Statistical Analysis Plan

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

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1. Abbreviations and definitions

1.1. Abbreviations:

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
ERS	European Respiratory Society
ED	Emergency Department
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
GLI	Global Lung Initiative
GP	General Practitioner
ICS	Inhaled Corticosteroid
LABA	Long Acting Beta Agonist
MDI	Metered Dose Inhaler
OTC	Over the counter
RCT	Randomised Controlled Trial
SABA	Short Acting Beta Agonist
SD	Standard Deviation
SMART	Symbicort as Maintenance and Reliever Therapy
SUSARs	Suspected Unexpected Serious Adverse Reactions

1.2. Definitions:

1.2.1. 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, emergency department (ED) visit or hospital admission) and/or
b. Worsening asthma resulting in the prescription 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.

The start date is defined as the first day of corticosteroid prescription, or high beta agonist use, or urgent medical review, during an exacerbation (whichever occurs first).

The end date is defined as the last day of corticosteroid prescription, or high beta agonist use, or urgent medical review, during an exacerbation (whichever occurs last).

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.

1.2.2. Severe Asthma Exacerbation:

A severe asthma exacerbation is:[2]

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

The start date is defined as the first day of corticosteroid prescription, or urgent medical review during an exacerbation (whichever occurs first).

1.2.3. Treatment failure:

Treatment failure is defined as:

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.

1.2.4. 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.

1.2.5. 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.

1.2.6. 24 hour period: From midnight to midnight, at local time to investigator site.

1.2.7. Hospitalisation: Admission to a hospital ward other than the ED.

1.2.8. ED Visit: Visit to the Emergency department that did not result in hospitalisation

2. Study Details

2.1. Study objectives

2.1.1. Primary objective

Primary objective	Outcome measures
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).	Asthma exacerbation rate expressed as number of exacerbations per patient per year (Primary outcome). See section 1.2.1 for asthma exacerbation definition. The proportion of exacerbations defined by each of the exacerbation criteria (See a, b and c from Section 1.2.1) The proportion of participants with at least one exacerbation Time to first exacerbation of asthma Proportion of participants withdrawn due to "treatment failure". See section 1.2.3 for definition The proportion of "treatment failures" defined by each of the criteria (See a, b and c from Section 1.2.3) Rate of severe exacerbations defined by the ATS/ERS criteria[2] Time to withdrawal due to severe exacerbation The proportion of severe exacerbations defined by each of the severe exacerbation criteria (See a and b from Section 1.2.2) Asthma Control Questionnaire (ACQ-5 score)[3] Global Initiative for Asthma (GINA) question category[4] (well, partly or un-controlled) On-treatment forced expiratory volume over 1 second (FEV_1), i.e. without withholding of bronchodilator medication On-treatment FEV_1 percentage predicted, i.e. without withholding of bronchodilator medication Fraction of exhaled nitric oxide (FeNO) (a measure of airways inflammation)[5]

Secondary objectives

Secondary objectives	Outcome measures
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).	Adverse Events: - Adverse Events - Serious Adverse Events
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.	Sensitivity analyses 1 and 2 on asthma exacerbation rate expressed as number of exacerbations per patient per year (Primary outcome). See section 1.2.1 for asthma exacerbation definition. Sub-group analysis on: Rate of asthma exacerbations, rate of severe exacerbations, and ACQ-5
To examine patterns of inhaler use with the randomised regimens.	Mean ICS dose per day (budesonide µg/day) Proportion of participants with at least 1 day of no ICS actuations Number of days of no ICS use Number of ≥7 consecutive day periods of no ICS use Number of ≥14 consecutive day periods of no ICS use Longest duration of no ICS use (days) High beta agonist use (see Section 1.2.4 for definition): - Proportion of participants with at least one episode of high use - Number of days of high use - Number of days of high use in participants with at least one day of high use - 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 - Proportion of high use episodes without medical review within 48 hours, 7 days or 14 days Marked beta agonist overuse (see Section 1.2.5 for definition): - Proportion of participants with at least one episode of marked overuse - Number of days of marked overuse - Number of days of marked use in participants with at least one day of marked overuse - 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

	- Proportion of marked overuse episodes without medical review within 48 hours, 7 days or 14 days Maximum number of beta agonist actuations in a 24 hour period Use of study medications in the 14 days prior to severe exacerbations
To determine systemic corticosteroid exposure	Total ICS dose Total oral corticosteroid dose Number of courses of oral corticosteroid per year Total systemic corticosteroid exposure*
To examine patient attitudes to and experience with the treatment regimens	Inhaler use for exercise induced asthma: - Proportion of participants who self-report use of reliever inhaler before exercise to prevent exercise induced asthma in the past 2 weeks - If yes, number of times in the past 2 weeks Qualitative interview results.
To examine patient attitudes and behaviours with medications in general	Adherence Starts with Knowledge 12 (ASK-12) questionnaire.[6]
To examine the cost effectiveness of each treatment regimen.	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.

* Composite systemic corticosteroid exposure/year in which the total ICS dose/year, converted to oral prednisone-equivalent dose for systemic effects on adrenal function,[7] 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).

2.2. Study design

The Novel START (Novel Symbicort Turbuhaler Asthma Reliever Therapy) study is a 52-week, open label, parallel group, multicentre, phase III, multinational randomised controlled trial RCT (see 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. Please see Figure 1 for the study structure. Please see Table 1 for a summary of the study visits.

