Title Page

Protocol Title:

A 52-week, open-label, randomised, multi-centre, parallel group, phase III, controlled trial in patients age 5 to 11 years with mild, moderate and severe asthma, evaluating the efficacy and safety of Budesonide-formoterol (Symbicort Turbuhaler®) maintenance and/or reliever therapy compared with standard therapy: Budesonide (Pulmicort Turbuhaler®) maintenance or Budesonide-formoterol (Symbicort Turbuhaler®) maintenance, both with Terbutaline (Bricanyl Turbuhaler®) reliever

Protocol Number: MRINZ/22/06

Amendment Number: 03

Brief Title: Randomised controlled trial of Budesonide-formoterol maintenance and/or reliever therapy vs standard therapy of Budesonide maintenance or Budesonide-formoterol maintenance, both with Terbutaline reliever, in children age 5 to 11 years with mild, moderate and severe asthma.

Study Phase: Phase III

Acronym: START CARE (**ST**ep-wise **A**nti-inflammatory **R**eliever **T**herapy **C**hildren's **A**sthma **RE**search)

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Universal Trial Number	U1111-1278-5798
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Protocol Amendments

DOCUMENT HISTORY		
Document	**Protocol Version No.**	**Date**
Amendment 03	3.1	29-Jun-2023
Amendment 02	3.0	16-Mar-2023
Amendment 01	2.0	26-Oct-2022
Original Protocol	1.0	22-Aug-2022

1. **Amendment 03 (29-June-2023)**
   This amendment is considered to be non-substantial by the Trial Management Group based on the Health and Disability Ethics Committee Guidance on amendments to approved studies, contained within their standard operating procedures.

2. **Overall Rationale for the Amendment:**

- The Clinical Data Management Application (CDMA) and electronic Case Report Form (eCRF) databases have been merged, whilst retaining the access rights of relevant site and Sponsor staff to ensure data protection and that access to identifiable data is appropriate. Text has been amended throughout the protocol to reflect the fact that there are no longer two separate databases housing source data (CDMA) and study data for analysis (eCRF) respectively.
- Appendix 11: The maintenance treatment GINA steps at trial entry table has been amended to clarify the maintenance doses for those taking budesonide-formoterol pre-study, to ensure the correct step is selected and those who are taking up to 400/24mcg of budesonide-formoterol are not excluded in error.
- Clarification has been added to 5.4 Screen Failures to confirm that if a participant is unable to meet the satisfactory Turbuhaler technique and/ or inspiratory flow criteria at Visit 2 then they cannot be re-screened.
- The requirement of the investigator to observe the first dose at Visit 1 has been removed as this not required.

3. **Summary of Changes**

Section # and Name	Description of Change	Brief Rationale
5.4 Screen Failures	Deletion of Visit 1 from the following: Individuals who do not meet the criteria for participation in this study (screen failure) ~~at Visit 1~~ may be re-screened on one more occasion.	Clarification that participants may be re-screened unless they are unable to meet the criteria for satisfactory use of the Turbuhaler and/ or inspiratory flow at Visit 2.

<table>
<tr><td></td><td>Addition of Visit 2 Inclusion criteria in the following:
Individuals who do not meet the Visit 2 Inclusion criteria (satisfactory Turbuhaler technique and/or inspiratory flow) for participation in this study cannot be re-screened.</td><td></td></tr>
<tr><td>8.1.2 Run-in period</td><td>Removal of text:
<s>Participants will take the first dose of their run-in period medication under the direct supervision of the study investigator, prior to completing the visit.</s></td><td>Observation of the first dose is not required given the exclusion criteria, use of a demonstration Turbuhaler for training purposes and the well-known side effect profile of the medications used in the run-in period.</td></tr>
<tr><td>Appendix 1: Regulatory, Ethical, and Study Oversight Considerations, 10.1.6 Data Protection and 10.1.19 Data Quality Assurance

10.4 Appendix 4: Abbreviations and Definitions</td><td>Various changes made to remove reference to the eCRF in 10.1.6 Data Protection and 10.1.19 Data Quality Assurance

eCRF removed from the abbreviations list</td><td>The eCRF and CDMA projects have been merged therefore reference to the eCRF is not required. There is no change to the underlying data protection aspects in terms of Sponsor staff access to identifiable data**,** only a minor change to how the data is handled within the existing clinical trial management system (REDCap).

No longer required.</td></tr>
<tr><td>Appendix 11: Maintenance treatment GINA steps at trial entry</td><td>Budesonide-formoterol GINA step 4 and 5 daily ICS maintenance dose ranges adjusted:
<table>
<tr><th>Daily maintenance dose</th><th>GINA step</th></tr>
<tr><td>>200/6 to 400/24mcg
amended to:
>200/12 to 400/24mcg</td><td>4</td></tr>
<tr><td>>400/12mcg
amended to:
>400/24mcg</td><td>5</td></tr>
</table></td><td>The daily budesonide-formoterol dose ranges overlapped across GINA steps in error, therefore this has been amended to ensure consistency of GINA step selection on entry to the study and that only those taking >400/24mcg of budesonide-formoterol would be ineligible/ categorised as GINA step 5.</td></tr>
</table>

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1 Protocol Summary

1.1 Synopsis

Trial Title:	A 52-week, open-label, randomised, multi-centre, parallel group, phase III, controlled trial in patients age 5 to 11 years with mild, moderate and severe asthma, evaluating the efficacy and safety of Budesonide-formoterol (Symbicort Turbuhaler®) maintenance and/or reliever therapy compared with standard therapy: Budesonide (Pulmicort Turbuhaler®) maintenance or Budesonide-formoterol (Symbicort Turbuhaler®) maintenance, both with Terbutaline (Bricanyl Turbuhaler®) reliever.
Short Title:	START CARE (**ST**ep-wise **A**nti-inflammatory **R**eliever **T**herapy **C**hildren's **A**sthma **RE**search)
Trial Design:	A multi-centre, parallel group, phase III, open label, 2-arm, 2-sided superiority randomised controlled trial.
Primary objective:	To compare the efficacy and safety of Budesonide-formoterol maintenance and/or reliever therapy vs. standard therapy: Budesonide maintenance or Budesonide-formoterol maintenance, both with Terbutaline reliever, in children age 5 to 11 years with mild, moderate and severe asthma.
Trial hypothesis:	Budesonide-formoterol maintenance and/or reliever therapy reduces the rate of moderate and severe asthma exacerbations, compared with standard therapy: Budesonide maintenance or Budesonide-formoterol maintenance, both with Terbutaline reliever, in children with mild, moderate and severe asthma (GINA step 2, 3 and 4).
Trial Participants:	Children age 5 to 11 years with mild, moderate and severe asthma currently taking maintenance ICS or ICS-LABA, plus SABA reliever (GINA steps 2 to 4).
Planned Sample size:	400 (200 per treatment arm)
Trial Period:	Recruitment: 130 weeks Run-in period: 4 weeks Treatment duration: 52 weeks Follow-up (post-trial) duration: Nil
Visit:	Six study-specific in-person visits. Enrolment will take place at Visit 1 (Week -4). Participants will undertake a 4-week run-in period. Randomisation will occur at Visit 2 (Week 0), followed by 3-monthly visits at weeks 13, 26, 39, and 52.

Intervention arm regimen:	Budesonide-formoterol 100/6 mcg DPI (Dry Powder Inhaler; Symbicort Turbuhaler®) as maintenance and/or reliever therapy	
Control arm regimen:	Standard therapy: Budesonide 100mcg DPI (Pulmicort Turbuhaler®) maintenance or Budesonide-formoterol 100/6mcg DPI (Symbicort Turbuhaler®) maintenance, both with as-needed Terbutaline 500mcg DPI (Bricanyl Turbuhaler®)	
Outcomes	Outcome	Time point
Primary	1. Asthma exacerbations (moderate and severe) as rate per participant per year	52 weeks
Secondary (efficacy)	2. Proportion of participants with at least one asthma exacerbation (moderate or severe)	52 weeks
	3. Proportion of participants with at least one severe asthma exacerbation	52 weeks
	4. Proportion of participants with at least one step up in treatment.	52 weeks
	5. Proportion of participants on each treatment step	52 weeks
	6. Severe asthma exacerbations as rate per participant per year	52 weeks
	7. Composite of asthma exacerbations (moderate and severe), or step up in treatment, as rate per participant per year	52 weeks
	8. Proportion of participants with at least one asthma exacerbation (moderate or severe), or step up in treatment	Maximum observation time 52 weeks
	9. Step up in treatment, as rate per participant per year	52 weeks
	10. Time to first moderate or severe asthma exacerbation	Maximum observation time 52 weeks
	11. Time to first severe asthma exacerbation	Maximum observation time 52 weeks
	12. Time to first asthma exacerbation (moderate or severe), or step up in treatment	Maximum observation time 52 weeks

	13. Time to first step up in treatment	Maximum observation time 52 weeks
	14. FeNO	1, 26, 52 weeks
	15. On-treatment FEV_1	1, 26, 52 weeks
	16. Days in hospital	52 weeks
	17. Days lost from school due to asthma	52 weeks
	18. Days lost from usual activities due to childcare for asthma (parent(s)/ guardian(s))	52 weeks
	19. ACQ-5	1, 26, 52 weeks
Secondary (safety)	20. Total inhaled corticosteroid dose	52 weeks
	21. Total systemic corticosteroid dose	52 weeks
	22. Total composite corticosteroid dose (inhaled and systemic)	52 weeks
	23. Total inhaled $beta_2$-agonist dose	52 weeks
	24. Growth velocity	13, 26, 39 and 52 weeks
	25. Adverse Events (AEs)	52 weeks
	26. Serious Adverse Events (SAEs)	52 weeks
	27. Proportion of participants who discontinue treatment or withdraw	52 weeks
Secondary (cost effectiveness)	28. Incremental cost per moderate and/or severe exacerbation averted	52 weeks
Secondary (carbon footprint)	29. Asthma-associated carbon footprint per participant	52 weeks
Statistical analysis:	Intention-to-treat by a biostatistician blinded to treatment allocation	

1.2 Schema

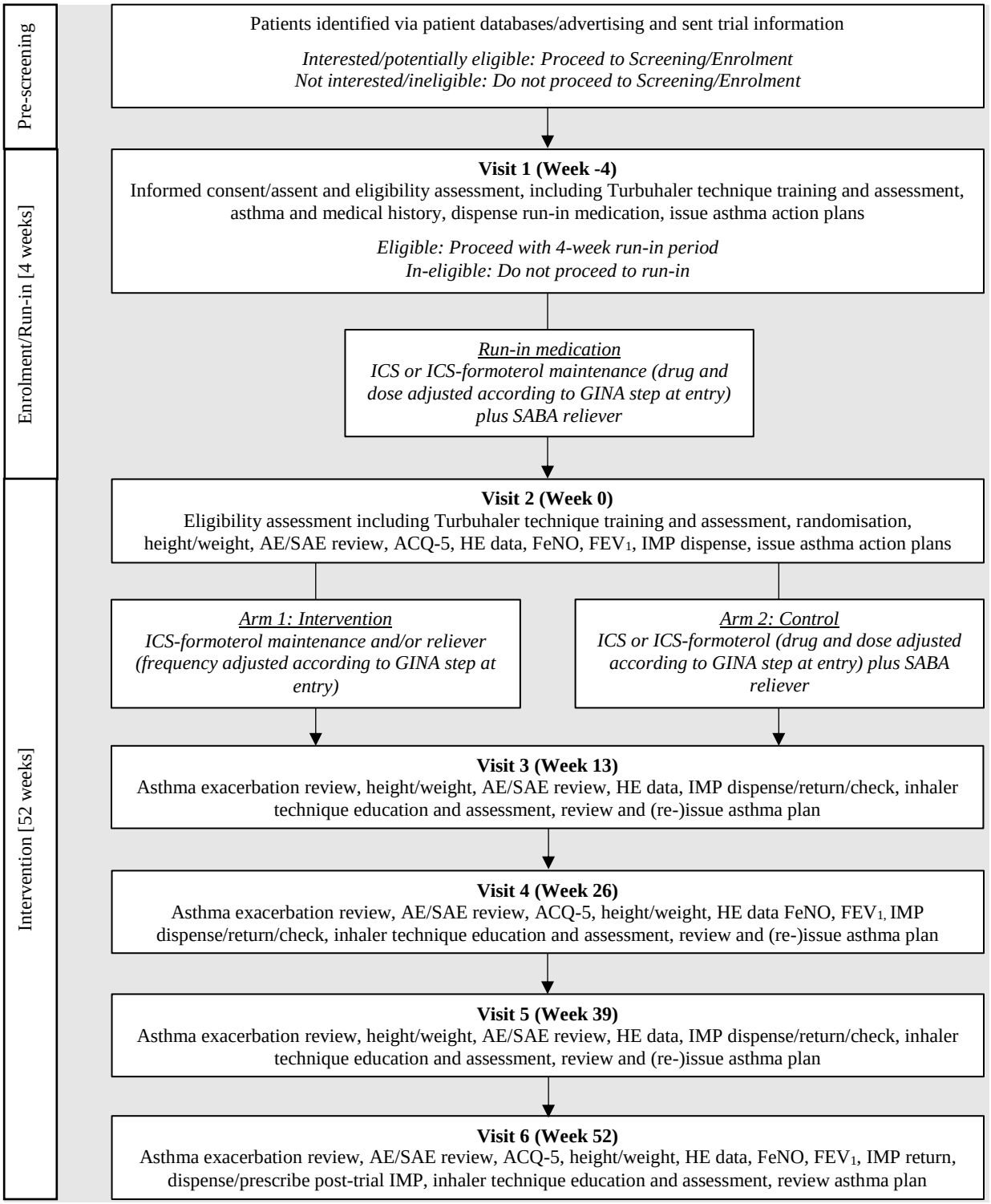
The START CARE study is a 52-week multi-centre, two-arm, open-label, parallel-group, phase III, two-sided superiority RCT. Four hundred children age 5 to 11 years with mild, moderate and severe asthma already using ICS maintenance or ICS-LABA maintenance, either with SABA reliever, corresponding to GINA treatment steps 2, 3 and 4, will be randomised 1:1 to either:

- **Intervention:** Budesonide-formoterol 100/6mcg DPI (Symbicort Turbuhaler®, AstraZeneca). Regimen and dose will be adjusted according to GINA step at study entry (**Table 1**), with maintenance and/or reliever use as needed for relief of asthma symptoms and prior to exercise.

- **Control:** Either Budesonide 100mcg DPI (Pulmicort Turbuhaler®, AstraZeneca) maintenance or Budesonide-formoterol 100/6mcg DPI (Symbicort Turbuhaler®, AstraZeneca) maintenance with the drug and dose adjusted according to GINA step at study entry; (**Table 1**), both with Terbutaline 500mcg DPI (Bricanyl Turbuhaler®, AstraZeneca) reliever, one inhalation as needed for relief of asthma symptoms and prior to exercise.

Participants will be assessed for eligibility and enrolled at Visit 1 (Week -4). Eligible participants will undertake a 4-week run-in period to ensure adequate Turbuhaler technique. Participants who demonstrate adequate technique will undergo randomisation at Visit 2 (Week 0). Subsequent follow up visits will occur at 3-monthly intervals (weeks 13, 26, 39, and 52) for a total of 6 visits. All visits will be in person at a participating research site.

