPRIGHT and shake well
2. **EXHALE**
   Breathe out, away from mouthpiece. Form a tight seal over mouthpiece with lips
3. **INHALE**
   Breathe in slowly and deeply while activating your inhaler by pressing down on canister, with your thumb under the canister
4. **REPEAT**
   Wait around 30 seconds then repeat the steps above for the second inhalation

REMEMBER
***Do not** activate (test fire) your inhaler in air*
1 inhalation = 1 activation of your inhaler

ASTHMA FLARE UPS

Have you visited your GP/ED or been admitted to hospital due to asthma?
If YES, please fill table below. If NO, please leave table blank.

Date	Type of visit	Prednisone given?		Prednisone dose	How long for?	Start date	Stop date	Comments
e.g.15/01/16	*e.g. GP/ED*	*Yes*	*No*	*e.g. 40mg*	*e.g. 4 days*	*e.g. 15/01/16*	*e.g. 19/01/16*	*e.g. Admitted*

OTHER MEDICATION

Have you started any new medication (other than prednisone - see above) OR have you had any changes to existing medication? If YES, please fill table below. If NO, please leave table blank

Medication started/ changed	Dose	How many times a day?	How long for?	Date started/ changed	Date stopped	Comments (e.g. reason for medication)
E.g. Amoxicillin	*e.g. 1g*	*e.g. Three times a day*	*e.g. 5 days*	*e.g. 15/01/16*	*e.g. 20/01/16*	*e.g. Reason for medication. Sore throat*

MRINZ/15/A1: ICS SABA Peak Flow Management Plan V1.4 (15/06/16)

Table: Prednisolone equivalent doses reported by the British National Formulary, accessed April 2014.

Equivalent anti-inflammatory doses of corticosteroids reported by the BNF- Prednisolone 5mg equals:
Betamethasone 750 micrograms
Deflazacort 6 mg
Dexamethasone 750 micrograms
Hydrocortisone 20 mg
Methylprednisolone 4 mg
Prednisone 5 mg
Triamcinolone 4 mg

Note the BNF states: This table takes no account of mineralocorticoid effects, nor does it take account of variations in duration of action

Appendix 2 – UK sites

RCT of the efficacy and safety of an ICS/ LABA reliever therapy regimen in asthma

Short title: Novel START (Novel Symbicort Turbuhaler Asthma Reliever Therapy)

Chief Investigator (UK sites only):	Prof Ian Pavord
Sponsor (UK sites only):	University of Oxford Clinical Trials and Research Governance Joint Research Office Block 60 Churchill Hospital Old Road Headington Oxford OX3 7LE
Funder:	AstraZeneca
Chief Investigator's Signature:	

There are no potential conflicts of interest.

1. PARTICIPANT IDENTIFICATION

1.1. Trial Participants

Participants with a diagnosis of mild asthma (as per inclusion/exclusion criteria) will be recruited into the study.

1.2. Participant identification

Participants will be identified by automated searches using GP surgeries data. Potential participants will be contacted by post by their local GP surgery and patients who are interested in taking part will then contact the research team. Some participants will also contact the research team directly through advertisements (e.g. posters, press, radio, social media).

2. TRIAL PROCEDURES

a. Screening and Eligibility Assessment

Once the potential participant has confirmed their interest in the study either by returning the reply slip or by contacting the research team directly, a member of the research team will discuss the study with them (by phone or in person) and confirm their eligibility by reviewing demographics, medical history (including hospital admissions in the last 12 months) and concomitant medication. Potential participants will be then invited for a consent/enrolment visit at the research site.

a) Informed Consent

The participant must personally sign and date 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: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; 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 signature and dated 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 Chief/Principal Investigator. A copy of the

signed Informed Consent will be given to the participant. The original signed form will be retained at the trial site.

b) Baseline Assessments

Baseline assessments are detailed in schedule 7 of the protocol.

c) Subsequent Visits

Follow-up visits are detailed in schedule 7 of the protocol. The follow-ups will be arranged at the main research sites (Oxford University Hospitals NHS Foundation Trust and Nottingham University Hospitals NHS Trust) or if the patient's local GP surgery is taking part in the study, the follow-ups can be arranged there if more convenient for the patient.

If a participant withdraws from the study, or fails to return the monitors or remaining study drug as applicable, the local research team may arrange for collection of these via an appropriate courier service.

If required, the study doctors will prescribe an appropriate interim treatment for patients following their completion or withdrawal from the study until they can be assessed by their own GP.

3. SAFETY

a. Monitoring

The UK sites will be monitored by the global Sponsor. The Global Sponsor may also request that the local Sponsor (University of Oxford) monitor the UK sites.

b. UK safety reporting requirements.

Serious Adverse Events occurring at UK sites will be recorded in the eCRF from the date of consent until the last study visit, and reported to the Global Sponsor within 24 hours of Investigators becoming aware of the event. It is the responsibility of the Principal Investigators at sites to ensure all SAEs are reported as per protocol.

If the eCRF system is not available, an SAE report should be faxed to the Global Sponsor within 24 hours, to +64 4 389 5707.

The Global Sponsor will receive notification of the SAE submission via the eCRF (or fax) and will review SAEs on an ongoing basis, within 1 working calendar day (based on NZ time) of submission by the Investigator. An assessment will be made by the Global Sponsor as to the causality and expectedness of the event, based on the Investigator's report and the relevant Summary of Product Characteristics. The Global Sponsor will then inform the UK trial co-ordinating centre (ORTU) of the event and the outcome of the assessment within 1 working

day (or earlier if necessary for Oxford to meet the reporting deadlines) of the event so that SUSARs can be reported to the relevant bodies.

All SUSARs will be reported to the relevant Competent Authority and to the REC and other parties as applicable by the UK trial co-ordinating centre (ORTU). For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the UK Sponsor is first aware of the event. 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.

4. DATA: UK- specific data retention

Study data (including personal data such as names and addresses collected for the purpose of patients' identification and follow-up) will be securely stored in line with the principles of GCP standards and the Data Protection Act. During the duration of the study, all data including identifiable personal data and research data (any data collected on data worksheets prior to data entry onto the study database) at each site will be kept locally in locked cabinets, in a locked or ID-access controlled area or on secure NHS or University computers.
Data entered onto the electronic study database will be will be stored on a validated and secure database provided and maintained by the global Sponsor (Medical Research Institute of New Zealand) with servers in Australia. Participants' data will be coded, with a unique number (a study ID). The study site staff will maintain a log, linking the identifiable information (e.g. name) to the coded study data. Any data sent off site to the Sponsor (or their nominated third party) or entered onto the database will be coded and therefore will not identify a participant.

The Medical Research Institute of New Zealand (MRINZ) will provide each site with their own data, on a CD (or other appropriate storage medium), at the end of the study. All the study data will be archived securely for at least 15 years after the completion of the study either locally or off site as per local procedures. The UK-TMF will be archived securely as per the Oxford Respiratory Trials Unit SOP on archiving.

5. INSURANCE

The University has a specialist insurance policy in place which would operate in the event of any UK participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). Standard NHS cover for negligent harm is in place for NHS procedures.

6. PREDNISOLONE

For patients taking part in the study in the UK, if required due to asthma exacerbations (as described in the main protocol), patients will be prescribed prednisolone rather than prednisone as per local clinical practice.