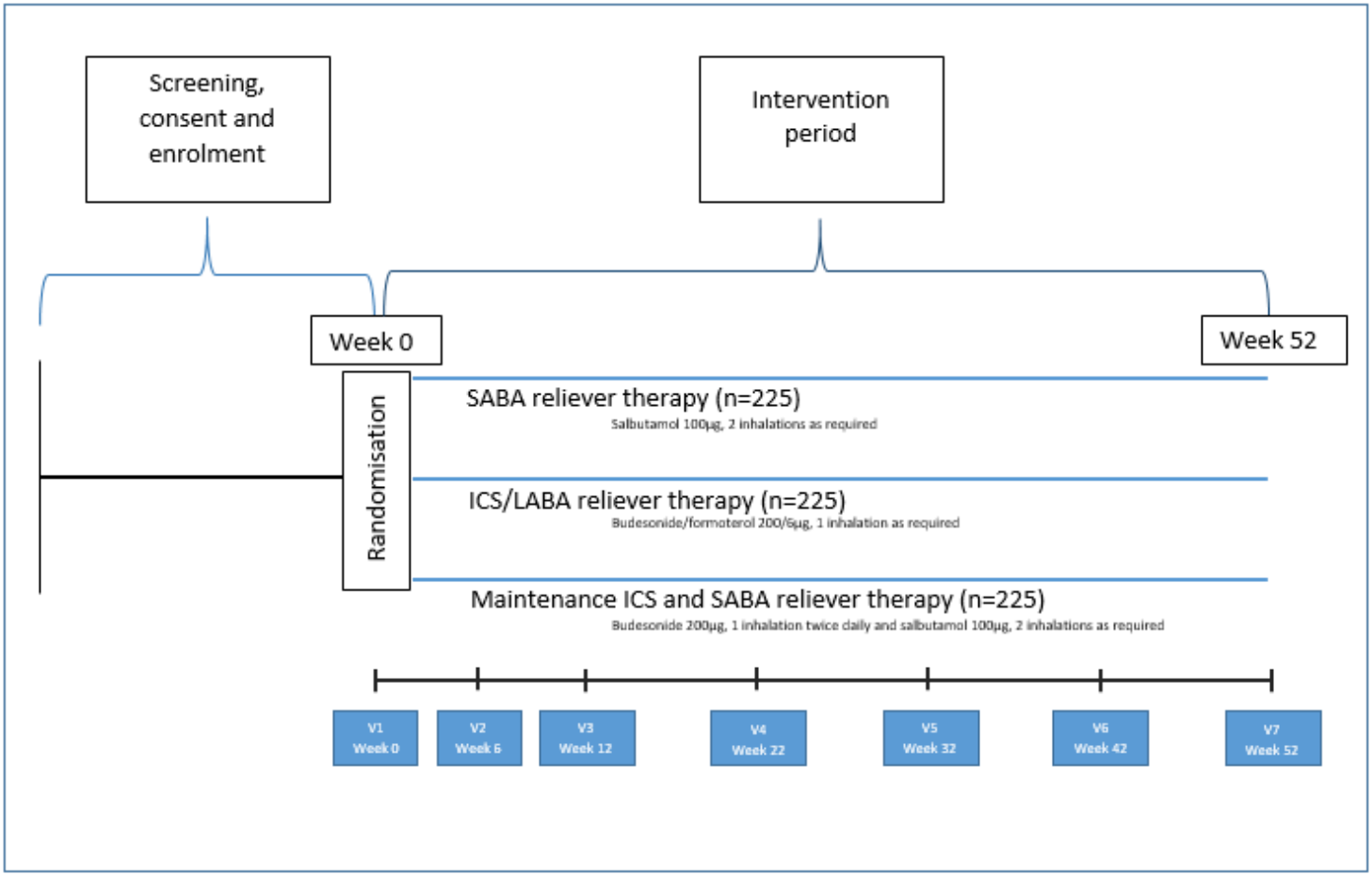

Figure 1 Study Design

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	

Table 1 Visit overview

*Performed if consent and enrolment done on a different day to Visit 1, n/a: not applicable
[#] Performed prior to spirometry
^ Investigator to inform Sponsor within 24 hours of becoming aware of an SAE (for further detail see Section 6)

2.3. 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.[8] 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[9] 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.[9] Furthermore, the reduction in exacerbations with ICS/LABA reliever therapy is expected to be greater than that due to ICS/SABA reliever[10] on which the power calculations are based.[9]

Sample size re-estimation at the interim analysis point

We plan a re-estimation of the required sample size for the trial at the interim analysis point. The currently planned 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.

The interim re-estimation of sample size will be performed blinded.

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3. Analysis sets

3.1. Participant inclusion in analysis

The study is of intention to treat design. All randomised participants will be included in analyses, unless consent to use the data is withdrawn.

3.2. Early termination

3.2.1. Where specified, data will be analysed with adjustment for treatment period.

3.2.2. When a participant is withdrawn, data collected from the electronic monitors after the date of withdrawal will not be used in medication use analyses. An exception to this is the situation where a participant is withdrawn due to an exacerbation. In this situation, unless another cause for withdrawal occurs prior or data collection is stopped, electronic monitor data collected until the last day of the participant's exacerbation will be used.

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4. Data collection

4.1. Participant recruitment

4.1.1. A paper pre-screening log will include:

4.1.1.1. Any patient assessed for eligibility

4.1.1.2. Outcome:

- Non-inclusion: Reason for and date
- Enrolment: Number and date

4.1.2. An enrolment log will include:

4.1.2.1. Participants who have provided consent

4.1.2.2. The participant's Enrolment number

4.1.2.3. Outcome:

- Exclusion: Reason and date
- Randomisation: Number and date

4.1.2.4. Data on the total number of enrolled participants excluded, with reason or exclusion will be uploaded to the eCRF

4.1.3. A randomisation log will include:

4.1.3.1. Randomisation number as allocated from the eCRF

4.1.3.2. Date of randomisation

4.2. Demographic data, patient characteristics and baseline values

All data will be recorded on the eCRF unless otherwise stated.

The following will be collected on the day of visit 1:

4.2.1. Data related to inclusion criteria:*

4.2.1.1. Date of birth and age.#

4.2.1.2. If the participant self-reports a doctor's diagnosis of asthma.

4.2.1.3. If the participant has had a severe exacerbation (See definition in Section 1.2.2) in the past 12 months, and if yes, how many. #

4.2.1.4. Use of a SABA* in the previous 4 weeks: #

4.2.1.4.1. Usual number of actuations per occasion

4.2.1.4.2. Average number of occasions per week, in the past 4 weeks

4.2.1.4.3. If the participant has used SABA on average ≤ 2 occasions per day, in the past 4 weeks, eligibility determined on stratification by presence or absence of severe exacerbations in last 12 months, as follows:

4.2.1.4.3.1. If there is 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, in participants who have had no severe exacerbations in the last 12 months.

4.2.1.4.3.2. If there is self-reported use of a SABA on average ≤2 occasions (maximum of 4 actuations) per day in the previous 4 weeks, in participants with a history of a severe exacerbation in the last 12 months.

4.2.1.5. If the participant is willing and able to give informed consent for participation in the trial.

4.2.1.6. If, in the Investigator's opinion, the participant is able and willing to comply with all trial requirements.

4.2.1.7. If the participant is willing to allow their General Practitioner and/ or consultant, if appropriate, to be notified of participation in the trial.

For inclusion the participant must: #

1. Be 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. Be willing and able to give informed consent for participation in the trial.

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

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

[#] Times must relate to the date of Visit 1.

Note Eligibility will be checked through a formulae on the electronic case report form (eCRF), using data from 4.2.1.1 and 4.2.1.7.

4.2.2. <u>Exclusion criteria* check, as to whether there is:</u>

4.2.2.1. 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.

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

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

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

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

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

4.2.2.7. 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.

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

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

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

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

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

4.2.2.13. An on treatment FEV1 ≤50% of predicted at Visit 1 (predicted values must be calculated using the Global Lung Function Initiative equations[18]).

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

* For inclusion the participant must NOT report and/ or demonstrate any of the above.

4.2.3.

4.2.4. Baseline/participant characteristic data

4.2.4.1. ACQ-5[3 #]

4.2.4.1.1. Results to individual questions

4.2.4.1.2. Overall score

4.2.4.2. ASK-12[6 #]

4.2.4.2.1. Results to individual questions

4.2.4.2.2. Overall and sub-scores

4.2.4.3. GINA questions[4]

4.2.4.3.1. Results to individual questions

4.2.4.3.2. Overall symptom control category

See appendix 2 for patient reported outcome assessment data processing

In the past four weeks, has the patient had:	Well controlled	Partly controlled	Uncontrolled
Daytime symptoms more than twice/week (yes or no)	None of these	1-2 of these	3-4 of these
Any night waking due to asthma (yes or no)			
Reliever needed* more than twice/week (yes or no)			
Any activity limitation due to asthma (yes or no)			

Table 2: GINA level of asthma symptom control[4]
* Excludes reliever taken before exercise.

4.2.4.4. Gender

4.2.4.5. Ethnicity based on Global Lung Initiative (GLI) classification (note multiple ethnicities may be selected):

- Caucasian
- African American
- North East Asian
- South East Asian
- Other

4.2.4.6. Additional ethnicity data for participants in Australia or New Zealand (note multiple ethnicities may be selected):

- Maori ethnicity
- Pacific Islander ethnicity
- Aboriginal or Torres Strait Islander origin
- None of the above

4.2.4.7. Smoking history:

4.2.4.7.1. Current status (one of the following):

- Current
- Ex
- Never

4.2.4.7.2. Date of last cigarette

4.2.4.7.3. Cigarette pack years

Note this is to be calculated by the investigator by multiplying the number of packs of cigarettes (1 pack= 20 cigarettes) smoked per day by the number of years the person has smoked.