Figure 1: Trial flow diagram



ACQ-5, Asthma Control Questionnaire, symptom only version (investigator administered); AE, Adverse Event; FEV_1, Forced Expiratory Volume in 1 second; FeNO, Fractional Exhaled Nitric Oxide; GINA, Global INitiative for Asthma; HE, Health Economics; ICS, Inhaled CorticoSteroid; IMP, Investigational Medicinal Product; SABA, Short-Acting $Beta_2$-Agonist; SAE, Serious Adverse Event.

Table 1: GINA step at trial entry and corresponding treatments during the run-in and intervention periods

GINA Step	Run-in period [4 Weeks]	Intervention period [52 Weeks]	
	All participants	**Control arm**	**Intervention arm**
2	**Low dose ICS plus SABA reliever** Budesonide 100mcg DPI (Pulmicort Turbuhaler®), 1 inhalation twice daily Terbutaline 500mcg DPI (Bricanyl Turbuhaler®), 1 inhalation as needed	**Low dose ICS plus SABA reliever** Budesonide 100mcg DPI (Pulmicort Turbuhaler®), 1 inhalation twice daily Terbutaline 500mcg DPI (Bricanyl Turbuhaler®), 1 inhalation as needed	**Very low dose ICS-LABA reliever** Budesonide-formoterol 100/6mcg DPI (Symbicort Turbuhaler®), 1 inhalation as needed
3	**Medium dose ICS OR low dose ICS-LABA plus SABA reliever** Budesonide 100mcg DPI (Pulmicort Turbuhaler®), 2 inhalations twice daily Terbutaline 500mcg DPI (Bricanyl Turbuhaler®), 1 inhalation as needed *OR* Budesonide-formoterol 100/6mcg DPI (Symbicort Turbuhaler®), 1 inhalation twice daily* Terbutaline 500mcg DPI (Bricanyl Turbuhaler®), 1 inhalation as needed	**Medium dose ICS OR low dose ICS-LABA plus SABA reliever** Budesonide 100mcg DPI (Pulmicort Turbuhaler®), 2 inhalations twice daily Terbutaline 500mcg DPI (Bricanyl Turbuhaler®), 1 inhalation as needed *OR* Budesonide-formoterol 100/6mcg DPI (Symbicort Turbuhaler®), 1 inhalation twice daily* Terbutaline 500mcg DPI (Bricanyl Turbuhaler®), 1 inhalation as needed	**Very low dose ICS-LABA maintenance and reliever** Budesonide-formoterol 100/6mcg DPI (Symbicort Turbuhaler®), 1 inhalation once daily, and 1 inhalation as needed
4	**Medium dose ICS-LABA plus SABA reliever** Budesonide-formoterol 100/6mcg DPI (Symbicort Turbuhaler®), 2 inhalations twice daily Terbutaline 500mcg DPI (Bricanyl Turbuhaler®), 1 inhalation as needed	**Medium dose ICS-LABA plus SABA reliever** Budesonide-formoterol 100/6mcg DPI (Symbicort Turbuhaler®), 2 inhalations twice daily Terbutaline 500mcg DPI (Bricanyl Turbuhaler®), 1 inhalation as needed	**Low dose ICS-LABA maintenance and reliever** Budesonide-formoterol 100/6mcg DPI (Symbicort Turbuhaler®), 1 inhalation twice daily, and 1 inhalation as needed

*Budesonide-formoterol 100/6mcg, 1 inhalation twice daily is the preferred maintenance treatment option at Step 3 in the control arm. Participants who enter the study on medium dose ICS will continue on this regimen. Participants who are escalated to Step 3 treatment during the intervention period will be preferentially started on low dose ICS-LABA maintenance therapy over medium dose ICS. DPI = Dry Powder Inhaler; GINA = Global INitiative for Asthma; ICS = Inhaled Corticosteroid; LABA = Long-Acting Beta$_2$-Agonist; SABA = Short-Acting Beta$_2$-Agonist.

1.3 Schedule of Activities (SoA)

Table 2: Schedule of Activities

	Enrolment/ Run-in	Randomisation	Intervention Period [52 weeks]					
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6/TD/EW**	**Unscheduled**	**Protocol Section**
Day	-28	0	91	182	273	365	-28 to 365	-
Visit window	N/A	±14	±7	±7	±7	±7	N/A	-
Informed consent/assent	X							8.1.1.1
Allocation of Screening code	X							8.1.1
Demographics	X							8.1.1.2
Inclusion and exclusion criteria	X	X						5.1 5.2
Medical and surgical history	X							8.1.1.3
Asthma history (including current treatment and history of severe asthma exacerbations)	X							8.1.1.3
Turbuhaler training and assessment of technique	X	X	X	X	X	X	X	8.1.1.4; 8.3.2
Run-in inhalers (dispense/return)	d	r						6.2
Randomisation		X						
Height and weight		X	X	X	X	X		8.3.1
ACQ-5 (IA)		X		X		X		8.2.3
HE data		X	X	X	X	X	X	8.9
FeNO*		X		X		X		8.2.4
FEV_1		X		X		X		8.2.5
DCE#						X		8.10
IMP (dispense/return/check)		d	d/r/c	d/r/c	d/r/c	r/c	d/r/c	6.2
SAE/AE review		X	X	X	X	X	X	8.4
Asthma review (including asthma exacerbations, time off school/usual activities)		X	X	X	X	X	X	8.2.1 8.2.2
Asthma action plan and log sheet education and (re-)issue	X	X	X	X	X	X	X	8.3.3
GP Communications	X	X				X	X	8.3.5
Dispense/prescribe post-trial medication						X		6.6
Provide parent/participant reimbursement and koha	X	X	X	X	X	X	X	10.1.3

*FeNO must be performed before FEV_1. #Selected sites only. Perform visit 6 procedures at Treatment Discontinuation/Withdrawal. A/R, as required; DCE, Discrete Choice Experiment; ACQ-5, Asthma Control Questionnaire, symptom only version (IA, Investigator Administered); c, check; d, dispense; EW, Early Withdrawal; HE, Health Economics; IP, In-Person; N/A, Not Applicable; r, return; TD, Treatment Discontinuation.

2 Introduction

The aim of this study is to compare the efficacy and safety of Budesonide-formoterol Maintenance And Reliever Therapy (MART) versus standard therapy; either of ICS maintenance, or ICS-LABA maintenance, plus as-needed SABA, in children with mild, moderate and severe asthma, as defined by the Global Initiative for Asthma, GINA, steps 2 to 4.

2.1 Study Rationale

Inhaled corticosteroid (ICS)-formoterol, used as both maintenance and/or reliever therapy, is now the GINA-preferred treatment option for adolescents and adults with asthma across all treatment steps.[1]

At GINA steps 1 and 2, the use of ICS-formoterol reliever as sole therapy in adolescents and adults is supported by a meta-analysis, consisting 9,657 participants from six randomised controlled trials.[2] Compared with traditional SABA-only reliever therapy, as-needed ICS-formoterol is associated with a 55% reduction in severe asthma exacerbations requiring systemic steroids: Odds ratio (95% CI) 0.45 (0.34 to 0.60). Compared with low dose ICS plus SABA reliever, ICS-formoterol reliever as sole therapy is also associated with a smaller relative risk of asthma exacerbation requiring systemic steroids: Odds ratio (95% CI) 0.79 (0.59 to 1.07). A pooled post hoc analysis of adolescents (12 to <18 years) enrolled in the Symbicort Given as needed in Mild Asthma (SYGMA) trials,[3] reported that as needed Budesonide-formoterol reduced the rate of severe asthma exacerbations compared with SABA (Terbutaline)-only reliever: Rate ratio (95% CI) 0.23 (0.09 to 0.65), SYGMA 1 data only; N=146. This was a larger relative rate reduction than that observed in the total adolescent and adult participants in the same study: Rate ratio 0.36 (0.27 to 0.49).[4] As-needed Budesonide-formoterol had a similar rate of severe asthma compared with low dose Budesonide plus terbutaline reliever: Rate ratio 1.16 (0.64 to 2.10), in the adolescent sub-group (SYMGA 1 and 2 data; N=321); and this lack of a statistically significant difference was also reported in the total study participants, rate ratio 0.83 (0.59 to 1.16).[4,5]

A recommendation to use Budesonide-formoterol as sole reliever therapy cannot yet be made for children aged 11 years and younger due to a lack of evidence. The studies discussed only recruited participants 12 years of age or older. The MRINZ is currently undertaking a clinical trial to evaluate the efficacy and safety of as needed Budesonide-formoterol versus as needed Salbutamol (GINA Step 1) in children age 5 to 15 years.[6]

At GINA steps 3 and 4, the use of ICS-formoterol as MART in adolescents and adults is supported by meta-analysis from 22,524 participants,[7] allowing for high certainty clinical recommendations. Among patients age 12 years or older, MART is associated with a reduced risk of asthma exacerbations compared to SABA as reliever therapy for each of: the same dose of ICS and LABA as maintenance therapy; risk ratio [RR] (95% CI) 0.68 (0.58 to 0.80); higher dose of ICS and LABA as maintenance therapy 0.77 (0.60 to 0.98); same dose of ICS alone as maintenance therapy 0.64 (0.53 to 0.78); and finally higher dose of ICS alone as maintenance therapy; 0.59 (0.49 to 0.71).[7]

Only a single study (n=341) has reported the efficacy and safety of ICS-formoterol MART in children age 4 to 11 years.[8] In that study, participants were randomised to 1) ICS-formoterol MART, 2) same-dose maintenance ICS-formoterol plus SABA reliever, or 3) higher-dose maintenance ICS plus SABA reliever. ICS-formoterol MART was associated with a reduction in asthma exacerbations compared with both alternative treatments: Risk ratio (95% CI) 0.28 (0.14 to 0.53), and 0.43 (0.21 to 0.87).[7] These point estimates of the risk ratios were smaller than observed in the larger study including 2,419 adolescents and adults,[9] suggesting potentially greater efficacy of this regimen in children. Importantly, ICS-formoterol MART had less of an impact on growth (mean difference 1cm, 95% CI 0.3 to 1.7cm) compared to higher-dose maintenance ICS plus SABA reliever. Because there has only been one study of ICS-formoterol MART the overall certainty of the evidence for this regimen in children age 5 to 11 is low.

Further research is urgently needed to evaluate the efficacy and safety of ICS-formoterol as maintenance and/or reliever therapy, and to bring the strength of evidence and available treatment options for children on par with adults and adolescents. If comparable efficacy with ICS-formoterol maintenance and/or reliever therapy is shown in childhood asthma, then implementation of this regimen would markedly reduce the burden of asthma in all children.

2.2 Background

Asthma is the most common chronic disease of childhood and the leading cause of childhood morbidity from chronic disease in terms of school absences, emergency department visits and hospitalisations. Prevalence rates for paediatric asthma, and notably for severe asthma, in New Zealand are amongst the highest in the world, making it an efficient location to enrol and study paediatric asthma treatments. One in seven children receive treatment for asthma, with over 3,500 children admitted to hospital with asthma exacerbations annually. This is the most common reason for paediatric admission to hospital.[10] This rate of hospitalisation is 327 per 100,000 children, nearly three times that of adults and accounts for 40% of all NZ asthma hospitalisations. In 2015 there were 15 asthma related deaths in children <15 years. The greatest individual burden of paediatric asthma is in those children with moderate and severe disease (GINA steps 2+).

The traditional approach to managing asthma is to prescribe a maintenance ICS or ICS-LABA inhaler and/or a SABA reliever, taken as needed for symptom relief. However, there are a number of safety concerns with this approach:

- The benefits of ICS are restricted in clinical practice by the overestimation of asthma control and, in some cases, steroid aversion. This leads to the under prescribing of ICS by clinicians, and reduced adherence to ICS by patients.
- The number of ICS inhalations patients can use each day are effectively capped, with no effective mechanism to titrate the ICS dose according to need, particularly during acute asthma exacerbations.
- SABAs can provide quick symptom relief but they lack activity against the underlying inflammatory processes in asthma. Overreliance during an acute attack can therefore lead to a delay in seeking medical assistance.

- Both ICS underuse and SABA overuse are associated with asthma mortality.

Combining an ICS with a fast-onset beta$_2$-agonist, such as formoterol, in a single inhaler offers a potential solution to protect against the dangers of beta$_2$-agonist monotherapy and poor ICS adherence, by ensuring that an ICS dose is delivered with each "reliever" inhalation. Equally as important, the ICS dose is titrated according to need, with increased steroid being delivered during an acute worsening episode requiring increased beta$_2$-agonist use.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

More information about the known and expected benefits and risks, and reasonably expected adverse events (AEs), of the study interventions are in Appendix 5: IMP Risk Assessment.

2.3.1.1 Turbuhaler device use in paediatric population

Dry Powder Inhalers (DPIs), including Turbuhalers, are uncommonly used by children with asthma in New Zealand. There is a potential risk that participants who use their inhaler infrequently (e.g. those on as needed only treatment) are less confident using their device during an acute asthma worsening episode. To mitigate this risk, all children will be educated on, and assessed for, satisfactory Turbuhaler technique and inspiratory flow, at enrolment. Children who demonstrate satisfactory technique will undertake a 4-week run-in period to ensure familiarity and comfort with using the device, prior to randomisation. During the study, all children will receive inhaler education and training at all study visits, and will have an inspiratory flow training device, and access to education resources in between visits, including their asthma action plan and an educational video.

Of note, children age 4 to 11 years enrolled in a previous study of Budesonide-formoterol maintenance and reliever therapy in asthma, were able to safely use Turbuhaler devices.[8]

2.3.1.2 Reaction to excipient in Bricanyl and Symbicort Turbuhaler devices

The Bricanyl Turbuhaler® and Symbicort Turbuhaler® devices contain the excipient lactose, which contains small amounts of milk proteins. This excipient may cause allergic reactions. It does not normally cause problems in lactose intolerant people. Known or suspected hypersensitivity (not intolerance) to lactose, milk protein or one of the active medicines within the Turbuhaler devices is an exclusion criterion.

The Pulmicort Turbuhaler® device contains only the active drug, Budesonide. There are no propellants, lubricants, preservatives, carrier substances or other additives.

2.3.1.3 Reliever inhalations

Most reliever inhaler regimens involve children taking two inhalations of their reliever inhaler per use episode. The minimum dose of formoterol per inhalation is 6mcg with a Symbicort Turbuhaler. This is broadly equivalent to 500mcg of Terbutaline and 200mcg of Salbutamol.[11] To avoid excessive dosing, participant should only use one inhalation per use episode. (This is the dosing regimen for adolescents and adults using ICS-formoterol anti-inflammatory reliever therapy).

In order to standardise the reliever dosing regimen between the two treatment arms, participants in the control arm will use one inhalation of Bricanyl Turbuhaler® (Terbutaline) 500mcg. This formulation will also be used by all participants during the run-in period, and will help to mitigate excessive reliever dosing in the intervention arm that could occur when switching from two reliever inhalations with Terbutaline 250mcg, to one reliever inhalation with Symbicort Turbuhaler® 100/6mcg.

There is a risk that some participants continue to take two or more reliever actuations per use episode, due to entrenched behaviour. To mitigate this, participants will be educated on correct Turbuhaler technique and their asthma action plans at each visit. The action plans specify how many inhalations to take per use episode and provide clear reliever use cut-points for when to seek medical review. Self-reported use of 16 or more inhalations within a 24-hour period will be recorded as extreme overuse (Section 6.7.3).

2.3.1.4 Control arm treatment regimen

Symbicort Turbuhaler® 100/6mcg and Pulmicort Turbuhaler® 100mcg are marketed products in New Zealand, approved for use in children age 4 to 11 years and 6 to 11 years respectively for the indication of asthma.

Bricanyl Turbuhaler® 500mcg is not currently available in New Zealand. (Note, Bricanyl Turbuhaler® 250mcg is a marketed product in New Zealand, approved for use in children age 3 to 12 years, for the indication of asthma). Use of Bricanyl Turbuhaler® 500mcg will require approval from the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) via the Standing Committee on Therapeutic Trials (SCOTT).

The stepwise asthma treatment track in the New Zealand child asthma guidelines[18] broadly aligns with the GINA stepwise track for children age 11 years and younger and is standard practice in New Zealand. As a result, participants randomised to the control arm are at no greater risk than that of standard care.

2.3.1.5 Intervention arm treatment regimen

The Symbicort Turbuhaler® 100/6 is a marketed product in New Zealand. It is approved for use in children age 4 to 11 years for the indication of asthma, as maintenance therapy or single-inhaler maintenance and reliever therapy.

The stepwise treatment approach in the intervention arm aligns with the GINA stepwise track for children age 11 years and younger, at steps 3 and 4.

In children age 12 years and older, and adults, the Symbicort Turbuhaler® 100/6 formulation is approved for use as single-inhaler maintenance and reliever therapy, and the Symbicort Turbuhaler® 200/6 formulation is approved for use as sole reliever therapy and as single-inhaler maintenance and reliever therapy. In these age groups, these regimens result in a significant reduction in severe asthma exacerbations, compared with traditional SABA reliever-based treatments.

The regimen at Step 2 in the intervention arm (Symbicort Turbuhaler® 100/6 mcg, 1 inhalation as needed) follows the GINA Step 2 recommendation for adolescents and adults with asthma, but with half the ICS dose, as recommended for children age <12 years.

As a result, participants randomised to the intervention arm are likely to be at no increased risk than standard care.

2.3.1.6 Respiratory testing (FeNO and Spirometry)

All participants will undertake respiratory testing. Participants may feel breathless or dizzy for a short period after breathing tests. This is uncommon. Participants will be monitored throughout the tests by trained clinical staff and if they feel unwell they can stop at any time.

2.3.2 Benefit Assessment

Benefits to the participants of being involved in this study are as follows:

- All products used in the study have a well-established, favourable efficacy and safety profile in the context of their use for the treatment of asthma, including in children. The risk profiles of the control arm and intervention arm medications are therefore deemed to be very low.
- The proposed treatment options are all recommended by GINA for children with asthma, with the exception of Step 2 in the intervention arm.
- The burden on participants is deemed to be low, with minimal respiratory testing procedures and collection of low-risk questionnaire data throughout the study period.
- All participants will have the ability to learn more about their asthma, with access to trained staff during the study visits who can answer their questions.
- All participants will have a better understanding of how to manage their asthma, through the use of the study asthma action plans and associated guidance provided by the study team.
- Participants enrolled in asthma clinical trials often achieve better asthma control.

- These benefits to the participant will help them to better manage their asthma after the clinical trial.
- All participants will have their inhaler treatment stepped up following a severe asthma exacerbation. This is recommended by asthma guidelines, though does not necessarily occur in clinical practice.
- Our hypothesis is that participants in the intervention arm will have significantly fewer asthma exacerbations than participants in the control arm, as demonstrated in adolescents and adults using Budesonide-formoterol single-inhaler maintenance and/or reliever therapy.

2.3.3 Overall Benefit Risk Conclusion

The risk to participants in the study are minimal. Considering all mitigating measures, the potential risks identified in association with Budesonide-formoterol as maintenance and/or reliever therapy are justified by the anticipated benefits.

3 Objectives, Endpoints

Objectives and Endpoints:

To compare the efficacy and safety of Budesonide-formoterol maintenance and/or reliever therapy versus standard therapy: Budesonide maintenance or Budesonide-formoterol maintenance, both with Terbutaline reliever, in children age 5 to 11 years with mild, moderate and severe asthma.

Objectives	Endpoints
Primary	
To compare the efficacy and safety of Budesonide-formoterol maintenance and/or reliever therapy versus standard therapy: Budesonide maintenance or Budesonide-formoterol maintenance, both with Terbutaline reliever, in children age 5 to 11 years with mild, moderate and severe asthma	• Asthma exacerbations (moderate and severe) as rate per participant per year, from randomisation to study completion at 52 weeks.
Secondary	
To compare the efficacy of Budesonide-formoterol maintenance and/or reliever therapy versus standard therapy: Budesonide maintenance or Budesonide-formoterol maintenance, both with Terbutaline reliever, in children age 5 to 11 years with mild, moderate and severe asthma	**Asthma exacerbations** • The proportion of participants with at least one moderate or severe asthma exacerbation from randomisation to study completion at 52 weeks. • The proportion of participants with at least one severe asthma exacerbation from randomisation to study completion at 52 weeks. • The proportion of participants with at least one step up in treatment, from randomisation to study completion at 52 weeks. • The proportion of participants on each treatment step at study completion at 52 weeks. • Severe asthma exacerbations as the rate per participant per year from randomisation to study completion at 52 weeks. • Composite of asthma exacerbations (moderate and severe), or step up in treatment, as the rate per participant per year,

	from randomisation to study completion at 52 weeks. • Proportion of participants with at least one asthma exacerbation (moderate and severe), or step up in treatment, from randomisation to study completion at 52 weeks. • Step up in treatment, as the rate per participant per year, from randomisation to study completion at 52 weeks. • The time to first moderate or severe asthma exacerbation, from randomisation until event with maximum observation time 52 weeks. • The time to first severe exacerbation, from randomisation until event with maximum observation time 52 weeks. • The time to first moderate or severe asthma exacerbation, or step up in treatment, from randomisation until event with maximum observation time 52 weeks. • The time to first step up in treatment, from randomisation until event with maximum observation time 52 weeks. **Lung inflammation** • FeNO at 26 and 52 weeks. **Lung function** • FEV_1 at 26 and 52 weeks. **Hospitalisation** • The number of days in hospital from randomisation to study completion at 52 weeks. **School/ usual activities absences** • The number of days lost from school due to asthma from randomisation to study completion at 52 weeks (participant) • The number of days lost from usual activities due to childcare for asthma (parent(s)/guardian(s)) from randomisation to study completion at 52 weeks **Asthma symptom control** • ACQ-5 scores at randomisation, 26 weeks and 52 weeks.

To compare the safety of Budesonide-formoterol maintenance and/or reliever therapy versus standard therapy: Budesonide maintenance or Budesonide-formoterol maintenance, both with Terbutaline reliever, in children age 5 to 11 years with mild, moderate and severe asthma	**Corticosteroid Dose** • Total inhaled corticosteroid dose at 52 weeks • Total systemic corticosteroid dose at 52 weeks • Total composite corticosteroid dose (inhaled and systemic) at 52 weeks. **Inhaled beta2-agonist Dose** • Total inhaled $beta_2$-agonist dose at 52 weeks **Impact on growth** • The change in height from randomisation to study completion at 13, 26, 39 and 52 weeks. **Adverse Events/Serious Adverse Events** • The number and proportion of AEs from enrolment to study completion at 52 weeks. • The number and proportion of SAEs from enrolment to study completion at 52 weeks. • The number of courses of antibiotics for respiratory tract infections **Discontinuation/Withdrawal** • Proportion of participants who discontinue treatment or withdraw
To compare the cost effectiveness of Budesonide-formoterol maintenance and/or reliever therapy versus standard therapy: Budesonide maintenance or Budesonide-formoterol maintenance, both with Terbutaline reliever, in children age 5 to 11 years with mild, moderate and severe asthma	**Cost-effectiveness** • The incremental cost per moderate and/or severe exacerbation averted will be reported. Cost-effectiveness acceptability curves will be generated to estimate the uncertainty around this value. • The base-case analysis takes a health system perspective (asthma-related resource utilisation) in the 12-month follow-up period. Secondary analyses will include monetised time off school (participant) and time off from usual activities (caregiver). •
To compare the asthma-associated carbon footprint of Budesonide-formoterol maintenance and/or reliever therapy versus standard therapy: Budesonide maintenance or Budesonide-formoterol maintenance,	**Carbon footprint** • Asthma-related greenhouse gas emissions per participant per year

both with Terbutaline reliever, in children age 5 to 11 years with mild, moderate and severe asthma	

4 Study Design

4.1 Overall Design

The START CARE study is a multi-centre, open label, parallel groups, 2-sided superiority randomised controlled trial (RCT) comparing Budesonide-formoterol maintenance and reliever therapy to standard treatments which, depending on asthma severity and current 'Step-up' recommendations will be either of: Maintenance ICS (Budesonide), or ICS-LABA (Budesonide-formoterol), both with Terbutaline as the reliever therapy.

The study will include children age five to 11 years with a doctor's diagnosis of asthma, who are already prescribed either maintenance ICS or ICS-LABA plus SABA reliever therapy, corresponding to GINA steps 2, 3, or 4. Children must have the ability to correctly use the Turbuhaler DPI.

Children with a significant respiratory comorbidity, e.g. cystic fibrosis or bronchiectasis, who are unable or unwilling to switch from their current treatment regimen, are already using an ICS-LABA or ICS-SABA reliever, or are currently being treated per GINA step 5, are not registered with a General Practitioner (GP), or who have used systemic corticosteroids in the 6 weeks prior to Visit 1, will not be recruited.

At the initial visit, following informed consent and assent, and confirmation of eligibility, children who are able to demonstrate satisfactory Turbuhaler technique will undertake a 4-week run-in period. During this time, all participants will be provided with Control arm treatment corresponding to their GINA step at trial entry. This is to encourage use and familiarity with the Turbuhaler device prior to randomisation, and to minimise withdrawals due to device use failure. Participants who experience worsening asthma resulting in an acute prescription of systemic corticosteroids and/or a change in asthma treatment during the run-in period will not be randomised.

At Visit 2, children who demonstrate satisfactory Turbuhaler technique and are willing to continue, will be randomised 1:1 to the Budesonide-formoterol or Terbutaline reliever-based treatments, at the step based on the baseline treatment, as outlined in Section 6.1. Randomisation will be performed using a computer-generated sequence with a variable site block size, generated by a statistician, independent of investigators. Randomisation will be stratified by a severe attack in the last 12 months, and by GINA step 2 versus >2.

Each study participant will be followed up during the intervention period for 52 weeks. Participants who discontinue from the study intervention will continue to be followed up per the study schedule. Participants/guardians may withdraw at any time, without having to give a reason.

An independent Data Safety Monitoring Committee (DSMC) will review summary data of all serious adverse events, and protocol deviations/violations and provide advice to the Trial Steering Committee, as outlined in Appendix 1.

4.2 Justification for Dose

4.2.1 Standardisation of ICS and delivery device

The standardisation of ICS to Budesonide in both treatment arms, delivered alone (Pulmicort Turbuhaler®) or in combination with Formoterol (Symbicort Turbuhaler®), in a DPI, prevents potential bias due to the different potency of different ICSs and different devices, and thereby provides a clearer comparison between two treatment concepts.

4.2.2 Control arm

The control arm follows the 2022 GINA Global strategy for asthma prevention and management recommended treatment and doses for children with asthma age 11 years or younger.

Terbutaline (DPI) 500mcg, 1 inhalation as needed, has a similar efficacy to 200mcg of Salbutamol and 6 mcg of formoterol, as reliever therapy in asthma.[11]

The doses of Budesonide prescribed in the control arm correspond with the GINA 2022 recommendations for "daily low dose ICS" at Step 2 (total daily budesonide dose, 200mcg) and "medium dose ICS" at Step 3 (total daily budesonide dose, 400mcg).

The doses of Budesonide-formoterol prescribed in the control arm correspond with the GINA 2022 recommendations for "low dose ICS-LABA" at Step 3 (total daily dose, 200/12mcg) and "medium dose ICS-LABA" at Step 4 (total daily dose, 400/24mcg).

4.2.3 Intervention arm

The intervention arm follows the 2022 GINA Global strategy for asthma prevention and management recommended treatment and doses for children with asthma age 11 years or younger, at Steps 3 and 4. ICS-formoterol as sole reliever therapy, i.e. without maintenance treatment, is not currently recommended for children with asthma. The dose and approach are based on evidence from studies of as-needed ICS-formoterol in adolescents and adults with asthma (which have informed the GINA recommendations), and from studies of as-needed ICS plus SABA (separate inhalers) in children and adolescents age 5 to 18 years. Our rationale is detailed below:

4.2.3.1 Step 2: Budesonide-formoterol as needed

The TREXA and ASIST trials demonstrated the safety and efficacy of as-needed Beclomethasone 50mcg with Salbutamol 100mcg (separate inhalers) in children and adolescents age five to 18 years.[12,13] Participants took two inhalations of both inhalers as needed for symptomatic relief (total ICS/SABA doses per use of 100/200mcg respectively).

The efficacy of beclomethasone 50mcg is similar to Budesonide 50mcg, and the efficacy of Salbutamol 200mcg is similar to formoterol fumarate 6mcg and Terbutaline 500mcg.

$Beta_2$-agonist doses are the same in adults and children. Total recommended daily ICS doses in children are half the doses in adults. Each as-needed use episode delivers the same equivalent $beta_2$-agonist dose as in adults using ICS-formoterol reliever therapy, but half the ICS dose (1 inhalation of 100/6 vs 1 inhalation of 200/6).

The 100/6 dose is half the ICS dose at Step 2 of the GINA preferred track for adolescents and adults with asthma using an ICS-formoterol reliever.

4.2.3.2 Step 3: Very low-dose budesonide-formoterol maintenance and reliever

Bisgaard et al. reported Budesonide-formoterol MART in children age four to 11 years using a dose of Symbicort Turbuhaler® 100/6mcg once daily and as needed, was safe and effective:[8]

- Budesonide-formoterol MART 100/6mcg once daily plus PRN reduced asthma exacerbations by 70% compared with Budesonide 400mcg once daily.
- Patients receiving Budesonide-formoterol MART grew significantly more than patients on fixed-dose Budesonide (mean difference 1 cm, 95% CI 0.3 to 1.7, p=0.0054).
- The number of patients with abnormal pre–ACTH- and post–ACTH-stimulated plasma cortisol levels were similarly low in all groups (2/51 MART patients vs 1/55 fixed-dose ICS patients).

The maintenance dose of ICS-formoterol 100/6mcg once daily follows the principle of using the lowest regular dose of ICS to achieve good asthma control and minimize medication side effects.

The GINA-recommended dosing regimen for very low dose ICS-formoterol MART at Step 3 in children is "1 inhalation once daily as maintenance treatment, PLUS 1 inhalation as needed for symptom relief".

4.2.3.3 Step 4: Low-dose budesonide-formoterol maintenance and reliever

Budesonide-formoterol MART at doses of 100/6mcg one inhalation twice daily, and one inhalation as needed, improves asthma control in adolescents (12 to 17 years) compared to higher fixed-dose Budesonide (400mcg daily).

There have been no studies of ICS-formoterol MART at these doses in children age 11 years and under. However, the Symbicort Turbuhaler® 100/6mcg is approved for use in children age four years and older at a standard maintenance dose of 1–2 inhalations twice daily (maximum daily maintenance dose: 4 inhalations).

The GINA-recommended dosing regimen for low dose ICS-formoterol MART at Step 4 is "1 inhalation twice daily as maintenance treatment, PLUS 1 inhalation as needed for symptom relief".