4.2.4.8. Asthma history:

4.2.4.8.1. Age of diagnosis

4.2.4.8.2. Whether the participant currently uses an asthma action plan, and whether it is with or without peak flow measurement

4.2.4.8.3. Number of courses of systemic corticosteroids for asthma in the last year, and number of days per course

4.2.4.8.4. Number of ED visits for asthma in the last year, and for each visit whether a systemic corticosteroid was administered

4.2.4.8.5. Number of hospital admissions* for asthma ever

4.2.4.8.6. Whether the participant has ever previously been prescribed ICS inhalers, and if so when last used.

4.2.4.8.7. Whether the participant usually uses a spacer.

* See Section 1 for definition

4.2.4.9. Other medical conditions:

4.2.4.9.1. Condition

4.2.4.9.2. Past or current

4.2.4.9.3. Medication required (yes or no)

4.2.4.9.4. Category:

- Cardiovascular
- Respiratory
- Gastro-intestinal
- Renal/urological
- Endocrine
- Neurological
- Previous surgery
- Musculoskeletal
- Skin conditions
- Allergy

- Other (to state)

4.2.4.10. Medications:

4.2.4.10.1. Medication name, dose, units, route

4.2.4.10.2. Date started

4.2.4.10.3. Date stopped (if applicable)

4.2.4.11. Sinusitis history (yes or no)

Sinusitis (Rhinosinusitis) is classified as 'yes' if there are two or more symptoms, one of which should be nasal obstruction or discharge (anterior/posterior nasal drip), which occur over 12 or more weeks of the last year, based on ARIA:[12] - blockage/congestion - discharge: anterior/postnasal drip (which can be discoloured) - facial pain/pressure - reduction or loss of smell

4.2.4.12. Number of years of schooling the participant has completed

4.2.4.13. Highest education level (one of the following):

- Primary School
- Middle/ Intermediate School
- High School
- Some College (Trade/Professional/Community)
- Three or more years of College/University
- None
- Unknown

4.2.4.14. Weight (kg) and height (m)

Note this data will be used by the eCRF to calculate body mass index which is calculated by the formula: [Weight (in kg)] / [Height (in m)]^2

4.2.5. <u>FeNO:</u>

4.2.5.1. Value (ppb)

4.2.5.2. Time of FeNO

4.2.5.3. Whether FeNO was compliant with ATS/ERS criteria[5]

4.2.6. Spirometry:

4.2.6.1. Best FEV_1 and forced vital capacity (FVC)

Note this data, combined with ethnicity, age, gender and height data will be used by the eCRF to calculate percentage predicted values using the method outlined in appendix 1.

4.2.6.2. Time of spirometry

4.2.6.3. Name, time, date, dose and number of actuations of bronchodilator medication(s) in past 24 hours

4.2.6.4. Whether spirometry was compliant with ATS/ERS criteria[13]

4.2.7. FBC sample:

4.2.7.1. Time taken

4.2.7.2. Whether processing occurred in accordance with protocol/study manual

4.2.7.3. Eosinophil count (10^9/L)

4.2.8. Periostin sample:

4.2.8.1. Time taken

4.2.8.2. Whether processing occurred in accordance with protocol/study manual

4.2.8.3. Periostin value (ng/mL)*

* Note Periostin value not entered on eCRF by investigator, but obtained by Sponsor directly from Covance.

4.3. Outcome data

The following may be collected at Scheduled Visits 1-7 or Unscheduled visits (see Table 1 for detail):

4.3.1. ACQ-5[3]

4.3.1.1. Results to individual questions

4.3.1.2. Overall score

4.3.2. ASK-12[6]

4.3.2.1. Results to individual questions

4.3.2.2. Overall and sub-scores

4.3.3. GINA questions[4]*

4.3.3.1. Results to individual questions

4.3.3.2. Overall symptom control category

* See Table 2 for question details.

4.3.4. Cost effectiveness

4.3.4.1. Number of days off work/study/school since last Visit

Note the medical costs (medications, emergency medical and ED visits, hospital admissions), and non-medical costs (days off work/study/school) will be estimated based on the data from the Asthma Exacerbation Log, the Electronic Monitor Devices, Concomitant Medications Log and self-reported days off work/study/school captured at each visit. Translation into cost will be estimated at the end of the study, for each country and presented in US Dollars.

4.3.5. Medications:

4.3.5.1. Whether prescribed randomised treatment is modified.*

* For a definition of modified see 1.2.3.

Note this data will be entered on to the eCRF Concomitant Medication log

4.3.6. FeNO (Visit 1, 3 and 7 only):

4.3.6.1. Value (ppb)

4.3.6.2. Time of FeNO

4.3.6.3. Whether FeNO was compliant with ATS/ERS criteria[5]

4.3.7. Spirometry:

4.3.7.1. Best FEV_1 and FVC

Note this data, combined with ethnicity, age, gender and height data will be used by the eCRF to calculate percentage predicted values using the method outlined in appendix 1.

4.3.7.2. Time of spirometry

4.3.7.3. Time and date of last bronchodilator medication(s)

4.3.7.4. Whether spirometry was compliant with ATS/ERS criteria[13]

4.3.8. End of study

4.3.8.1. Date of completion

4.3.8.2. Reason for completion:

4.3.8.2.1. Participant completed study protocol

4.3.8.2.2. Participant withdrawn from study prior to end of protocol, if yes, a withdrawal form will be completed (See section 4.7).

4.4. Asthma exacerbation log

For each time the participant has an exacerbation the following will be recorded:

4.4.1.1. Type of exacerbation (exacerbation or severe exacerbation)

4.4.1.2. Exacerbation start date

4.4.1.3. Exacerbation end date

4.4.1.4. Exacerbation events (usual GP, after hours, ED, hospitalisation, or high use episode)* and for each event:

4.4.1.4.1. Start date

4.4.1.4.2. End date

4.4.1.4.3. Whether oral steroids were taken, and if yes:

4.4.1.4.3.1. Start date

4.4.1.4.3.2. Stop date

4.4.1.4.3.3. Whether oral steroids were taken for 3 or more days

* See Section 1 for definition

Note: Data entered on high use entered into the eCRF by the Investigator will be used to evaluate withdrawal criteria and adverse events during the study. The Investigator will discount data from visit days and that fulfils dose dumping criteria[15] as part of reviewing the electronic data within the eCRF , and this data will not be entered into the Asthma Exacerbation Log. Dose dumping criteria is defined as greater than or equal to 100 actuations in a three hour period.

The Investigator will assess the medication use data that is displayed in the eCRF, for the purposes of determining high-use episodes. The data collected by each electronic monitor device is uploaded into the SmartInhalerLive system and transferred to the eCRF. As part of the transfer the data undergoes processing to remove medication logs that are within 3 seconds of another medication log – see Appendix 4 for more information.

At the end of the study data relating to inhaler use will be formally calculated using data downloaded from the eCRF and/or SmartInhalerLive to an electronic database.

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

The start date is defined as the first day of corticosteroid use, or high beta agonist use, or urgent medical review, during an exacerbation (whichever occurs first).

The end date is defined as the last day of corticosteroid use, or high beta agonist use, or urgent medical review, during an exacerbation (whichever occurs last).

4.5. AE and SAE logs

4.5.1. AEs:

Whether there were any AEs, and if yes, for all AEs:

4.5.1.1. Event term

4.5.1.2. Maximum Severity (mild, moderate or severe)

4.5.1.3. Date when AE started

4.5.1.4. Outcome (ongoing, resolved, resolved with sequelae) and date of outcome (for resolved and resolved with sequelae only)

4.5.1.5. Relationship to study product (related, unrelated, unknown)*

4.5.1.6. Expectedness (expected, unexpected)[#]

4.5.1.7. Study product (continued, interrupted (stop and restart date), stopped (stop date))

4.5.1.8. Whether concomitant medication(s) taken

4.5.1.9. Whether AE is an SAE

4.5.1.10. Whether AE caused subject to withdraw from study

4.5.1.11. Whether AE is an exacerbation of asthma

* AEs considered definitely related, probably related, or possibly related will be classified as 'related'.

Expectedness is assessed by the Investigator based on the data available from the Summary of Product Characteristics (or similar document) for each study medication.

4.5.2. SAEs:

For SAEs the following data will be recorded in addition to the data from 4.5.1:

4.5.2.1. Date AE became SAE

4.5.2.2. Event narrative/ details

4.5.2.3. Date and time investigator became aware of SAE

4.5.2.4. SAE category (death, immediately life threatening, persistent/significant disability/incapacity, congenital anomaly, serious as assessed by investigator, hospitalisation/prolonged hospitalisation, other (state))

4.5.2.5. Date of admission (hospitalisation/prolonged hospitalisation only)

4.5.2.6. Date of discharge (hospitalisation/prolonged hospitalisation only)

4.5.2.7. Probable cause of death, date of death and any autopsy results (if applicable)

Investigators are required to notify the Sponsor within 24 hours of becoming aware of an SAE (see Section 7).

The DSMC will review reported SAEs as per section 8. AEs relating to asthma and asthma exacerbations will be reported as per section 7.

Any event fulfilling expedited reporting requirements (e.g. SUSARs) will be reported by the Investigator/ Local Sponsor as per local/ country requirements and the Sponsor will report all expedited reports to AstraZeneca.

4.6. Concomitant medications log

4.6.1. Whether there any other new medications or changes to (including concomitant), and if yes, for all changes:

4.6.1.1. Medication name, dose, units, route

4.6.1.2. Reason for medication use (AE, medical history, other stated)

4.6.1.3. Date started

4.6.1.4. Date stopped (if applicable)

Concomitant medications will be cross checked against adverse events, exacerbations of asthma and medical history items as applicable. Concomitant medications may be given to a participant as required by the investigator, or by their usual health care provider and will be recorded as above in the Concomitant Medications Log.

4.7. Withdrawal form

4.7.1. Reason for withdrawal will be recorded as one or more of the following:

- The participant was found to be incorrectly enrolled in the study
- Treatment failure:
  - The participant experienced a severe exacerbation (see definition in Section 1)
  - The participant meets any of the exacerbation criteria on three separate occasions during the study period (see definition in Section 1)
  - Randomised treatment was modified* by the participant's GP or other healthcare provider during the study. Modifications are to be recorded on the concomitant medication log.
- The participant obtained OTC SABA
- The participant decided to discontinue (withdrawal of informed consent)
- The participant became pregnant
- Any safety reason as judged by the investigator (to be stated)
- The participant was lost to follow up
- The participant withdrew due to an AE (AE number to be stated)
- Sponsor decision (to be stated)
- Other (to be stated)

* For a definition of modified see 1.2.3. If the reason for withdrawal is modification of randomised treatment, the following options will be recorded, depending on randomisation group:

<u>SABA reliever therapy</u>

- Change in: SABA
- Addition of:
    - ICS
    - LABA
    - ICS/LABA
    - leukotriene receptor antagonists
    - mast cell stabilisers
    - theophylline
    - monoclonal antibody therapy
    - other

ICS/LABA reliever therapy

- Change in:
    - ICS/LABA (increase in Symbicort dose per actuation, change to SMART regimen or change in product (e.g. Fluticasone Propionate/ Salmeterol))

- Addition of:
    - SABA
    - ICS
    - LABA
    - leukotriene receptor antagonists
    - mast cell stabilisers
    - theophylline
    - monoclonal antibody therapy
    - other

Maintenance ICS and SABA reliever therapy

- Change in:
    - SABA
    - ICS (increased maintenance dose or change in product (e.g. fluticasone))

- Addition of:
    - LABA
    - ICS/LABA
    - leukotriene receptor antagonists
    - mast cell stabilisers
    - theophylline
    - monoclonal antibody therapy
    - other

4.8. Medication and electronic monitor dispensing and collection

4.8.1. Date, type and number of inhalers dispensed (excludes visit 7)

4.8.2. Date, type and number of inhalers collected (excludes visit 1)

4.8.3. Date and ID of all electronic monitors dispensed (excludes visit 7)

4.8.4. Date and ID of all electronic monitors collected (excludes visit 1)

Data will be captured on each visit eCRF for all medications and electronic monitors that are dispensed and collected. Any dispensing or collection errors made by the Investigator will be captured on the Protocol Deviation Log. For clarity, this does not refer to errors occurring within the electronic monitors (e.g. failure to pass a pre-dispensing check), which will be captured in the Electronic Monitor Log.
Investigators will assign a unique code to each inhaler dispensed, comprising the Site ID, Study ID and a sequential number (e.g. SITE/0001/001). Each inhaler will have a corresponding electronic monitor assigned to it, with the ID number recorded as part of source data and within the eCRF as above.

4.9. Electronic monitor Log

4.9.1. Monitors lost to follow up

4.9.1.1. Monitor ID

4.9.2. Monitor failures

4.9.2.1. Monitor ID

4.9.2.2. Date of test

4.9.2.3. Check type (initial site, pre-dispensing, collection)

4.9.2.4. Reason (low battery, missing actuation, spurious actuation, upload difficulty, obvious external damage to monitor, other (to state))

4.9.2.5. Allocation to a subject (with Randomisation ID if applicable)

The electronic monitor log will capture all monitor failures, regardless of whether they were associated with a subject. Monitors will be reviewed by Adherium, in order to attempt to obtain data for those monitors that failed but had been dispensed to a subject.

4.10. Protocol deviation log

4.10.1. Date of deviation

4.10.2. Reason for deviation:

- Enrolment of ineligible subject
- Study medication error
- FeNO not performed according to ATS/ERS
- Spirometry not performed according to ATS/ERS
- Subject not withdrawn in error
- Laboratory sample issue: FBC
- Laboratory sample issue: Periostin
- Other (to be stated)

4.10.3. Description of event

4.10.4. Corrective action

Reasons for deviations will be summarised as above, for each treatment group. It is noted there will be other minor deviations from protocol (not affecting the study results) which may be recorded during the study. These will not be formally presented either to the DSMC or in the final report, however they will be checked and recorded as part of study monitoring. These include but are not limited to:

- Missing data from incomplete assessments
- Visits performed outside of window

5. Outcome variables

Outcome variables are taken directly from data entered by the Investigator into the eCRF unless otherwise stated

5.1. Primary outcome variable

5.1.1. Asthma exacerbation* rate expressed as number of exacerbations per patient per year (Primary outcome). An asthma exacerbation is defined as:

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

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

5.1.1.3. 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]

* See section 1 for further definition details.

5.2. Participant characteristics/baseline data

5.2.1. History

5.2.1.1. ACQ-5[3]

5.2.1.2. ASK-12[6]

5.2.1.3. GINA questions[4]

5.2.1.4. Gender

5.2.1.5. Ethnicity

5.2.1.6. Smoking status

5.2.1.7. Pack years

5.2.1.8. Age of asthma diagnosis

5.2.1.9. Whether the participant currently uses an asthma action plan, and whether it is with or without peak flow measurement

5.2.1.10. Number of courses of prednisone in the last year, and number of days per course

5.2.1.11. Number of previous ED visits for asthma requiring systemic corticosteroids in the last year

5.2.1.12. Number of hospital admissions for asthma ever

5.2.1.13. Whether the participant has ever previously been prescribed ICS inhalers, and if so when last used.

5.2.1.14. Other medical conditions

5.2.1.15. Medications

5.2.1.16. Sinusitis history

5.2.1.17. Highest education level

5.2.2. Measurements

5.2.2.1. Weight and height

5.2.2.2. BMI

5.2.2.3. FeNO

5.2.2.4. Best FEV1 and FVC

5.2.2.5. Eosinophil count

5.2.2.6. Periostin level

5.3. Secondary outcome variables

5.3.1. Clinical outcomes

5.3.1.1. The proportion of exacerbations defined by each of the above criteria (5.1.1.1-5.1.1.3)

5.3.1.2. The proportion of participants with at least one exacerbation

5.3.1.3. Time to first exacerbation of asthma

Calculated using study database as: ([start date of the first exacerbation*]-[Visit 1 date]) *See definition in section 1.

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

5.3.1.4.1. One severe exacerbation, or
5.3.1.4.2. Three exacerbations, or

5.3.1.4.3. If randomised treatment is modified by the participant's GP or other healthcare provider during the study (see section 1.2.3 for detail).