4.2.4 Treatment escalation

Participants who have a severe asthma exacerbation, or change in treatment during the run-in period will be excluded (i.e. not randomised).

Participants on treatment steps 2 and 3 who have a severe asthma exacerbation, or 2 moderate exacerbations within the same treatment step, during the intervention period will be stepped up to the next level of treatment indicated by the treatment track relating to their randomised treatment (see Appendix 7). Participants on Step 4 treatment will continue on their current treatment.

The preferred maintenance treatment at Step 3 in the control arm is low-dose ICS-formoterol; all participants who are escalated from Step 2 should be started on this regimen.

Participants will be advised to contact their study team as soon as possible if they experience an asthma exacerbation (moderate or severe). The study team will arrange for an urgent review (unscheduled visit), within seven days of a severe exacerbation or a second moderate exacerbation occurring within their current treatment step. Their standard treatment will be stepped up during this review, in accordance with the START CARE stepwise treatment approach, if not already done so by their usual doctor or their treating medical team.

Investigators will only escalate treatment following a severe exacerbation or 2 moderate exacerbations that have occurred within the same treatment step. A participant's usual doctor may choose to step up a participant's treatment for another reason, such as poor asthma symptom control. Change of treatment to non-study medication will not result in the participant being withdrawn from the study. If necessary, the participant's inhaler medication will be changed to the appropriate study medication at their treatment step (e.g. a Beclomethasone inhaler will be switched to a Budesonide inhaler).

Treatment can only be "stepped up" during the trial and will not be "stepped down".

The participant's usual healthcare provider will be informed of any change of treatment during the trial.

4.3 End of Study Definition

A participant is considered to have completed the study if they have completed their final visit (either Visit 6 or withdrawal).

The end of study is defined as the date of the last visit of the last participant.

5 Study Population

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Patients of any gender age five to 11 years (inclusive) at Visit 1
2. Doctor diagnosis of asthma (self-report by parent/participant or healthcare provider-reported)
3. Use of ICS or ICS-LABA maintenance plus SABA reliever therapy (corresponding to GINA step 2, 3 or 4) in the 6 months prior to Visit 1
4. Registered with a General Practitioner
5. Satisfactory Turbuhaler technique
6. Inspiratory flow measurement of between 30 and 90 L/min
7. Provision of written informed consent (parent/guardian) and assent (participant)
8. Able and willing to switch from current treatment regimen

For randomisation at Visit 2, participants should fulfil the following criterion:

9. Satisfactory Turbuhaler technique
10. Inspiratory flow measurement of between 30 and 90 L/min

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Already using ICS-formoterol or ICS-Salbutamol as a reliever
2. Any use of high dose ICS-LABA (New Zealand Child Asthma Guidelines Step 5), biologics, maintenance oral corticosteroids (i.e. GINA Step 5), or leukotriene receptor antagonists in the last 6 months
3. Any use of systemic corticosteroids in the 6 weeks prior to Visit 1
4. Use of a beta-blocker in the 6 months prior to Visit 1
5. Any medical condition which, at the Investigator's discretion, may present a safety risk or impact the feasibility of the study or the study results (including, but not limited to, other significant respiratory comorbidities, such as cystic fibrosis and bronchiectasis)
6. Any known or suspected hypersensitivity (including rash, urticaria, angioedema, bronchospasm and anaphylactic reaction) to the active substances prescribed in the study (budesonide, formoterol, terbutaline), lactose or milk protein (excipient)
7. Any intravenous therapy for the treatment of asthma, in the last year.
8. Previous Intensive Care Unit admission for asthma, or ventilation for asthma, ever

9. Participation in another clinical trial of an investigational medicinal product in the 30 days prior to Visit 1

For randomisation at Visit 2, participants are excluded from the study if the following criteria apply:

10. Any severe exacerbation, or 2 moderate exacerbations (per protocol defined criteria) and/or a change in asthma treatment other than run-in study medication from Visit 1 until Visit 2.

5.3 Lifestyle Considerations

In general, there are no lifestyle restrictions during the study period. There are requirements to avoid food, drink and strenuous exercise/activity prior to undertaking of FeNO and Spirometry measures. These restrictions are set out in the applicable sub sections of Section 8, Study Assessments and Procedures.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened on one more occasion. Re-screened participants should be assigned a new participant number at the screening/re-screening event.

Individuals who do not meet the Visit 2 Inclusion criteria (satisfactory Turbuhaler technique and/or inspiratory flow) for participation in this study cannot be re-screened.

5.5 Criteria for Temporarily Delaying Study Intervention

Not Applicable

6 Study Intervention(s) and Concomitant Therapy

6.1 Study Intervention(s) Administered

Delivery of study medication during the run-in and intervention periods will be via DPI, for all participants.

6.1.1 Run-in period (Visit 1)

The inhalers, including the minimum number to be issued at each visit, per GINA treatment step at trial entry, are detailed below. The details of the individual inhalers used during the run-in period are described in Appendix 6.

Table 3: Run-in period inhalers at each treatment step

Treatment step	Regimen	Inhaler(s)	Minimum issued per visit
2	LD ICS + SABA PRN	Pulmicort Turbuhaler® 100	2
		Bricanyl Turbuhaler® 500	2
3	LD ICS-LABA + SABA PRN MD ICS + SABA PRN	Symbicort Turbuhaler® 100/6 *OR* Pulmicort Turbuhaler® 100	2
		Bricanyl Turbuhaler® 500	2
4	MD ICS-LABA + SABA PRN	Symbicort Turbuhaler® 100/6	2
		Bricanyl Turbuhaler® 500	2

LD = Low Dose; MD = Medium Dose; ICS = Inhaled CorticoSteroid; LABA = Long-Acting Beta-Agonist; SABA = Short-Acting Beta-Agonist; PRN = as required

6.1.2 Intervention period (Visits 2 to 6)

The inhalers, including the minimum number to be issued at each study visit, per treatment arm and treatment step, are detailed below. The details of the individual inhalers used during the intervention period are described in Appendix 6.

Table 4: Intervention period inhalers at each treatment step

Treatment arm	Treatment step	Regimen	Inhaler(s)	Minimum issued per visit
Control arm	2	LD ICS + SABA PRN	Pulmicort Turbuhaler 100	2

			Bricanyl Turbuhaler 500	3
	3	LD ICS-LABA + SABA PRN MD ICS + SABA PRN	Symbicort Turbuhaler 100/6 *OR* Pulmicort Turbuhaler 100	2
			Bricanyl Turbuhaler 500	3
	4	MD ICS-LABA + SABA PRN	Symbicort Turbuhaler 100/6	4
			Bricanyl Turbuhaler 500	3
Intervention arm	2	VLD ICS-formoterol PRN	Symbicort Turbuhaler 100/6	3
	3	VLD ICS-formoterol MART	Symbicort Turbuhaler 100/6	4
	4	LD ICS-formoterol MART	Symbicort Turbuhaler 100/6	5

LD = Low Dose; MD = Medium Dose; ICS = Inhaled CorticoSteroid; LABA = Long-Acting Beta-Agonist; SABA = Short-Acting Beta-Agonist; PRN = as required; VLD = Very Low Dose; MART = Maintenance And Reliever Therapy.

6.1.3 Post-trial

See Section 6.6.

6.2 Preparation, Handling, Storage, and Accountability

Further guidance and information for IMP and AMP (run-in and post-study inhalers) are provided in the IMP Handling Plan.

6.2.1 Preparation

6.2.1.1 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling.

6.2.1.2 Turbuhaler priming

All Turbuhaler inhalers need to be primed before their initial use. This should be done by the study team, as follows:

1. Unscrew and remove the cover.

2. Hold the inhaler upright.
3. Twist the base anticlockwise and then back until you hear a click. Do this twice.
4. The Turbuhaler is now primed and ready for use.

The procedure should be done for all Turbuhalers dispensed from Visit 1 onwards.
The priming should only be executed once per Turbuhaler (priming should not be repeated even if the inhaler is not used regularly). To avoid the misconception that priming is required before every use, all Turbuhalers dispensed will be primed by the study team, before they are given to the participant. Therefore, the participant will receive "ready-to-use" inhalers.

Instructions on how to use the Turbuhaler will be provided with the asthma action plans.

6.2.2 Handling

The investigator or designee must confirm on arrival to their site that the study interventions are not damaged and that the amounts and batch numbers received match the packing slip. Any discrepancies should be reported and resolved before use of the study intervention.

Used or unused IMP or AMP may be returned to the sponsor by site personnel only after approval has been provided by the sponsor. Destruction will be performed by the sponsor according to local regulations.

All destruction should be documented and the destruction records retained by the investigator and sponsor.

6.2.3 Storage

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

6.2.4 Accountability

Only participants enrolled in the study may receive study intervention, and only authorised site staff may supply or administer study intervention.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

Participants will be advised not to share their allocated inhalers and not to use other non-study inhalers or nebulisers, unless indicated by their doctor. If a participant does use a non-study inhaler, or nebulisers, they/their guardian will be asked to document this. Participants who use non-study inhalers or nebulisers will not be withdrawn from the trial.

6.2.5 Dispensing

The individual number of inhalers for a participant is prepared from a bulk supply, where the preparation and labelling of the inhalers will be confirmed by a second member of the study site staff.

Participant/guardian receipt of all IMP and AMP must be confirmed by study staff.

6.2.5.1 IMP Dispensing

Participants who are randomised will be provided with a 3-month supply of IMP at visits 2, 3, 4, and 5. The type of inhalers, and the number of inhalers, dispensed at each visit will vary according to treatment arm and treatment step. The number of inhalers dispensed at each visit will be recorded.

IMP will be returned at all subsequent visits after Visit 2. Returned medication will be stored at site until the Sponsor confirms it may be destroyed.

6.2.5.2 AMP (Auxiliary Medicinal Products) Dispensing:

Participants will be issued with inhalers for the run-in period at Visit 1, to be returned at Visit 2. Participant/guardian receipt of inhalers must be confirmed by study staff.

Participants will be issued with post-study inhalers at Visit 6 (or withdrawal/treatment discontinuation if required). Participant/guardian receipt of inhalers must be confirmed by study staff.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study in which the participants, their parent(s)/guardian(s), and the study team are aware of the randomised treatment. Blinding is not being performed in order to maintain the potential real-world advantage of the use of a single inhaler with the Budesonide-formoterol single-inhaler maintenance and/or reliever therapy regimen (intervention arm), which would not be possible with the use of dummy devices. A participant's treatment allocation will only be revealed to the researchers when that participant is randomised. The study statistician will be masked while performing the primary analysis of the primary outcome variable.

Eligible participants will be randomised 1:1 to either the Budesonide-formoterol maintenance and/or reliever (intervention) arm or the Budesonide/Budesonide-formoterol plus Terbutaline reliever (control) arm, with stratification according to their:

- History of a severe asthma exacerbation in the previous 12 months (0 or ≥1)

- GINA Step (2 or >2)

Randomisation will be performed using a computer-generated sequence to maintain allocation concealment. Block size will vary by site. The schedule will be generated by the study statistician, independent of the Investigators. 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 number). Randomisation codes will be sequentially assigned at the point of randomisation. Randomisation codes cannot be re-used.

6.4 Study Intervention Compliance

No formal compliance measures will be performed. For each Turbuhaler device, the number of inhalations remaining at dispensing will be recorded. All dispensed inhalers that are returned by participants will be returned to the sponsor for performing dose counting, for the purpose of the total inhaled steroid dose and carbon footprint analyses. Participants will be asked at each visit if they have been using their inhaler as directed and/or used any other inhalers. Participants will be issued asthma action plans, which include guidance for what constitutes high use and instructions on when to seek medical help. Non-adherence will not result in withdrawal.

A record of the quantity of study inhalers dispensed to, and administered by, each participant will be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded.

6.5 Dose Modification

See Section 4.2.3.

6.6 Continued Access to Study Intervention after the End of the Study

After completion of study treatment (visit 6/withdrawal) patients will receive asthma medication prescribed according to the investigator's judgment and local medical practice. The exception is if the participant’s asthma treatment is already being managed by their usual healthcare provider, as in the case of treatment discontinuations.

Participants will be provided with at least one of the following “reliever” inhalers:

- Symbicort Turbuhaler® (Budesonide-formoterol) 100/6mcg (age <12 years at their final study visit) or 200/6mcg (age 12 years at their final study visit) DPI; or
- Respigen (Salbutamol) 100mcg pMDI with spacer (Airflow Space Chamber Plus)

Participants will also be provided with a prescription for at least one maintenance inhaler and at least one further reliever inhaler. The choice of post-trial maintenance treatment is up to the investigator in consultation with the participant and their parent/guardian. They should consider

device and regimen preference and all prescribed treatments should consider the relevant guideline recommendations at the time of prescribing. Participants will be advised to follow up with their usual doctor within one month of finishing the study, to review their ongoing asthma management.

All participants will receive a relevant NZ Asthma and Respiratory Foundation asthma action plan. This will detail the prescribed regimen.

6.7 High use/ Extreme Overuse episodes

The risks associated with overdosage of Budesonide (Pulmicort Turbuhaler®), Budesonide-formoterol (Symbicort Turbuhaler®), and Terbutaline (Bricanyl Turbuhaler®) are considered to be small, as the safety margins for inhaled budesonide, formoterol, and terbutaline are substantial.

Participants will be advised to seek medical advice if they meet the threshold for high beta$_2$-agonist use (as detailed in their asthma action plan (Appendix 8 and Section 6.7.2)) or experience any side effects of concern.

6.7.1 Inhaled corticosteroids (Budesonide)

Budesonide 100mcg, is approved for use in children 6 years and older in New Zealand.

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic corticosteroid effects may appear, such as hypercortisolism and adrenal suppression.

6.7.2 Beta$_2$-agonists (Formoterol and Terbutaline)

Formoterol 6mcg, in combination with budesonide 100mcg, is approved for use in children age 4 years and older in New Zealand. A total daily dose of more than 4 inhalations (400/24mcg) is not normally needed, however a total daily dose of up to 8 inhalations (800/48mcg) can be used temporarily. This limit of 8 inhalations per day is the same as the threshold set in the one previous study of ICS-formoterol maintenance and reliever therapy in children age 4 to 11 years.[8]

A total daily dose of more than 8 inhalations of Terbutaline 500mcg (i.e. 4000mcg) should not be exceeded. In clinical practice, an upper limit on the number of total daily inhalations is rarely imposed. Advice in acute asthma is to give bursts of 6 inhalations of a short-acting beta$_2$-agonist (equivalent to Terbutaline 1500mcg), repeated every 15 to 20 minutes as required to achieve good effect.

Terbutaline 500mcg (1 inhalation) and Formoterol 6mcg (1 inhalation) achieve a similar bronchodilator response.[11]

The advice in Table 5 is provided to participants and is incorporated in their asthma action plans (provided at Visit 1 and reviewed at all subsequent in-person visits).

Table 5: High use episodes and action required

Intervention arm: **High ICS-formoterol use**	**Control arm:** **High SABA use**	**Action**
More than 4 reliever inhalations a day, for one week	More than 4 reliever inhalations a day, for one week	See their GP within one week to review, add, or amend their current maintenance therapy
More than 6 reliever inhalations a day	More than 6 reliever inhalations a day	See their GP or attend ED today
More than 8 reliever inhalations a day	More than 8 reliever inhalations a day	They need to attend ED immediately

An overdose of formoterol or terbutaline would likely lead to effects that are typical for beta$_2$-agonists: tremor, headache, palpitations, and tachycardia. Hypotension, metabolic acidosis, prolonged QTc-interval, arrhythmia, nausea, vomiting, hypokalaemia and hyperglycaemia may also occur.