5.3.1.5. The proportion of "treatment failures" defined by each of the above criteria (5.3.1.4.1-5.3.1.4.3)

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

5.3.1.6.1. The prescription of systemic corticosteroids for at least 3 days, or
5.3.1.6.2. Hospitalisation or ED visit because of asthma, requiring systemic corticosteroids

5.3.1.7. Time to withdrawal due to severe exacerbation defined by the ATS/ERS criteria[2]

Calculated using study database as: ([start date of the first severe exacerbation*]-[Visit 1 date]) *See definition in section 1.

5.3.1.8. The proportion of severe exacerbations defined by each of the above criteria (5.3.1.6.1, 5.3.1.6.2)

5.3.1.9. Asthma Control Questionnaire (ACQ-5 score)[3]

5.3.1.10. GINA question category[4] (well, partly or un-controlled)

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

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

5.3.1.13. FeNO (a measure of airways inflammation)[5]

5.3.2. <u>Medication use</u>

Medication use data is calculated using algorithms applied to data directly downloaded from the SmartInhalerLive website and the eCRF.

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

5.3.2.2. Periods without ICS use:

5.3.2.2.1. Proportion of participants with at least 1 day of no ICS actuations
5.3.2.2.2. Number of days of no ICS use
5.3.2.2.3. Number of ≥7 consecutive day periods of no ICS use
5.3.2.2.4. Number of ≥14 consecutive day periods of no ICS use
5.3.2.2.5. Longest duration of no ICS use (days)

5.3.2.3. Total oral corticosteroid dose

5.3.2.4. Number of courses of oral corticosteroid per year

5.3.2.5. 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,[7] 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 2).

5.3.2.6. High beta agonist use:

5.3.2.6.1. Proportion of participants with at least one episode of high use
5.3.2.6.2. Number of days of high use
5.3.2.6.3. Number of days of high use in participants with at least one day of high use
5.3.2.6.4. Number of days of high use without medical review within 48 hours, 7 days or 14 days in participants with at least one high use episode
5.3.2.6.5. Proportion of high use episodes without medical review within 48 hours, 7 days or 14 days

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

5.3.2.7.1. Proportion of participants with at least one episode of marked overuse
5.3.2.7.2. Number of days of marked overuse
5.3.2.7.3. Number of days of marked use in participants with at least one day of marked overuse
5.3.2.7.4. Number of days of marked overuse without medical review within 48 hours, 7 days or 14 days in participants with at least one marked overuse episode
5.3.2.7.5. Proportion of marked overuse episodes without medical review within 48 hours, 7 days or 14 days

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

5.3.2.9. Use of study medications in the 14 days prior to severe exacerbations, as previously defined,[14] 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.

5.3.2.10. Inhaler use for exercise induced asthma

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

5.3.3. Adverse events

5.3.3.1. Adverse events.

5.3.3.2. Serious adverse events.

5.3.4. Cost-effectiveness

5.3.4.1. 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.

5.3.5. Patient attitudes

5.3.5.1. ASK-12 questionnaire.[6]

5.3.5.2. Qualitative interview results.

5.4. Other outcomes collected

5.4.1. Concomitant medications

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6. Statistical analysis

General Principles

Provisionally SAS version 9.3 will be utilised, however should there be a requirement for a different version or different program to analyse particular variables or data, then this will be specified in the statistical analysis report.

All tests will be 2-sided and at 5% level of significance unless otherwise stated.
For all repeated measures analyses, missing at random (MAR) will be assumed.

In general continuous variables will be summarised by the number of observed and missing values, mean and standard deviation, median and inter-quartile range, and minimum to maximum; and other quantiles as appropriate. Categorical variables will be described by numerators and denominators with proportions. Ordinal variables may be described in both ways. Time variables will be summarised graphically by survival plots. For continuous variables appropriate plots such as frequency histograms and box-plots may be used.

Primary outcome variable analysis:

This will be an 'intention to treat' superiority analysis. The primary analysis of the primary outcome variable of asthma exacerbation [5.1.1 (SAP), 9.1.1 (protocol)] 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. The dependent variable will be exacerbation rate, the independent variable will be treatment. 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

The primary hypothesis test is whether there is evidence that any of the exacerbation rates are different. The pre-specified comparisons are nominated above. The pre-specified comparisons will be estimated, even if the overall hypothesis of at least one arm different is not statistically significant, so that type II error can be evaluated based on the confidence intervals of the pre-specified comparisons.

SAS Proc GENMOD will be used.

Two sensitivity analyses will be performed:

Sensitivity analysis 1:

The same Poisson regression model will be used as described for the primary outcome analysis with the addition of two co-variates. These will be 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:

The same Poisson regression model will be used as described for the primary outcome analysis with the addition of the following co-variates:

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

Sex and smoking status (defined as current, ex, and never) will be fit as categorical variables and the remainder treated as continuous variables.

If the data is highly skewed FeNO and serum periostin level will be fitted on the logarithm scale for consistency.

If the outcome data are sparse it may not be possible to include all of the confounding variables for the second sensitivity analysis. Co-variates will be included in the order of priority as listed.

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, the independent variable will be treatment and dependent variables will be as follows:

- Rates of severe exacerbation by the ATS/ERS criteria [5.3.1.6 (SAP), 9.2.1.6 (protocol)]
- Number of days of no ICS use [5.3.2.2.2 (SAP), 9.2.2.2.2 (protocol)]
- Number of days of high use [5.3.2.6.1 (SAP), 9.2.2.6.2 (protocol)]
- Number of days of high use in participants with at least one day of high use [5.3.2.6.3 (SAP), 9.2.2.6.3 (protocol)]
- 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 [5.3.2.6.4 (SAP), 9.2.2.6.4 (protocol)]
- Number of days of marked over use [5.3.2.7.2 (SAP), 9.2.2.7.2 (protocol)]
- Number of days of marked overuse in participants with at least one day of marked overuse [5.3.2.7.3 (SAP), 9.2.2.7.3 (protocol)]
- 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 [5.3.2.7.4 (SAP), 9.2.2.7.4 (protocol)]
- Number of courses of oral corticosteroid per year [5.3.2.4 (SAP), 9.2.2.4 (Protocol)]

Descriptive data:

- Use of study medications in the 14 days prior to severe exacerbations [5.3.2.9 (SAP), 9.2.2.9 (protocol)]

The descriptive variables will be displayed as mean, median, Standard Deviation, interquartile range, minimum and maximum, in addition to individual patient data.

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 [5.3.1.3 (SAP), 9.2.1.3 (protocol)]
- Time to withdrawal due to severe exacerbation [5.3.1.7 (SAP), 9.2.1.7 (protocol)]

The Kaplan-Meier plots and the summaries of quantiles of survival will be produced using Proc LIFETEST in SAS.

Simple t-tests by time of measurement and mixed linear models for repeated measures by time, dependent variables will be as follows:

- ACQ-5 score [5.3.1.9 (SAP), 9.2.1.9 (protocol)]
- FEV_1 [5.3.1.11 (SAP), 9.2.1.11 (protocol)]
- FEV_1 percentage predicted [5.3.1.12 (SAP), 9.2.1.12 (protocol)]

- 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 [5.3.1.13 (SAP), 9.2.1.13 (protocol)]
- 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 [5.3.2.3 (SAP), 9.2.2.3 (protocol)]. 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 per year are likely to be on a logarithm transformed scale [5.3.2.5 (SAP), 9.2.2.5 (protocol)]
- Simple estimation of costs [5.3.4.1 (SAP), 9.2.4.1 (protocol)]

For the mixed linear models the fixed effects will be: treatment (a categorical predictor variable), baseline measurements of continuous variables, and time of measurement (as a categorical predictor) as well as the interaction between treatment and time. Individual participants will be treated as a random intercept effect. Proc MIXED will be used in SAS.

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

- Mean ICS dose per day [5.3.2.1. (SAP), 9.2.2.1 (protocol)]

For the general linear model the fixed effects will be: treatment (a categorical predictor variable), baseline measurements of continuous variables, and time of measurement (as a categorical predictor) as well as the interaction between treatment and time. Individual participants will be treated as a random intercept effect. Proc MIXED will be used in SAS.