Normally, an overdose of Budesonide-formoterol or Terbutaline should not require any special treatment. However, if signs of adrenergic effects occur, these should be counteracted by supportive and symptomatic treatment, according to local routines.

6.7.3 Extreme overuse reporting

For the purpose of this study, self-report of an accidental or deliberate intake of beta$_2$-agonist treatment of more than 16 inhalations of Budesonide-formoterol (≥1,600/96mcg) in the intervention arm or 16 inhalations of Terbutaline (≥8,000mcg) in the control arm, during a 24-hour period, is defined as extreme overuse. The Investigator or other site personnel must inform the sponsor immediately, or no later than 24 hours of when they become aware of it.

The designated sponsor representative will work with the investigator to ensure that all relevant information is provided to the sponsor.

An extreme overuse event with associated AEs is recorded as the AE diagnosis on the relevant AE form. An extreme overuse event without associated symptoms should not be recorded as an AE.

For extreme overuse events associated with a SAE, the standard reporting timelines apply.

6.8 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study will be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Concomitant medications will be reviewed at the screening visit to ensure the participant fulfils the eligibility criteria in respect to current use of asthma medications. The monitor/medical monitor should be contacted if there are any questions regarding concomitant or prior therapy and whether the participant meets the eligibility criteria.

Should a participant be prescribed additional asthma treatments, this will be documented, and the participant will remain in the study.

Should a participant be prescribed a beta blocker medication, the site should discontinue randomised treatment.

7 Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant may remain in the study (i.e. attend study visits and engage with study procedures).

Reasons for discontinuation of the study intervention include:

- Participant and/or parent/guardian decision.
- Adverse Event.
- Unsatisfactory Turbuhaler technique and/or inspiratory flow rate, despite education and training.
- Severe non-compliance with the study intervention.

At the time of discontinuing from the study intervention, a treatment discontinuation visit should be conducted (procedures as for Visit 6; see the SoA for data to be collected at the time of discontinuation of study intervention).

A participant who decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If the participant discontinues trial treatment due to an AE or SAE, the Investigator will arrange for any necessary follow-up until the AE or SAE has resolved or stabilised.

All study IMP should be returned by the participant. Their asthma care (including medications) will be managed by their usual doctor.

Data will continue to be collected from participants and their parent(s)/guardian(s).

7.2 Withdrawal from the Study

Participants will be withdrawn if they experience a life-threatening exacerbation (requiring intensive care admission or intravenous treatment). Parent/guardians will be able to withdraw their child at any stage. Importantly, participants who have their treatment escalated by a non-study clinician (e.g. due to chronic asthma symptoms), will not be withdrawn.

- A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, a withdrawal visit should be conducted, as shown in the SoA (Section 1.3.). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the parent(s)/guardian(s) withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. In addition, to ensure the data for the primary outcome is complete, for those that withdraw consent or are lost to follow-up, consent will be obtained to access medical records for the purpose of obtaining data regarding healthcare visits due to worsening asthma and/or prescription of medications for the treatment of asthma (e.g. systemic corticosteroids), that occurred during the period from withdrawal/loss to follow-up to 1 year from the date of randomisation.
- All study IMP should be returned by the participant. Their asthma care (including medications) will be managed by their usual doctor.
- The participant will not attend future study visits or provide participant-reported data.
- Withdrawn participants will not be replaced.

7.3 Lost to Follow up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (at least 5 telephone calls, an email, and a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's trial record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

The date of lost to follow up will be the date that the study team last had contact with the participant. This will be determined retrospectively at 365 days after the date of randomisation.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3.).

- In the event of a natural disaster or national public health restrictions preventing usual study conduct (such as a COVID-19 pandemic wave), provision will be made for study visits to be done virtually using video conferencing software. This is detailed in a separate document.
- Immediate safety concerns should be discussed with the sponsor upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Deviations from the protocol or guidance documents should be reported to the sponsor as soon as possible.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log (or equivalent report) to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1 Screening and run-in periods

8.1.1 Screening (Visit 1)

Potential participants will attend a screening visit where, if appropriate, they will undergo informed consent/assent and their eligibility will be assessed based on inclusion and exclusion criteria (see section 5.1 and 5.2). A Screening number (sequential number at that site prefaced with the letter S and the designated site number) will be assigned during the consent/assent process. Those who do not meet the eligibility criteria will not proceed to the run-in period and/or randomisation. The reason for ineligibility will be recorded.

8.1.1.1 Informed consent and assent

Both assent of the participant, and consent of a parent/ guardian, are required to enrol in the trial. If the participant or parent/guardian declines to assent/ consent, the participant will not be enrolled.

Electronic consent and assent will be obtained and confirmed by means of parent/guardian- and participant-dated e-signatures, and a dated e-signature of the investigator who presented the study information and obtained the informed consent and assent. The parent/guardian will be provided with a copy of the e-signed informed consent and assent form (either by email or in printed hard copy form).

Where it is not possible to gain written consent and assent electronically during an in-person visit, written consent and assent will be obtained and confirmed by means of parent/guardian- and participant-dated wet-ink signatures, and the dated wet-ink signature of the Investigator who presented the study information and obtained the informed consent and assent. The parent/guardian

will be provided with a copy of the signed paper informed consent and assent form; the original signed form will be retained at the trial site.

Only one parent or legal guardian is required to provide informed consent on the participant's behalf. If an investigator becomes aware that the person who provided consent on behalf of the participant has lost their authority to give such consent, they should seek consent from the participant's new legal guardian as soon as possible.

8.1.1.2 Demographics

The following basic demographic information will be collected during the screening visit:

- Date of birth
- Age
- Ethnicity
- Ethnicity for Spirometry (GLI reference values)
- Sex at birth
- Participant and parent/guardian contact details and emergency contact details
- GP contact details

8.1.1.3 Asthma History and Medical History

The following information should be collected as part of the eligibility assessment at Visit 1 and Visit 2:

- Age at symptom onset and age at asthma diagnosis
- Current (last 6 months) and previous medications (ever) for asthma
- Current maintenance inhaler (ICS or ICS-LABA) use in the last 4 weeks
- Total number of asthma or wheeze exacerbations (moderate, severe) in the last 52 weeks
- Prescription of systemic corticosteroids in the last 6 weeks, and 52 weeks
- ED visits for asthma in the last 52 weeks
- Hospitalisation for asthma in the last 52 weeks, and intensive care unit admissions or requirement for ventilation ever
- Current use of an asthma action plan
- Other medical conditions and medications
- Current household exposure to tobacco smoke and e-cigarette fumes

8.1.1.4 Turbuhaler technique and inspiratory flow rate

As part of their eligibility assessment, participants will receive education and training on how to correctly use a Turbuhaler. Education will include demonstration by a member of the study team, and an educational video. Participants will be asked to demonstrate satisfactory technique using a Turbuhaler demonstration device (Appendix 11). They will also be required to demonstrate an inspiratory flow rate of between 30 to 90 L/min using an Inspiratory Flow measurement device.

The participant will practice their technique with the training devices as many times as necessary, as judged by the supervising study staff. Participants who are unable to demonstrate satisfactory Turbuhaler technique and/or inspiratory flow rate will not proceed to the run-in period.

Participants will be provided with both an inspiratory flow training device and an upload of the educational video for use throughout the run-in and intervention periods.

At visit 2, prior to randomisation, Turbuhaler technique and inspiratory flow rate will be reassessed, with retraining provided as required. Participants who are unable to demonstrate satisfactory Turbuhaler technique and/or an inspiratory flow rate will not be randomised.

8.1.2 Run-in period

Participants who fulfil the inclusion and none of the exclusion criteria at visit 1 will enter a 4-week run-in period.

Participants will be asked to stop taking their prescribed asthma medication used at the time of study entry. All participants will receive a Bricanyl Turbuhaler® 500mcg for 'as needed' use during the run-in period. In addition, all participants will receive a maintenance inhaler, with the drug and dose prescribed dependent on the participant's prescribed asthma medication and GINA treatment step at study entry (visit 1):

- Participants prescribed low or medium dose ICS (Appendix 12) at study entry will use the Pulmicort Turbuhaler® 100mcg.
- Participants prescribed low or medium dose ICS-LABA (Appendix 12) at study entry will use the Symbicort Turbuhaler® 100/6mcg.
- Participants entering the study on Step 4 treatment will use the Symbicort Turbuhaler® 100/6mcg regardless of what maintenance they were taking on entry to the study

8.1.3 Randomisation

The Investigator should confirm eligibility prior to randomisation (see Sections 5.1 and 5.2). Participants who fail to meet the eligibility criteria must not be randomised.

Randomisation codes will be assigned sequentially as participants become eligible for randomisation. If a participant withdraws from participation in the study, their randomisation code cannot be reused.

Participants entering the study that are randomised to the control arm will enter the study on the same maintenance inhaler regime as they have been on for the run-in period:

- Participants prescribed Budesonide (Appendix 11) for run-in will use the Pulmicort Turbuhaler® 100mcg.
- Participants prescribed ICS-LABA (Appendix 11) for run-in will use the Symbicort Turbuhaler® 100/6mcg.

8.2 Efficacy Assessments

8.2.1 Asthma exacerbations

An "asthma exacerbation" encompasses both moderate and severe asthma exacerbations.

- A severe asthma exacerbation is defined as worsening asthma leading to either:
    - An urgent, unplanned medical review (e.g. primary care or emergency department (ED) visit) or hospital admission; resulting in an acute prescription of systemic corticosteroids (tablets, suspension, or injection); OR
    - The use of systemic corticosteroids for 3 or more days.
    - A hospital admission for ≥24 hours.
- A moderate asthma exacerbation is defined as worsening asthma leading to either:
    - An urgent, unplanned medical review (e.g. primary care or ED visit) or hospital admission for less than 24 hours; **not** resulting in an acute prescription of systemic corticosteroids (tablets, suspension, or injection – e.g. oral prednisone); OR
    - The use of systemic corticosteroids for less than 3 days, which does not meet the criteria for a severe asthma exacerbation (e.g. use of systemic corticosteroids from a non-acute prescription, such as a home supply or delayed script).

The start date for each asthma exacerbation will be recorded.

- For severe asthma exacerbations, the start date is the day they were first prescribed or used systemic (i.e. not inhaled) corticosteroid treatment (e.g. Redipred) or the first day of hospitalisation. If the same asthma exacerbation includes both systemic corticosteroid treatment and hospitalisation, the start date is the first day that either criteria was fulfilled. The date of discharge must also be recorded for hospitalisations for asthma.
- For moderate attacks, the start date is the date the participant attended their first urgent, unplanned medical review for the current asthma exacerbation or used systemic steroids.
- If an exacerbation meets the criteria of both a moderate and severe exacerbation, it will be counted as a severe exacerbation.

- If an exacerbation also meets the criteria of a step up in treatment it will be considered a single event for the composite outcome of an asthma exacerbation (moderate and severe), or step up in treatment.

Children on higher treatment steps may be prescribed a home supply of systemic corticosteroids (such as Redipred) to take when their asthma flares up. For this reason, the use of oral steroids is incorporated in to the severe attack definition (for 3 or more days) and the moderate attack definition (less than 3 days).

It is possible that more than one urgent, unplanned medical review and/or prescription for systemic corticosteroids for worsening asthma may occur during a single asthma exacerbation. Each prescription and healthcare encounter must be recorded.

For a severe asthma exacerbation to be counted as a separate event, it must be preceded by at least seven days during which no criteria for a severe asthma exacerbation are fulfilled.

For a moderate asthma exacerbation to be counted as a separate event, it must be preceded by at least seven days during which no criteria for a moderate or severe asthma exacerbation are fulfilled.

8.2.2 Days lost from school and/or usual activities due to asthma

Data on days lost from school due to asthma (participant) and days lost from usual activities due to childcare for asthma (parent/guardian) will be collected at all visits during the treatment period.

Time off school equals time off education. If a participant is home-schooled or studying from home due to government advice (e.g. during a pandemic lockdown), any time out of their studies due to asthma is considered time off school.

8.2.3 Asthma Control Questionnaire, five-question version (ACQ-5)

The ACQ-5 (Appendix 9) will be administered, in accordance with the ACQ-5 user guide at visits 2, 4, and 6. An interviewer-administered version of the ACQ-5 should be used for all children.[14]

8.2.4 Fractional exhaled Nitric Oxide (FeNO)

FeNO will be measured in accordance with guidelines published by the ATS,[15] using a NIOX VERO® device (Circassia), at visits 2, 4 and 6/treatment discontinuation/withdrawal. Appropriate infection control procedures will be followed at each study site. Participants will be advised to abstain from food, drink and strenuous exercise for one hour prior to the measurement being taken. Participants will not be required to withhold medication. FeNO will be obtained prior to spirometry being performed. Further guidance for performing FeNO measures is found in the Study Reference Manual.

8.2.5 Forced Expiratory Volume over 1 second (FEV_1)

Spirometry will be performed according to standard technique in line with the ATS/ERS 2019 standards, using an NND Easy on-PC Spirometer,[16] at visits 2, 4 and 6/treatment discontinuation/withdrawal. Appropriate infection control procedures will be followed at each study site. Participants will not be required to withhold medication. Reversibility testing is not required at any visit. The results will be interpreted according to ATS criteria,[17] using GLI reference ranges. Site personnel will be trained on spirometry technique to ensure quality. Training will be completed prior to or at the site initiation visit, and during the study as required. In addition, spirometry reports will be over-read by specialists to confirm the spirometry data that can be included in the analysis dataset. Further guidance for performing spirometry measures is found in the Study Reference Manual.

8.3 Safety Assessments

Section 8.4 outlines the requirements for reporting of Adverse Events and Serious Adverse Events.

8.3.1 Height and weight

Height will be measured at visits 2 (randomisation), 3, 4, 5 and 6/treatment discontinuation/withdrawal using a stadiometer, to determine growth velocity during the study. Weight will be measured at visits 2 and 6/treatment discontinuation/withdrawal with electronic weighing scales. Participants will take off their shoes for both measurements.

8.3.2 Turbuhaler technique

Turbuhaler technique and inspiratory flow rate will be reassessed at all visits (scheduled and unscheduled). Participants will be provided with both an inspiratory flow training device and access to the educational video for use throughout the run-in and intervention periods.

Participants will be re-educated as necessary. Participants will also receive written instructions on correct technique as part of their asthma action plan.

In between visits, participants will have access to education videos on inhaler technique, as well as asthma action plans.

At visit 6/treatment discontinuation/withdrawal, participants will be educated/trained on the appropriate technique for their choice of post-trial inhaler device (pMDI or DPI).

8.3.3 Asthma Action Plans

All participants will be provided with a study-specific asthma action plan relating to their randomised arm (Appendix 8) at visit 2. These plans have been adapted from the Asthma and

Respiratory Foundation of New Zealand asthma action plans (both child and adult versions) with guidance from paediatric respiratory specialists and a paediatric emergency medicine physician.

The purpose of these plans is to reinforce the randomised treatment regimens, and to provide written instructions on what to do in the event of worsening asthma (including when to see a GP and when to seek emergency treatment). Participants should be educated on how to use their plans at each visit, with plans reissued as appropriate (e.g. lost plan, or change in treatment).