<u>Comparison of proportions by logistic regression, dependent variables as follows:</u>

- The proportion of exacerbations defined by each criterion [5.3.1.1 (SAP), 9.2.1.1, (protocol)]
- The proportion of participants with at least one exacerbation [5.3.1.2 (SAP), 9.2.1.2 (protocol)]
- The proportion of participants withdrawn due to “treatment failure” [5.3.1.4 (SAP), 9.2.1.4 (protocol)]
- The proportion of “treatment failures” defined by each criteria [5.3.1.5 (SAP), 9.2.1.5 (protocol)]
- The proportion of severe exacerbations defined by each criteria [5.3.1.8 (SAP), 9.2.1.8 (protocol)]
- The proportion of participants with at least one day of no ICS use [5.3.2.2.1 (SAP), 9.2.2.2.1 (protocol)]
- The proportion of participants with at least one episode of high use [5.3.2.6.1 (SAP), 9.2.2.6.1 (protocol)]
- The proportion of high use episodes without medical review within 48 hours, 7 days or 14 days. [5.3.2.6.5 (SAP), 9.2.2.6.5 (Protocol)]
- The proportion of participants with at least one episode of marked overuse [5.3.2.7.1 (SAP), 9.2.2.7.1 (protocol)]
- The proportion of marked overuse episodes without medical review within 48 hours, 7 days or 14 days. [5.3.2.7.5 (SAP), 9.2.2.7.5 (Protocol)]
- The proportion of participants who self-report use of reliever inhaler before exercise to prevent exercise induced asthma in the past two weeks [5.3.2.10.1 (SAP), 9.2.2.10.1 (protocol)]

The comparison of proportions will be by logistic regression, with the treatment as a categorical predictor variable. Proc Logistic will be used in SAS.

Other:

- GINA question category [5.3.1.10 (SAP), 9.2.1.10 (protocol)] and ASK-12 [5.3.5.1 (SAP), 9.2.5.1 (protocol)] category 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) [5.3.2.2.5 (SAP), 9.2.2.2.5 (protocol)], the maximum number of beta agonist actuations in a 24 hour period [5.3.2.8 (SAP), 9.2.2.8 (protocol)], number of times a reliever inhaler was used before exercise to prevent exercise induced asthma in the past 2 weeks [5.3.2.10.2 (SAP), 9.2.2.10.2 (protocol)], 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) [5.3.2.2.3, 5.3.2.2.4 (SAP), 9.2.2.2.3, 9.2.2.2.4 (protocol)] 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.
- For ASK-12 [5.3.5.1 (SAP), 9.2.5.1 (protocol)] the analysis of change in overall score, domains scores and responses to individual questions will be descriptive.Adverse events [5.3.3.1 (SAP), 9.2.3.1 (protocol)] will be summarised by the number and percentage of participants with at least 1 adverse event.
- Serious adverse events [5.3.3.1 (SAP), 9.2.3.2 (protocol)] will be summarised by the number and percentage of participants with at least 1 serious adverse event.

Sub-group analysis

We will conduct sub-group analyses of interactions between baseline variables and treatment for each of the three outcome variables: rate of exacerbations, rate of severe exacerbations, and end of study ACQ-5. The baseline variables will be: 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, FEV1 % 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.[16]

Subgroup analyses by country will be undertaken for baseline characteristics and cost.

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

Supplementary Analyses

1. For the primary analysis of the primary outcome variable a sensitivity analysis will be conducted, excluding exacerbations that have not been able to be 100% source data verified.

Wherever severe exacerbations are analysed, a separate sensitivity analysis will be performed using the interpretation of a severe exacerbation that has been used in the PRACTICAL study[19] ie self-reported use of corticosteroids for 3 or more days because of asthma, rather than prescription of systemic corticosteroid for at least 3 days because of asthma.

2. Additional analyses will be conducted to identify significant exacerbation predictors: these analyses will be pre-specified in a subsequent SAP.

7. Specific detail regarding AEs and SAEs

7.1. 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.

7.2. 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.

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.

7.3. 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.

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8. Data Safety Monitoring Committee (DSMC) and interim analysis

A DSMC will be established, which is independent from the study team. The DSMC will review all serious adverse events (pooled) 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 and followed up. 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 DSMC will review protocol deviations and withdrawals for pooled data and have the capacity to request an analysis with masked treatment code for any variable amongst the treatment arms.

Unblinded data can be made available at the DSMCs request.

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9. **Monitoring**

The Sponsor will monitor the study in accordance with Good Clinical Practice guidelines and the Study Monitoring Plan. A 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 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.

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Appendix

APPENDIX 1: METHOD FOR CALCULATING PREDICTED NORMAL FEV1

1. **Predicted normal FEV1 values will be calculated according to Quanjer et al 2012.[18]**

The equation for calculating predicted normal FEV1 is of the form:
PN FEV1 = exp(a0 + a1·ln(Height) + a2·ln(Age) + a3·AfrAm + a4·NEAsia + a5·SEAsia + a6·Other + Mspline)

The following input variables are used in the predicted normal FEV1 equation:

- Height is the patient's height in cm (to the nearest 0.1 cm, recorded at Visit 1)
- Age is the patient's age in years (to the nearest 0.1 years) – this should be recalculated based on the visit date and patient's date of birth
- AfrAm is equal to 1 if the patient's ethnic population is African American, 0 otherwise
- NEAsia is equal to 1 if the patient's ethnic population is North East Asian, 0 otherwise
- SEAsia is equal to 1 if the patient's ethnic population is South East Asian, 0 otherwise
- Other is equal to 1 if the patient's ethnic population is Other/Mixed, 0 otherwise

The constants a0, a1, a2, a3, a4 and a5 depend on the patient's sex, as outlined in the table below:

CONSTANT	MALES	FEMALES
A0	-10.3420	-9.6987
A1	2.2196	2.1211
A2	0.0574	-0.0270
A3	-0.1589	-0.1484
A4	-0.0351	-0.0149
A5	-0.0881	-0.1208
A6	-0.0708	-0.0708

The final term in the predicted normal FEV1 equation, Mspline, is obtained a lookup table based on the patient's age and sex.
For patients aged 25 or over, the following equation may be used to approximate Mspline in place of the lookup tables:
Mspline = b0 + b1·(Age/100) + b2·(Age/100)2 + b3·(Age/100)3 + b4·(Age/100)4 + b5·(Age/100)5
where b0, b1, b2, b3, b4 and b5 are constants that depend on the patient's sex, as outlined in the table below:

CONSTANT	MALES	FEMALES
B0	0.3901	0.0552
B1	-1.0579	1.6029
B2	1.4743	-6.4845
B3	-2.1077	10.2723
B4	-0.1215	-9.8630
B5	0.8873	3.8802

2. Lookup table for final term

The following lookup table is used for determining the value of Mspline in the equation for calculating predicted normal FEV1. For ages other than those listed here, the value is derived using linear interpolation of the two nearest ages (i.e. those ages either side of the patient's actual age).

The lookup table is available from the Global Lung Function Initiative website (URL at the time of writing: http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/quanjer-gli-2012-regression-equations-and-lookup-tables.aspx).

AGE	MALE	FEMALE	AGE	MALE	FEMALE	AGE	MALE	FEMALE
18	0.19237	0.17849	26.75	0.17601	0.16972	35.5	0.10782	0.13368
18.25	0.19560	0.17972	27	0.17393	0.16895	35.75	0.10592	0.13223
18.5	0.19840	0.18076	27.25	0.17184	0.16818	36	0.10401	0.13075
18.75	0.20082	0.18162	27.5	0.16975	0.16741	36.25	0.10208	0.12925
19	0.20288	0.18232	27.75	0.16766	0.16662	36.5	0.10015	0.12772
19.25	0.20462	0.18289	28	0.16558	0.16583	36.75	0.09820	0.12616
19.5	0.20605	0.18333	28.25	0.16352	0.16503	37	0.09624	0.12458
19.75	0.20719	0.18366	28.5	0.16147	0.16422	37.25	0.09428	0.12298
20	0.20807	0.18391	28.75	0.15943	0.16339	37.5	0.09230	0.12136
20.25	0.20868	0.18407	29	0.15741	0.16255	37.75	0.09032	0.11971
20.5	0.20904	0.18415	29.25	0.15541	0.16169	38	0.08833	0.11805
20.75	0.20918	0.18416	29.5	0.15342	0.16082	38.25	0.08633	0.11636
21	0.20911	0.18410	29.75	0.15144	0.15993	38.5	0.08432	0.11466
21.25	0.20886	0.18397	30	0.14946	0.15903	38.75	0.08230	0.11293
21.5	0.20844	0.18377	30.25	0.14750	0.15811	39	0.08028	0.11119
21.75	0.20787	0.18351	30.5	0.14554	0.15718	39.25	0.07825	0.10942
22	0.20715	0.18318	30.75	0.14360	0.15623	39.5	0.07621	0.10764
22.25	0.20629	0.18279	31	0.14166	0.15527	39.75	0.07416	0.10584
22.5	0.20530	0.18234	31.25	0.13973	0.15429	40	0.07210	0.10402
22.75	0.20419	0.18182	31.5	0.13781	0.15329	40.25	0.07003	0.10219
23	0.20296	0.18125	31.75	0.13589	0.15226	40.5	0.06795	0.10034
23.25	0.20162	0.18062	32	0.13399	0.15121	40.75	0.06587	0.09847
23.5	0.20018	0.17994	32.25	0.13210	0.15014	41	0.06378	0.09659
23.75	0.19865	0.17922	32.5	0.13021	0.14903	41.25	0.06168	0.09469
24	0.19704	0.17847	32.75	0.12833	0.14791	41.5	0.05958	0.09278
24.25	0.19536	0.17770	33	0.12646	0.14675	41.75	0.05747	0.09085
24.5	0.19361	0.17690	33.25	0.12460	0.14557	42	0.05536	0.08891
24.75	0.19180	0.17610	33.5	0.12274	0.14436	42.25	0.05326	0.08696
25	0.18994	0.17529	33.75	0.12089	0.14312	42.5	0.05115	0.08500
25.25	0.18804	0.17447	34	0.11904	0.14185	42.75	0.04904	0.08303
25.5	0.18610	0.17366	34.25	0.11718	0.14055	43	0.04694	0.08105
25.75	0.18413	0.17286	34.5	0.11532	0.13923	43.25	0.04484	0.07906
26	0.18213	0.17206	34.75	0.11346	0.13788	43.5	0.04274	0.07707
26.25	0.18011	0.17128	35	0.11159	0.13651	43.75	0.04065	0.07507
26.5	0.17807	0.17050	35.25	0.10971	0.13511	44	0.03855	0.07306

AGE	MALE	FEMALE	AGE	MALE	FEMALE	AGE	MALE	FEMALE
44.25	0.03647	0.07105	55	-0.06031	-0.02274	65.75	-0.18163	-0.13976
44.5	0.03438	0.06903	55.25	-0.06286	-0.02517	66	-0.18462	-0.14277
44.75	0.03230	0.06701	55.5	-0.06544	-0.02762	66.25	-0.18761	-0.14580
45	0.03022	0.06499	55.75	-0.06802	-0.03008	66.5	-0.19061	-0.14884
45.25	0.02814	0.06296	56	-0.07063	-0.03255	66.75	-0.19361	-0.15190
45.5	0.02606	0.06093	56.25	-0.07324	-0.03504	67	-0.19661	-0.15496
45.75	0.02398	0.05889	56.5	-0.07588	-0.03754	67.25	-0.19961	-0.15804
46	0.02190	0.05685	56.75	-0.07853	-0.04006	67.5	-0.20262	-0.16114
46.25	0.01981	0.05480	57	-0.08119	-0.04259	67.75	-0.20563	-0.16424
46.5	0.01771	0.05274	57.25	-0.08387	-0.04514	68	-0.20864	-0.16736
46.75	0.01562	0.05068	57.5	-0.08656	-0.04770	68.25	-0.21165	-0.17049
47	0.01351	0.04861	57.75	-0.08927	-0.05027	68.5	-0.21467	-0.17362
47.25	0.01140	0.04654	58	-0.09199	-0.05286	68.75	-0.21768	-0.17677
47.5	0.00928	0.04446	58.25	-0.09473	-0.05546	69	-0.22070	-0.17993
47.75	0.00715	0.04237	58.5	-0.09748	-0.05808	69.25	-0.22372	-0.18310
48	0.00502	0.04027	58.75	-0.10024	-0.06071	69.5	-0.22674	-0.18627
48.25	0.00287	0.03817	59	-0.10302	-0.06335	69.75	-0.22976	-0.18946
48.5	0.00071	0.03605	59.25	-0.10581	-0.06601	70	-0.23278	-0.19265
48.75	-0.00146	0.03394	59.5	-0.10861	-0.06868	70.25	-0.23580	-0.19585
49	-0.00364	0.03181	59.75	-0.11143	-0.07137	70.5	-0.23882	-0.19906
49.25	-0.00583	0.02967	60	-0.11425	-0.07407	70.75	-0.24185	-0.20227
49.5	-0.00804	0.02752	60.25	-0.11709	-0.07678	71	-0.24486	-0.20549
49.75	-0.01026	0.02536	60.5	-0.11994	-0.07951	71.25	-0.24788	-0.20872
50	-0.01250	0.02320	60.75	-0.12281	-0.08224	71.5	-0.25090	-0.21195
50.25	-0.01475	0.02102	61	-0.12568	-0.08500	71.75	-0.25392	-0.21519
50.5	-0.01701	0.01883	61.25	-0.12856	-0.08776	72	-0.25693	-0.21843
50.75	-0.01929	0.01663	61.5	-0.13146	-0.09054	72.25	-0.25994	-0.22168
51	-0.02157	0.01441	61.75	-0.13436	-0.09333	72.5	-0.26296	-0.22493
51.25	-0.02388	0.01219	62	-0.13727	-0.09613	72.75	-0.26597	-0.22819
51.5	-0.02619	0.00995	62.25	-0.14019	-0.09895	73	-0.26897	-0.23145
51.75	-0.02852	0.00770	62.5	-0.14312	-0.10178	73.25	-0.27198	-0.23472
52	-0.03087	0.00544	62.75	-0.14606	-0.10462	73.5	-0.27498	-0.23798
52.25	-0.03323	0.00316	63	-0.14900	-0.10748	73.75	-0.27798	-0.24125
52.5	-0.03561	0.00087	63.25	-0.15194	-0.11034	74	-0.28097	-0.24452
52.75	-0.03800	-0.00143	63.5	-0.15489	-0.11322	74.25	-0.28396	-0.24780
53	-0.04042	-0.00374	63.75	-0.15785	-0.11612	74.5	-0.28695	-0.25107
53.25	-0.04284	-0.00607	64	-0.16081	-0.11903	74.75	-0.28993	-0.25434
53.5	-0.04529	-0.00841	64.25	-0.16377	-0.12195	75	-0.29291	-0.25762
53.75	-0.04775	-0.01077	64.5	-0.16674	-0.12488	75.25	-0.29589	-0.26090
54	-0.05023	-0.01314	64.75	-0.16971	-0.12783	75.5	-0.29886	-0.26417
54.25	-0.05273	-0.01552	65	-0.17269	-0.13079	75.75	-0.30182	-0.26744
54.5	-0.05524	-0.01791	65.25	-0.17567	-0.13377			
54.75	-0.05776	-0.02032	65.5	-0.17865	-0.13675			

3. Predicted FEV1 Data Processing

The relevant demographic data from the eCRF (age, sex, height and ethnicity) will be exported into excel format and imported (according to the instructions and process outlined) into the GLI-2012 Excel Sheet Calculator Version 4, 25 May 2014 (URL at time of writing available at http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/excel-sheet-calculator.aspx).