Participants will not be required to measure their peak flow or to fill in a record card every day.

The reverse side of the asthma action plans contains a log sheet for recording asthma-related events. It also contains information on how to use and look after their inhalers.

8.3.4 Unscheduled visits

Unscheduled visits should be undertaken in the following circumstances:

8.3.4.1 Unscheduled visit following a severe asthma exacerbation or two moderate exacerbations

Acute management of a severe asthma exacerbation is determined by the medical team treating the participant. Following discharge, participants should follow any prescribed weaning regimen (this will likely include a SABA for both treatment arms). Participants will be asked to record the dose and duration of this treatment.

Participants should contact investigators as soon as possible if they experience an asthma exacerbation (moderate or severe). Investigators should arrange for urgent review within seven days of a severe asthma exacerbation or after a second moderate exacerbation occurs within the same treatment step. During this review, participants will have their standard treatment stepped up in accordance with the START CARE stepwise treatment track appropriate to their treatment arm (Appendix 7), if not already done so by their usual doctor or the medical team treating their acute asthma.

Investigators will only escalate treatment following a severe exacerbation or 2 moderate exacerbations that have occurred within the same treatment step. A participant's usual doctor may choose to step up a participant's treatment for another reason, such as poor asthma symptom control. Change of treatment to non-study medication will not result in the participant being withdrawn from the study. If necessary, investigators will change the participant's inhaler medication to align with the START CARE stepwise treatment track (e.g. changing a Beclomethasone inhaler to a Budesonide inhaler). Treatment will not be de-escalated. The GP will be informed of any change of treatment.

8.3.4.2 Unscheduled visit for IMP dispensing and/or training

Participants or their parent(s)/guardian(s) should contact a member of the study team to arrange a visit as soon as practically possible if they require additional inhalers due to high-use, as outlined in Section 6.7, or if the inhaler(s) are not working properly.

At the visit, participants will be reviewed for AEs and SAEs and their inhaler technique assessed (with re-training as necessary). If a participant or their parent(s)/guardian(s) report high-use, then they should be managed as detailed in Section 6.7.2.

Participants and their parent(s)/guardian(s) should be advised to contact a member of the study team if they have any concerns with their inhaler technique. The study team should meet with the participant to assess technique and provided education and training as necessary to achieve satisfactory technique.

If a participant requires additional inhalers due to losing their existing supply, or due to expiry, then unscheduled dispensing can be performed. This does not require an in-person visit, inhalers may be dispensed and couriered/ supplied to the participant/ parent(s)/guardian(s) as required. The investigator should ensure that an in-person unscheduled visit is not required (i.e. that re-supply is not required due to high use or any other safety concern).

8.3.4.3 Unscheduled visit for consideration of withdrawal

Participants and their parent(s)/guardian(s) have the right to withdraw from the study at any time. They do not have to provide a reason.

Investigators may withdraw a participant from the study at any time. Reasons for withdrawal include:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- An adverse event which results in inability to comply with trial procedures

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. This is to take place as soon as practically possible. Participants and their parent(s)/guardian(s) will be asked to bring all dispensed inhalers to the visit.

At this visit, an investigator will undertake an asthma review. If the participant withdraws, or is withdrawn, the visit should be conducted as for visit 6. An exception to this is if the participant, or their parent(s)/guardian(s), declines consent or assent. In addition to visit 6 procedures, the reason for withdrawal should be documented. If the participant and/or their parent(s)/guardian(s) declines to give a reason, as is their right, then this should be documented.

If the participant is withdrawn, they will be provided with post-trial treatment, as outlined in section 6.6. The investigator will inform the participant's GP of their withdrawal from the study.

8.3.5 GP Communications

The participant's usual healthcare provider (i.e. their GP) must be informed of the participant's involvement in the trial. At a minimum, the participant's GP will receive a letter from an investigator when the participant:

- Is enrolled in the study
- Is randomised (must include the participant's randomised treatment and treatment track)
- Has their treatment changed (including treatment discontinuation)
- Completes or withdraws early from the study

The participant should also receive a copy of these letters.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3.

AEs will be reported by the participant or, by a guardian, or the participant's legally authorised representative.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the informed consent/assent forms until the final visit (either visit 6 or early withdrawal) at the timepoints specified in the SoA (Section 1.3).

All AEs will be collected from enrolment (visit 1) until final visit (either visit 6 or early withdrawal) at the timepoints specified in the SoA (Section 1.3).

Medical occurrences that do not meet serious adverse event criteria, that begin before the start of study intervention will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be

reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant/guardian is the preferred method to inquire about AE occurrences. AEs/SAEs may also become apparent through review of completed asthma action plans, in which case investigators should confirm the necessary details with the parent/guardian, including further questioning, in order to complete the AE form.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). AEs should be followed up whilst the participant remains on study. Where appropriate the investigator should ensure that the participant's GP/healthcare provider is aware of AEs that are unresolved at the time of study completion, to ensure appropriate ongoing management.

Further information on follow-up procedures is provided in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

All SAEs have to be reported, whether or not considered causally related to the investigational product. The Sponsor is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with NZ regulatory requirements relating to safety reporting to the regulatory authority, the responsible Ethics Committee, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the relevant reference safety information (e.g. Investigator's Brochure or applicable Medsafe Datasheet) and will notify the responsible Ethics Committee, if appropriate according to their requirements.

In addition to the above, SAEs related to the IMP will be provided to AstraZeneca within 24 hours of sponsor knowledge, on an ongoing basis, as individual case reports. SAEs unrelated to the IMP

will be provided to AstraZeneca as individual case reports on an ongoing basis. SAEs that do not require expedited reporting to the regulatory authorities will still be reported to AstraZeneca as individual case reports, on an ongoing basis.

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to AstraZeneca at the same time these events are notified to the Regulatory Authority.

At the end of the Study, a final summary line listing of all SAEs will be provided to AstraZeneca to enable reconciliation of safety information held by AstraZeneca for its product.

8.5 Pharmacokinetics

Not Applicable. PK parameters are not evaluated in this study

8.6 Genetics

Not Applicable. Genetics are not evaluated in this study.

8.7 Biomarkers

Fractional Exhaled Nitric Oxide (FeNO) is measured as outlined in Section 8.2.3

8.8 Immunogenicity Assessments

Not Applicable. Immunogenicity is not evaluated in this study.

8.9 Health Economics

The investigator and study site personnel will collect data about health care resource utilisation associated with medical encounters and medication use.

The data collected will include:

- Incidence of asthma exacerbations (from asthma exacerbation review)
- Concomitant medications used for the treatment of asthma
- Time taken off school due to asthma
- Time taken off usual activities (parent/ guardian) due to participant's asthma
- Healthcare visits due to asthma (routine/ planned and unplanned/ urgent)
- Expenses incurred due to asthma

The sponsor may use the collected data to conduct economic analyses.

8.10 Discrete Choice Experiment (DCE) Sub-study

Participants over the age of 10 years and all parents/guardians of participants enrolled in the START CARE study at a site participating in the START CARE DCE sub-study will be asked to participate. There is a separate protocol document for this sub-study.

9 Statistical Considerations

The statistical analysis plan will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses than described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Any deviation(s) from the original statistical plan will be described and justified in the final report.

9.1 Statistical Hypotheses

The primary objective is to identify if Budesonide-formoterol single-inhaler maintenance and/or reliever therapy is superior to standard ICS maintenance, or ICS-LABA maintenance, with SABA reliever-based treatments, in achieving a reduction in asthma exacerbation rates up to 52 weeks after randomisation. Thus, the null hypothesis tested in relation to the primary endpoint is: Budesonide-formoterol single-inhaler maintenance and/or reliever therapy is not different from traditional ICS or ICS-LABA maintenance and SABA reliever-based treatments for asthma exacerbation rates up to 52 weeks after randomisation.

9.1.1 Multiplicity Adjustment

All estimates will be given as 95% confidence intervals, with a nominal two-sided type I error rate of 5%. We will not adjust secondary analyses for multiple analyses; the secondary analyses will be considered exploratory.

9.2 Analysis Sets

Analysis Set	Description
Full intention-to-treat analysis set	All randomised participants (excluding those who were randomised, but subsequently determined to be ineligible). Participants will be included in the analyses according to the intervention to which they were randomised.
Per protocol analysis set	All randomised participants (excluding those who were randomised, but subsequently determined to be ineligible). Participants will be included in the analyses according to the intervention to which they were randomised. Data will be censored at the point of treatment discontinuation or study completion/withdrawal.

Analysis Set	Description
Safety analysis set	All randomised participants (including those who were randomised, but subsequently determined to be ineligible) that received at least one dose of the run-in period study medication. Participants will be included in the analyses according to the intervention to which they actually received.

9.3 Statistical Analyses

9.3.1 General Considerations

Analysis will be by intention-to-treat by a biostatistician blinded as to treatment allocation.

9.3.2 Primary Endpoint(s) Analysis

Analysis will be by intention-to-treat superiority analysis by a biostatistician blinded as to treatment allocation. The primary analysis is by estimation of the relative rate of total asthma exacerbations per participant per year by Poisson regression with an offset for the time of observation and a fixed effect of randomised treatment allocation. Over-dispersion will be evaluated prior to analysis and a corrected analysis applied if necessary.

A sensitivity analysis will include the following potentially important predictors of response at baseline: age, sex, ethnicity, ACQ-5 score, GINA step (2 or ≥2), FeNO, trial site, and the number of severe asthma exacerbations in the previous 12 months, to account for possibly different distributions of these variables in the treatment groups and to potentially increase precision of the estimates of differences. Ethnicity will be treated as: European, Māori, Pacific, Other; if there are low numbers, particularly for other, we will merge with European.

9.3.3 Secondary Endpoint(s) Analysis

Secondary outcomes will be analysed using Poisson regression for rates, logistic regression for dichotomised outcomes, ANCOVA for continuous variables, and survival analyses for time to event outcomes e.g. time to first asthma exacerbation.

All estimates will be given as 95% confidence intervals, with a nominal two-sided type I error rate of 5%. We will not adjust secondary analyses for multiple analyses; the secondary analyses will be considered exploratory.

9.3.3.1 Poisson regression with an offset for the time of observation and a fixed effect of randomised treatment allocation:

- Severe asthma exacerbations per participant per year

- Composite of asthma exacerbations (moderate and severe), or step up in treatment, as the rate per participant per year.
- Step up in treatment, as the rate per participant per year.
- Number of days lost from school due to asthma (participant)
- Number of days lost from usual activities due to childcare for asthma (parent(s)/guardian(s))
- Number of days in hospital

Data for the number of days in hospital is likely to be sparse. If it is not possible or appropriate to use Poisson regression, the data will be analysed descriptively.

9.3.3.2 Comparison of proportions by logistic regression:

- The proportion of participants with at least one asthma exacerbation
- The proportion of participants with at least one severe asthma exacerbation
- The proportion of participants with at least one step up in treatment, with baseline GINA step as a covariate.
- Proportion of participants with at least one asthma exacerbation (moderate and severe), or step-up in treatment with baseline GINA step as a covariate
- The proportion of participants on each treatment step, with baseline GINA step as a covariate
- The proportion of participants discontinued from treatment and reason
- The proportion of participants withdrawn and reason
- Adverse events
- Serious adverse events

9.3.3.3 Survival analysis illustrated by Kaplan-Meier plots and use of Cox's proportional hazards regression to estimate the hazard ratio in relation to the randomised treatment:

- Time to first asthma exacerbation
- Time to first severe asthma exacerbation
- Time to first moderate or severe asthma exacerbation, or step up in treatment
- Time to first step up in treatment

9.3.3.4 ANCOVA with baseline (where available) as a continuous covariate

- FEV_1
- FEV_1 z-score

- FEV_1 % predicted
- FEV_1 prediction value (GLI values)
- FeNO (on the logarithm-transformed scale)
- Growth velocity

9.3.3.5 ANCOVA and mixed linear models for repeated measures by time:

- ACQ-5

9.3.3.6 Analysis dependent on data distribution:

- Total systemic corticosteroid dose
- Total inhaled corticosteroid dose
- Total composite systemic corticosteroid dose
- Total inhaled $beta_2$-agonist dose
- The number of courses of antibiotics for respiratory tract infections

Data for total corticosteroid dose may be sparse. Methods that will be explored include: dichotomous variable "had a course of oral steroids or not"; attempt at Mann-Whitney test with Hodges-Lehmann confidence interval; and Poisson regression, treating courses of oral steroids as a count variable. For composite systemic corticosteroid exposure per year, this will be calculated as the total inhaled corticosteroid dose per year (converted to oral prednisone equivalent dose for systemic effects on adrenal function using the conversion factor of budesonide 5,000mcg inhaled to prednisone 10mg oral, defined in a previous bioequivalence study) added to the oral corticosteroid dose per year. For inhaled $beta_2$-agonist dose, Terbutaline 500mcg is considered equivalent to Formoterol 6mcg.

9.3.4 Tertiary/Other Endpoint(s) Analysis

- Proportion of screen fails and participants not randomised due to unsatisfactory Turbuhaler technique, by age and reason for unsatisfactory technique.

9.3.5 Sub-group and sensitivity analysis

Sub-group analyses will be performed for three outcome variables: rate of asthma exacerbations, rate of severe asthma exacerbation, and ACQ-5. In these sub-group analyses the differential effect of treatment on outcome will be explored with each of the following potential moderating variables:

- Severe asthma exacerbation in the 12 months prior to enrolment

- Age at enrolment
- Sex
- Ethnicity
- Trial site
- Smoking exposure
- ACQ-5 score at randomisation (for asthma exacerbations and severe asthma exacerbations outcomes only)
- FeNO at randomisation
- FEV_1 % predicted at randomisation
- Treatment step at randomisation

For illustration on the Forest Plot, baseline ACQ-5 score, and baseline FEV_1 % predicted will be dichotomised at the mean value of the control arm, and for baseline FeNO, the median value of the control arm.

9.3.6 Other Analyses

9.3.6.1 Economic analysis

The incremental cost per moderate and/or severe exacerbation averted will be reported. The probability that the intervention is cost-effective at various willingness-to-pay values for averting a moderate and/or severe exacerbation will be estimated by cost-effectiveness acceptability curves.

The base-case analysis will take a health system perspective (asthma-related resource utilisation) in the 12-month follow-up period. Caregivers' self-reported healthcare resource utilisation will consist of: asthma inhalers (by actuations); antibiotics; oral corticosteroids; GP visits, after hours clinics; ED visits; paediatric outpatient visits; inpatient hospitalisations (admissions and days per admission).

Secondary analyses will monetise time off school for the participant and time off usual activities (due to asthma caregiving) for the parent(s)/guardian(s).

Subgroup analyses will stratify the sample, as defined at randomisation, by (1) mild, (2) moderate, and (3) severe asthma.

9.3.6.2 Carbon footprint analysis

Carbon footprint per participant, expressed in kilograms of carbon dioxide equivalents (kg CO_2e), will be calculated based on inhaler device actuations (derived from the number of doses remaining on each returned inhaler) and healthcare encounters for asthma exacerbations.

9.3.6.3 Ethnicity analysis

Additional analyses will be undertaken to explore differences in outcomes according to ethnicity, in particular looking at outcomes of participants identifying as Māori or Pacific. This analysis will be defined in an additional analysis plan.

9.3.6.4 Missing data

For those variables with a baseline and more than one subsequent measurement, we will use mixed linear models as a preferred approach to incorporating observed values into the final outcome assessments, which assume missing data are missing at random.

9.3.6.5 Individual Patient Data meta-analyses

We plan to undertake individual patient meta-analyses combining the data from this study with:

- **NZ children's studies: PRECARE, SMART CARE and CARE.** The primary purpose of the individual participant meta-analysis for the NZ studies recruiting children is to get more precise estimates of the effect on asthma exacerbations. Asthma exacerbations will be treated in two ways; firstly, as a rate variable (number of asthma exacerbations per unit time) and analysed by Poisson regression with time in study as an offset variable and individual study as a confounding variable for randomised treatment. As secondary analyses of this set of studies effect modification will be explored by appropriate interaction terms between treatment and potential effect modifiers such as age and GINA step.
- **International SMART CARE consortium studies (Australia, NZ and UK)** in which 3 different Budesonide/formoterol maintenance and reliever therapy-based algorithms are to be investigated. A similar approach will be used for the international SMART CARE consortium studies with the additional predictor variable of type of Budesonide/formoterol maintenance and reliever therapy-based algorithm.
- **NZ portfolio of studies including the Novel START, PRACTICAL, SMART, PRECARE SMART CARE, and CARE** providing evidence across the spectrum of asthma severity in children, adolescents and adults. For the NZ portfolio of studies, the primary aim is to more precisely estimate the effects of modification variables.

9.4 Sample Size Determination

Severe asthma exacerbation rates in similar age children receiving GINA Step 2 to Step 4 treatment ranges from approximately 0.3 to 1.4 per patient per year, depending on the baseline level of severity and control, and whether there was a step up or step down in treatment. In the current CARE study of children with mild asthma, the number of moderate attacks is slightly higher than the number of severe attacks, indicating that the number of moderate and severe attacks is likely

to be at least double that of severe attacks. As a result, a baseline rate of moderate and severe attacks in the control regimen of 1.0 in this proposed study can be considered conservative.

By simulation from appropriate Poisson distributions, we estimate 320 participants are required to detect a difference in asthma exacerbation rates between 1.0 in the control arm and 0.67 in the Budesonide-formoterol intervention arm; rate ratio 0.67, with 90% power and two-sided alpha of 5%. Assuming a dropout rate of 20%, a total of 400 participants (200 in each arm) will be recruited.

The rate ratio of 0.67 compares with the relative rate of severe attacks of 0.28 in the single study of Budesonide-formoterol MART in children,[8] and the risk ratio of 0.32 for severe attacks reported in the systematic review and meta-analysis of the ICS-formoterol MART regimen vs ICS-LABA maintenance plus SABA in adolescents and adults.[7]

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
- Applicable ICH Good Clinical Practice (GCP) guidelines.
- Applicable laws and regulations.
- Ethical guidelines for health research with children and young people, specifically: the NZ National Ethics Advisory Committee's Ethical Guidelines for Intervention Studies: Revised Edition (2012) and the NZ Ministry of Health's Operational Standard for Ethics Committees: Updated Edition (2006).
- Guideline on the Regulation of Therapeutic Products in New Zealand Part 11: Clinical trials – regulatory approval and good clinical practice requirements.

The protocol, protocol amendments, ICF, investigator's brochure and other relevant documents (e.g. advertisements) must be submitted to an Ethics Committee by the investigator and reviewed and approved by the Ethics Committee before the study is initiated.

This study requires approval from the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) via the Standing Committee on Therapeutic Trials (SCOTT) under Section 30 of the Medicines Act 1981, as Bricanyl Turbuhaler 500mcg is not an approved product in New Zealand.

Any substantial amendments to the protocol will require Ethics Committee approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require Medsafe approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The co-ordinating investigator will be responsible for the following:

- Providing written summaries of the status of the study to the Ethics Committee and Medsafe annually or more frequently in accordance with the requirements, policies, and procedures established by the Ethics Committee and Medsafe.
- Notifying the Ethics Committee and Medsafe of SAEs or other significant safety findings that would halt or temporarily halt the study, as required by Ethics Committee and Medsafe procedures

- Notifying Medsafe of any suspected unexpected serious adverse reactions (SUSARS) in accordance with their requirements.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the Ethics Committee, Medsafe, and all other applicable local regulations.

In the case of safety concerns arising during the study, investigators may deviate from the protocol in order to ensure the health and wellbeing of participants. The 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

10.1.2 Māori and Pasifika participation

We plan to recruit Māori participants to ensure that Māori tamariki directly benefit from the outcomes of this research. When providing information, answering questions and taking consent, every effort will be made to ensure the concept of Manākitanga is upheld by addressing cultural sensitivity, cultural safety and Māhaki (respectful conduct), as per the 'HRC Guidelines for Researchers on Health Research involving Māori'.

We plan to recruit Pasifika participants. Every effort will be made to ensure appropriate cultural approaches are used, including the practice of Teu le Vā, ensuring polite and respectful communication.

A communication plan will be developed as part of ongoing consultation with Māori and Pasifika, outlining engagement with communities in regard to recruitment approaches, study procedures and results dissemination.

10.1.3 Expenses and Inducements

The parents(s)/guardian(s) of participants will be reimbursed for expenses resulting from attending trial visits (such as fuel and parking). In addition to this reimbursement parent(s)/guardian(s) will be paid a stipend/ honoraria per visit, to recognise the time taken out of work/usual activities to attend each visit. Payment amounts will be approved by the Sponsor and set as agreed with the approving Ethics Committee.

Participants (i.e. children) will receive a gift card (koha) at each visit as a thank you for participating in the study.

This information will be included in the PIS-CF.

10.1.4 Ethical Considerations

Clinicians and researchers with extensive experience of working with children have been involved in the design of this trial, and will continue to supervise and oversee its conduct (through the TMG, TSC, and DSMC).

All participants randomised to the control arm will receive treatment per the current GINA recommendations and standard of care in New Zealand (based on the Asthma and Respiratory Foundation of New Zealand guidelines).

All participants randomised to the intervention arm will receive treatment per the current GINA recommendations at steps 3 and 4. Step 2 treatment is based on best practice evidence for adolescents and adults with asthma, recommended by GINA and the Asthma and Respiratory Foundation of New Zealand guidelines. This "Anti-Inflammatory Reliever" (AIR) approach is associated with significantly fewer asthma exacerbations in adolescents and adults. Participants in the intervention arm should not be at increased risk of an asthma exacerbation compared with the control arm/standard care (we hypothesise that they will be at lower risk than standard of care).

Participants deemed to be at 'high risk' will be excluded.

Participants enrolled in the study will receive regular follow up (a total of six scheduled study visits), asthma education (including inhaler technique training), and lung function testing. They will also be able to contact an Investigator directly regarding any study-related queries.

All participants will receive study- and treatment-specific asthma action plans, which detail what to do in the event of worsening asthma.

Investigators may choose to withdraw a study participant at any time due to safety concerns.

The prescribed randomised treatment can be modified at any stage during the study if it is considered the child needs an increase in their routine treatment. This decision will be taken by the Investigators or GP on a per participant basis and has been protocolised to ensure consistency).

10.1.5 Funding, Insurance and Financial Disclosure

10.1.5.1 Funding

This study is funded by AstraZeneca through the Externally Sponsored Research pathway, reference: ESR-22-21744.

10.1.5.2 Insurance

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

10.1.5.3 Financial Disclosure

Financial disclosures are not required for this study.

10.1.6 Data Protection

Data will be collected, used and stored in accordance with applicable site and sponsor standard operating procedures (SOPs) and the Health Information Privacy Code 2020, the Code of Health and Disability Services Consumers Rights 1996, and the Bill of Rights Act 1990.

Participants/guardians will be informed of what data will be collected, how it is managed and where it is stored, within the PIS-CF and assent form so that they can consent to the use of their personal data for the study. This includes that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate Ethics Committee members, and by inspectors from regulatory authorities, to ensure that the study is being properly.

The study staff will ensure that participant and guardian privacy is maintained. Participant identifiable data including name, contact details and full date of birth will be captured as part of source data, which will only be accessible to authorised site staff members, monitors (sponsor staff) and auditors (Ethics Committee or Regulator), thereby maintaining participant confidentiality.

Privacy breaches will be reported to the sponsor and will be assessed by the sponsor's privacy officer. Onward reporting of breaches will be in accordance with the NZ Privacy Act 2020.

A Clinical Data Management Application (CDMA), which is designed to collect all the study information at a site (including source data) will be implemented at selected sites. The CDMA is accessible to site staff and sponsor staff, however Sponsor staff (except the study Monitors) will be unable to access identifiable data (e.g. name, contact details). Access to identifiable data is possible for Sponsor system administrators, however this will only be performed with specific permission on an as-needed basis. The Study Monitors will have access to all source data, including identifiable information, for the purpose of monitoring. . If a site does not implement the CDMA, source data will be captured on paper or electronically via a site-specific e-source system, which will only be accessible to site staff and the Study Monitors.

The CDMA is an encrypted, secure system, protected by unique username and password requirements for log-in, which are only provided to trained study staff.

Data recorded in the CDMA will be securely stored on servers in New Zealand and Sydney, Australia.

No study reports will contain any information that could individually identify a study participant.

10.1.7 Committees Structure

10.1.7.1 Trial Steering Committee

The study will be overseen by the Trial Steering Committee (TSC). The TSC will ensure that the study is running properly and that ethical and regulatory standards are being met to ensure participant safety and wellbeing. The TSC will provide advice on study amendments, supervise the trial towards its objectives and resolve issues that may occur during the conduct of the study.

The conduct and responsibilities of the TSC are outlined in the TSC Charter.

The TSC will meet formally at least every six months to discuss the progress of the trial, including DSMC correspondence and the outcome of site monitoring visits, quality control and quality assurance processes, if appropriate.

10.1.7.2 Data and Safety Monitoring Committee

An independent DSMC will oversee the safety aspects of the study, to safeguard the interests of trial participants, assess the safety and efficacy of trial interventions, and monitor the overall conduct of the trial. The conduct and responsibilities of the DSMC are outlined in the DSMC charter.

The DSMC will review trial conduct data (e.g. recruitment, withdrawals, protocol deviations, and serious breaches) and safety data (e.g. SAEs, SARs, and SUSARs) in a regular basis, as defined in the DSMC Charter. The DSMC may recommend termination of the trial, however the TSC will make the final decision.

10.1.7.3 Trial Management Group

The Trial Management Group (TMG) will oversee the day to day running of the study. The TMG will meet regularly to discuss the progress of the trial and for the purpose of assuring quality, in their role of executing the functions of sponsor. The TMG will be formed of sponsor staff with relevant expertise in conducting multi-centre trials.

10.1.8 Dissemination of Clinical Study Data

The study findings will be published by the sponsor (via the CI), in a scientific peer reviewed journal, according to the International Committee of Medical Journal Editors recommendations (see Publication Policy).

Results of the study will be sent to participants (as a lay summary) 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.

Data may be shared on request. Data sharing will be in accordance with the sponsor Data Sharing Policy.

10.1.9 Data Quality Assurance

An electronic Clinical Data Management Application (CDMA) created using REDCap will be used to enable study data collection. REDCap is a secure, HIPAA (United States Health Insurance Portability and Accountability Act 1996) compliant web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2)

audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages, including de-identified data sets; and 4) procedures for importing data from external sources.

Site staff will be given appropriate access to enter data into the CDMA after they have received appropriate training. If a site is not using the CDMA to collect source data, data will be transcribed into the CDMA from site specific source documents.

The electronic CDMA will be designed to collect data in real time during clinic visits. Data will also be collected through documentation on the back of the participant's asthma management plan or, if unrecorded by the participant, through self-report at each study visit. Where data are collected on paper, or derived from other sources, site staff will complete study data entry into the CDMA (as appropriate) on an ongoing and timely basis.

For the primary outcome measure, data collection will be through participant-reported data/logs (with reference to medical records where necessary). Participant-reported data will include a log of asthma exacerbations (urgent medical review and prednisone/prednisolone use), a log of days lost from school or usual activities (parent(s)/ guardian(s)) due to asthma, and use of additional prescribed asthma medications. Medical records and self-reported data will be reviewed together.

Discrepancies and queries raised by monitors or via pre-programmed checks will be arbitrated by investigators using predefined criteria.

The Sponsor will have access only to de-identified data held within the CDMA, with the exception of the delegated study monitor(s), who will have access to identifiable source data held in the CDMA, for the purpose of enabling trial-related monitoring. Sponsor REDCap Administrators may technically access all CDMA data, as their access is unrestricted. Administrators will not access the CDMA except where specifically required to do so. The system audit trail will record Administrator access to CDMA data and this will be checked as part of sponsor monitoring activity to ensure compliance.

Guidance on completion of study data will be provided in the study reference manual and/or during site training.

The sponsor will contract with each site to ensure that the investigator permits study-related monitoring, audits, Ethics Committee review, and regulatory agency inspections and provide direct access to source data documents.

Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the final study report.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Data contained within the CDMA will be held on Sponsor controlled secure servers, hosted by Amazon Web Services, located in Sydney, Australia. Summarised trial related data (not containing any participant identifiable data) may also be held on Sponsor controlled secure servers in NZ, and Sydney, Australia.

The following records will be retained by the investigator and/or sponsor for 10 years after the youngest child in the study turns 16 years old or 15 years after the completion of the trial, whichever is longer:[44]

- Source and essential documents
- Study data held within the CDMA
- Essential documents held in the Trial Master File (TMF)

No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Investigators may continue to access data held within the CDMA after database lock/data archive has occurred. The data will be read-only to prevent unauthorised changes. Access requests will be facilitated by the sponsor, including access in the case of a regulatory audit.

10.1.10 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported in the CDMA that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available where required.

Source data refers to where data are first recorded, and from which participants' study data are obtained. Source documents include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, radiographs, correspondence and audio recordings. Study data will be collected into a CDMA, in which entries will be considered source data if the CDMA is the site of the original recording (e.g. there is no other written or electronic record of data).

The defined origin of source data can be found in the source document agreement with each study site.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CDMA.

Investigators will have continuous access to the source data they have entered into the CDMA. The investigator and site retain ownership of the data they have entered.

Study monitors will perform ongoing source data verification to confirm that data entered into the CDMA by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.11 Study and Site Start and Closure

10.1.11.1 First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open (formal approval to recruit received from sponsor) and will be the study start date.

10.1.11.2 Study/Site Termination

The Sponsor will stop the study prematurely if any safety concerns are apparent, either arising from this study, of if the 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.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the responsible Ethics Committee or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the responsible Ethics Committee and Medsafe (if applicable), of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator

shall promptly inform the participant and will ensure appropriate post-study participant therapy is provided, along with appropriate follow-up.

10.1.12 Publication Policy

The main study findings will be published in a primary manuscript, which will be co-ordinated by the CI. The investigators listed on page one will be listed as authors, in recognition of their contribution to the design, implementation and oversight of the study.

Study findings may also be published in secondary manuscripts (e.g. economic analysis, meta analyses), and authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

The results of this study may be published or presented at scientific meetings. The investigator agrees to submit all manuscripts or abstracts to the funder before submission. This allows the funder to protect proprietary information (either of its own, or third parties) and to provide comments.

Authorship of any further study findings will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

Clinical laboratory testing is not required as part of the trial.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. Events meeting the definition of an AE:

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose/ extreme overuse of either study intervention or a concomitant medication. Overdose/ extreme overuse per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses/ extreme overuse should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT meeting the definition of an AE:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence whether or not related to the investigational product that:

a. Results in death.

b. Is life threatening: The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation.