The output from this process (FEV1 predicted) will then be imported into the final analysis dataset.

APPENDIX 2: PATIENT REPORTED OUTCOMES PROCESSING

1. Adherence Starts with Knowledge-12 Questionnaire (ASK-12)

The ASK-12 questionnaire contains the following sub-sections; behaviour (5 items: 8–12; all reverse-scored), health beliefs (4 items: 4-7), and inconvenience/forgetfulness (3 items: 1-3; all reverse-scored). To score the ASK-12, each subscale score is computed as the sum of all items within that scale, and the total score is the sum of all 12 items. If a participant did not complete 1 item within a subscale, the subscale score can be computed by substituting the mean of the available responses for the missing response. If more than 1 item within a subscale is missing, that subscale score should not be computed. If responses are not available for up to 3 items, the total score can be computed using the same imputation strategy. If more than 3 items are unavailable, then the total score should not be computed. The total score has a possible range of 12–60. Higher ASK-12 scores indicate more barriers to adherence or greater problems with adherence behaviour.[6]

For the purposes of analysis, the total score and sub-scores will be computed for each participant, as above, and presented as part of the Visit 1 and Visit 7 variables.

2. Asthma Control Questionnaire-5 (ACQ-5)

The 5-item version of the ACQ questionnaire contains five questions on participants' symptoms, which are assessed on a 7-point scale from 0 (representing good control) to 6 (representing poor control). The overall score is the mean score of all questions for which responses are provided. A minimum of 4 out of 5 questions must be answered for a valid overall ACQ score. The ACQ is conducted at Visits 1 to 7, with overall score evaluated at each visit.[3]

Analysis of the overall ACQ-5 score will occur as per section 6.

APPENDIX 3: BRITISH NATIONAL FORMULARY CORTICOSTEROID DOSE CONVERSION

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 4: ELECTRONIC MEDICATION USE DATA PROCESSING

Processing of the data obtained by electronic monitor devices attached to each inhaler will take place in accordance with the following:

Rationale:
For a pMDI and a turbuhaler delivery system, a patient cannot inhale 2 doses of medication within 3 seconds, therefore any actuation that is logged within 3 seconds of another actuation does not represent actual medication use. There is therefore a requirement to remove these false medication events from the medication use data, prior to an investigator performing the assessment for high-use episodes (as per the protocol criteria) to ensure that participants are not withdrawn incorrectly.

Data Processing:
The SmartinhalerLive system is unable to perform the data processing required. Medication use data will therefore be transferred from the SmartinhalerLive system (Adherium Ltd), to the Novel START eCRF (Spiral Ltd), to allow processing of actuations according to an algorithm. The algorithm will run on the raw data from the SmartinhalerLive site, removing actuations that are logged ≤3 seconds of another actuation.
For dose dumping criteria, assessment of whether there have been 100 actuations within a 3 hour period will be performed prior to removing actuations that have occurred ≤3 seconds of each other. Data fulfilling dose dumping criteria will be removed from the dataset prior to the Investigator reviewing the data.

Data Transfer Process:
Data will be transferred from the SmartinhalerLive system via secure FTP of CSV files, containing the raw actuation data from the device. Transfer to the eCRF will occur within 30 seconds of data being uploaded from the device to SmartinhalerLive (the data is automatically pushed to the eCRF on upload to SmartinhalerLive).

Medication Use Data Review:
A new page will be added to the eCRF to allow the investigators at site to view the processed medication use data.
Data will be displayed in graphical format, with a cut-off line applied to the display, for Ventolin and Symbicort medication use data. The line will be shown as per the protocol defined high-use episode criteria, which is more than 16 actuations of Ventolin and more than 8 actuations of Symbicort taken in one day; as defined in the protocol as midnight to midnight. The investigator can therefore easily read off the high use episodes, in relation to the other data displayed.
Data will also be tabulated. The table will list all days where high-use criteria has been met, so that the Investigator can easily transfer this data into the asthma exacerbation log.
The investigator may select the display date range for the medication use data. By default, the medication use data on the day of a visit will not be displayed, however this may be viewed by the Investigator by selecting the relevant option.
Each participant has multiple inhalers provided to them at any one time during the study. The display will therefore also indicate which monitor device IDs are included in the combined dataset. This ensures that all devices dispensed to a participant can be accounted for in the assessment of high use episodes. The Investigator should check for missing devices (i.e. check the dispensed device IDs within the inhaler/monitor log against the display of device IDs listed for the medication use data) and ensure that the data from these is reviewed as soon as possible. Should a participant forget an inhaler/ device and data is subsequently uploaded to the system at a later date, the investigator must review the combined medication use data for the period in question, ensuring that all high use episodes are correctly entered into the asthma exacerbation log. If this results in a participant meeting withdrawal criteria, they should be contacted and attend for Visit 7 as soon as practicable.

Medication Use Data Reporting:
The proportion of actuations deleted, due to application of the 3 second rule algorithm, will be reported, by randomisation arm.

APPENDIX 5: Clarification of End Dates for the purpose of outcome variable datasets

Two different exposure time end dates will be used in the analysis. These end dates will only differ where the participant is withdrawn from the study due to an exacerbation.

Definitions:

End Date A: The date at which a protocol specified withdrawal criteria was first met, or if no withdrawal criterion was met, the date of the final study visit.

End Date B: the date at which the last exacerbation criteria was met (5.1.1.1.; 5.1.1.2.; 5.1.1.3.), within the exacerbation that resulted in withdrawal criteria being met; or if no withdrawal criterion was met, the date of the final study visit.

For both definitions, should a patient be prescribed an increase in inhaled therapy to aid asthma control the date of withdrawal will be the date of prescription of that therapy (however therapy must have been prescribed for more than 14 days to meet withdrawal criteria).

The following outcome variables will use End Date A:

5.1.1. Asthma exacerbation rate expressed as number of exacerbations per patient per year (Primary outcome). An asthma exacerbation is defined as:

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

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

5.1.1.3. 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

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

5.3.1.6.1. The prescription of systemic corticosteroids for at least 3 days, or
5.3.1.6.2. Hospitalisation or ED visit because of asthma, requiring systemic corticosteroids

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

5.3.2.2. Periods without ICS use:

5.3.2.2.1. Proportion of participants with at least 1 day of no ICS actuations
5.3.2.2.2. Number of days of no ICS use
5.3.2.2.3. Number of ≥7 consecutive day periods of no ICS use
5.3.2.2.4. Number of ≥14 consecutive day periods of no ICS use
5.3.2.2.5. Longest duration of no ICS use (days)

Corticosteroid use:

5.3.2.3. Total oral corticosteroid dose per year. The oral corticosteroid dose taken for the severe exacerbation is used for this calculation.

5.3.2.4. Number of courses of oral corticosteroid per year

5.3.2.5. 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,[7] 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 2).

The above corticosteroid variables refer to corticosteroids for asthma only. All other oral corticosteroid use will be excluded from the analysis of the variables specified above.

The following outcome variables will use End Date B:

5.3.2.6 High beta agonist use:

5.3.2.6.1. Proportion of participants with at least one episode of high use
5.3.2.6.2. Number of days of high use
5.3.2.6.3. Number of days of high use in participants with at least one day of high use
5.3.2.6.4. Number of days of high use without medical review within 48 hours, 7 days or 14 days in participants with at least one high use episode
5.3.2.6.5. Proportion of high use episodes without medical review within 48 hours, 7 days or 14 days

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

5.3.2.7.1. Proportion of participants with at least one episode of marked overuse
5.3.2.7.2. Number of days of marked overuse
5.3.2.7.3. Number of days of marked use in participants with at least one day of marked overuse
5.3.2.7.4. Number of days of marked overuse without medical review within 48 hours, 7 days or 14 days in participants with at least one marked overuse episode
5.3.2.7.5. Proportion of marked overuse episodes without medical review within 48 hours, 7 days or 14 days

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