- In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.
- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Is an important medical event requiring medical or surgical intervention to prevent serious outcome.

10.3.3 Definition of Adverse Reactions (AR), Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reactions (SUSAR)

Any AR is an untoward and unintended response to an Investigational Medicinal Product related to any dose administered.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the Investigational Medicinal Product qualify as adverse reactions.

Any SAE that occurs during research with a medicinal product is a **Serious Adverse Reaction (SAR)** if there is a certain degree of probability that the SAE is a harmful and undesired reaction to the Investigational Medicinal Product, regardless of the administered dose.

Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious adverse reaction (SAR) which is also unexpected. In this case 'unexpected' means that the nature and severity of the SAR do not match with the reference safety information (Appendix 5).

10.3.4 Diagnosis versus signs and symptoms

A diagnosis (if known) should be recorded rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

10.3.5 Site identification and recording of adverse events

Each site will be responsible for identifying, recording and following up on AEs in accordance with the protocol and their own SOPs or standard practices.

The sponsor will ensure that:

- All sites have appropriate practices and staff for identifying, recording and managing AEs.
- All sites are appropriately trained in the AE reporting requirements of the protocol.
- All sites will have access to the Clinical Data Management Application (CDMA), or electronic data capture tool, which will include AE reporting forms, or can otherwise meet reporting requirements to the Sponsor.
- All sites are appropriately trained in the use of the CDMA/electronic data capture tool.

Non-serious AEs will be collected from the start of the intervention period and throughout the treatment period, up to and including the final follow-up visit/last day of study. The expected minimum data to be collected will include:

- Event description
- Onset date and time (where time is applicable)
- Outcome, including resolution date and time (where time is applicable)
- Narrative description of the event
- Causality (to intervention, concomitant medication or device)
- Expectedness
- Intensity
- Action taken in regard to intervention

- Confirmation of seriousness
- Any treatments given for the event (yes/no). (More specific details will be captured in the concomitant medication form)
- Date and time of the person recording the event
- Identification of staff member recording the event
- Ongoing narrative relating to the event if required, including ongoing follow-up of the event, interactions with other medical personnel, information from other medical records and so on.

10.3.6 Site reporting of non-serious AEs

Where sites are capturing source data not via Direct Data Capture, they will be required to enter AE data into the CDMA/electronic data capture tool within 5 working days of obtaining the data, or within the number of days the site has agreed to enter data by contract, whichever is the shortest time period.

10.3.6.1 Timeliness of reporting to queries on non-serious AEs

All sites will respond to queries raised by the Medical Monitor, the Medical Terminology Assigners or the Monitor within 5 working days of the query being raised.

10.3.6.2 Follow up of non-serious AEs

AEs must be followed-up until symptoms cease or the condition becomes stable.

Each ongoing event will be reviewed with the participant at every visit, or for longer visits or overnight stays, they should be reviewed several times over the day.

Events ongoing at study completion will be followed up as clinically indicated.

All attempts to follow up with the participant will be recorded on the site AE record form, or documented within the source data.

10.3.7 Site identification and recording of serious adverse events

SAEs will be recorded from the time of informed consent up to and including the participant's final follow-up visit/last day of study.

The expected minimum data to be collected will include those items listed in "site identification and recording of adverse events" and;

- Category of seriousness
    - Death (date of death)

  - Life-threatening
  - Required inpatient hospitalisation (admission and discharge dates)
  - Prolonged existing hospitalisation (admission and discharge dates)
  - Resulted in persistent or significant disability/incapacity
  - Resulted in a congenital abnormality or birth defect
  - Other important medical event (to be specified)
- Date event became serious
- Date study team aware of event
- Autopsy details and report (where applicable)

10.3.8 Site reporting of Serious AEs

SAE Reporting to sponsor via the CDMA/ Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the sponsor will be the CDMA/ electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see below reporting via telephone) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) and to the monitor/ Project Manager by telephone. • Contacts for SAE reporting can be found below.
SAE Reporting to sponsor via telephone
• If the electronic system is unavailable then the site will use the paper SAE data collection tool and contact the Sponsor by telephone to report the event. • In addition, if urgent advice is required for an SAE, or a safety issue, the contact details are: **Sponsor telephone:** +64 (0)4 805 0240 • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.

10.3.8.1 Timeliness of reporting of Serious AEs

Sites are required to report these events to the sponsor within 24 hours of becoming aware of the event, via the methods outlined above.

10.3.8.2 Timeliness of Responding to Queries on Serious AEs

All sites will respond to queries raised by the Medical Monitor, the Medical Terminology Assigners or the Monitor within 2 working days of the query being raised.

10.3.8.3 Follow up of Serious AEs

Events must be followed-up until symptoms cease or the condition becomes stable. Events ongoing at study completion will be followed up until resolution or as clinically indicated.

All attempts to follow up with the participant will be recorded on the site AE record form, or documented within the source data.

Follow-up data will be sent to the sponsor within 24 hours of being known.

10.3.9 Assessment of intensity

The investigator will assess the intensity of each event reported during the study according to the following table:

Intensity *(based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0)*		
Grade		**Grade Description**
1	**Mild**	asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	**Moderate**	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.
3	**Severe**	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling limiting self-care ADL.
4	**Life threatening**	Life-threatening consequences; urgent intervention indicated
5	**Death**	Death related to AE
Activities of Daily Living (ADL)		
Instrumental ADL	Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.	
Self-care ADL	Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden	

NOTE: The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (as in the table above); the event itself may be of relatively minor medical

significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the CDMA.

10.3.10 Assessment of causality

The investigator will assess the relationship between study intervention and each occurrence of each event in accordance with the following table.

Causality (based on National Cancer Institute AE reporting requirements and the WHO/UMC Causality Criteria – see Appendix 1 and 2)	
Relationship	**Description**
Definite	• The AE is ***clearly related*** to the intervention • Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological Phenomenon)
Probable	• The AE is ***likely related*** to the intervention • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable
Possible	• The AE ***may be related*** to the intervention • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• The AE is ***doubtfully related*** to the intervention • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unrelated	• The AE is ***clearly NOT related*** to the intervention • There is no evidence of any causal relationship, disease or other drugs provide plausible explanations

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. The investigator will also consult the reference safety information (Appendix 5), in his/her assessment.

For each event, the investigator must document in the participant notes that he/she has reviewed the event and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the sponsor. The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.3.11 MedDRA Coding of Adverse Events

MedDRA preferred terms and System Organ Class will be assigned to adverse events for data safety reporting.

10.3.12 Sponsor Review of AEs

The sponsor will promptly evaluate all events to identify and expeditiously communicate possible new safety findings to investigators, the Data and Safety Monitoring Committee, Ethics Committees and applicable regulatory authorities based on applicable legislation. To determine reporting requirements for single adverse event cases, the sponsor will assess the expectedness of these events using the applicable IB or Medsafe Datasheet for each individual IMP used in the study (Appendix 5). The sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference safety information document. Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed.

10.3.13 Sponsor Reporting of SUSARs

The sponsor will expedite the reporting of SUSARs to all concerned investigators. Initial SUSAR reports will be expedited within 48 hours of knowing the event occurred and SUSAR updates may be issued after the SUSAR has been reviewed and additional details/data obtained.

The sponsor will expedite the reporting of SUSARs to AstraZeneca, regulatory authorities and ethics committees in accordance with their requirements.

10.4 Appendix 4: Abbreviations and Definitions

10.4.1 Abbreviations

ACQ-5	Asthma Control Questionnaire
ADL	Activities of Daily Living
AE	Adverse Event
AR	Adverse Reaction
AZ	AstraZeneca
ATS	American Thoracic Society
CDMA	Clinical Data Management Application
CI	Confidence Interval
DCE	Discrete Choice Experiment
DSMC	Data and Safety Monitoring Committee
DPI	Dry Powder Inhaler
ED	Emergency Department
ERS	European Respiratory Society
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume over 1 second
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GP	General Practitioner
GSK	GlaxoSmithKline
HDEC	Health and Disability Ethics Committee
HRC	Health Research Council of New Zealand
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid
IMP	Investigational Medicinal Product
LABA	Long-Acting $Beta_2$-Agonist
LTRA	Leukotriene Receptor Antagonist
MART	Maintenance and Reliever Therapy
MRINZ	Medical Research Institute of New Zealand
NZ	New Zealand
PI	Principal Investigator
PIS	Participant Information Sheet
PIS-CF	Participant Information Sheet-Consent Form
PIS-AF	Participant Information Sheet-Assent Form
pMDI	pressurised Metered-Dose Inhaler
REDCap	Research Electronic Data Capture

RCT	Randomised Controlled Trial
SABA	Short-Acting Beta$_2$-Agonist
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom

10.4.2 Definitions

Asthma Exacerbation:

An "asthma exacerbation" encompasses both moderate and severe asthma exacerbations.

- A severe asthma exacerbation is defined as worsening asthma leading to either:
  - An urgent, unplanned medical review (e.g. primary care or emergency department (ED) visit) or hospital admission; resulting in an acute prescription of systemic corticosteroids (tablets, suspension, or injection); OR
  - The use of systemic corticosteroids for 3 or more days.
  - A hospital admission for ≥24 hours.
- A moderate asthma exacerbation is defined as worsening asthma leading to either:
  - An urgent, unplanned medical review (e.g. primary care or ED visit) or hospital admission for less than 24 hours; **not** resulting in an acute prescription of systemic corticosteroids (tablets, suspension, or injection – e.g. oral prednisone); OR

The use of systemic corticosteroids for less than 3 days, which does not meet the criteria for a severe asthma exacerbation (e.g. use of systemic corticosteroids from a non-acute prescription, such as a home supply or delayed script).

End of Study:

The end of study is defined as the date of the last visit of the last participant.

Extreme Overuse

Self-reported accidental or deliberate intake of beta$_2$-agonist treatment of more than 16 inhalations of Budesonide-formoterol (≥1,600/96mcg) in the intervention arm or 16 inhalations of

	Terbutaline (≥8,000mcg) in the control arm, during a 24-hour period, is defined as extreme overuse
Participant:	Refers to the child enrolled in the study.
Study visits:	A scheduled study visit refers to any of the pre-specified study participant consultations. An unscheduled study visit refers to any visit arranged in addition to the scheduled consultations and takes place outside of scheduled visit windows.

10.5 Appendix 5: IMP Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Short-Acting Beta Agonist (SABA) **Bricanyl Turbuhaler® 500mcg inhalation powder**		
Undesirable Effects The most common (affecting ≥1/100 and <1/10 patients) effects are tremor and headache, a known class effect of SABAs, particularly with high/frequent use. Other undesirable effects are stated in the product Data Sheet. **Contraindications** Patients with a history of hypersensitivity to any of its components. Non-selective beta blocking agents.	Investigator's Brochure Bricanyl Turbuhaler 29/06/1999. Australian Product Information Bricanyl® Turbuhaler® (terbutaline sulfate) Powder for inhalation 09/04/2020	Participants will be reviewed regularly during the study by the study investigators and will receive care as needed under their usual healthcare provider. Adverse events will be recorded during the study and treatment discontinuation may occur should it be indicated, i.e. that the participant is unable to tolerate the medication. The asthma action plans outline how and when to use the medication, and the requirement to seek help based on high use of reliever medication, which should result in healthcare provider review and acute treatment where necessary. Eligibility criteria exclude those with known hypersensitivity. Taking non-selective beta blockers is an exclusion criterion and would result in treatment discontinuation if started on study. Participants taking Terbutaline in accordance with the protocol/asthma action plan are at no greater risk than that for standard care.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Inhaled Corticosteroids (ICS) **Pulmicort Turbuhaler® 100mcg inhalation powder**		
Undesirable Effects Very common (affecting ≥1/10 patients) effects are candidiasis of mouth and throat. Common (affecting ≥1/100 to <1/10 of patients) effects are hoarseness and contusions. Possible systemic effects such as Cushing's Syndrome or growth retardation may occur if used at high doses for long periods. Other undesirable effects are stated in the product Data Sheet. **Contraindications** Patients with a history of hypersensitivity to Budesonide propionate or to any of the excipients listed in the Data Sheet.	Medsafe PULMICORT® TURBUHALER® New Zealand Data Sheet 03/08/2020	Participants will be reviewed regularly during the study by the study investigators and will receive care as needed under their usual healthcare provider. Adverse events will be recorded during the study and treatment discontinuation may occur should it be indicated, i.e. that the participant is unable to tolerate the medication. The asthma action plans outline how and when to use the medication, reducing the risk of non-adherence with maintenance therapy and to ensure high doses of ICS are avoided. Rinsing of the mouth after use is recommended, to mitigate candidiasis of mouth and throat. Eligibility criteria exclude those with known hypersensitivity. Participants taking Budesonide in accordance with the protocol/asthma action plan are at no greater risk than that of standard care.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Inhaled Corticosteroid/Long-Acting Beta Agonist (ICS-LABA) **Symbicort Turbuhaler® 100/6mcg inhalation powder**		
The effects for the combination medication are consistent with the effects of the individual constituent components of Budesonide (ICS) and formoterol (LABA). Common (affecting ≥1/100 to <1/10 of patients) effects are palpitations, candida infections in oropharynx, headache, tremor, mild irritation in the throat, coughing and hoarseness. Possible systemic effects such as Cushing's Syndrome or growth retardation may occur if used at high doses for long periods. Other undesirable effects are stated in the product Data Sheet. **Contraindications** Patients with a history of hypersensitivity to Budesonide, formoterol or to lactose.	Medsafe SYMBICORT TURBUHALER® New Zealand Data Sheet 20/07/2020	Participants will be reviewed regularly during the study by the study investigators and will receive care as needed under their usual healthcare provider. Adverse events will be recorded during the study and treatment discontinuation may occur should it be indicated, i.e. that the participant is unable to tolerate the medication. The asthma action plans outline how and when to use the medication, reducing the risk of non-adherence with maintenance therapy to ensure high doses of ICS are avoided. The asthma action plans also state the requirement to seek help based on high use of reliever medication, which should result in healthcare provider review and acute treatment where necessary. Rinsing of the mouth after use is recommended, to mitigate candidiasis of mouth and throat. Eligibility criteria exclude those with known hypersensitivity. Participants taking Budesonide-formoterol in accordance with the protocol/asthma action plan are deemed to be at no greater

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		risk than that of standard care and in fact may be at lesser risk of experiencing an asthma exacerbation.

10.6 Appendix 6: Study Interventions Administered

10.6.1 Run-in period and Intervention period inhalers

Intervention Label	**Symbicort Turbuhaler®**	**Bricanyl Turbuhaler®**	**Pulmicort Turbuhaler®**
Intervention Name	Budesonide-formoterol (Symbicort Turbuhaler® DPI)	Terbutaline (Bricanyl Turbuhaler® DPI)	Budesonide (Pulmicort Turbuhaler® DPI)
Intervention Description	100/6mcg one inhalation as required; 100/6mcg one inhalation once daily + one inhalation as required; 100/6mcg one inhalation twice daily + one inhalation as required 100/6mcg two inhalations twice daily	500mcg one inhalation as required	100mcg one inhalation twice daily 100mcg two inhalations twice daily
Type	Drug	Drug	Drug
Dose Formulation	Dry Powder	Dry Powder	Dry Powder
Unit Dose Strength(s)	100mcg/6mcg	500mcg	100mcg
Dosage Level(s) NB: Dose amount is dependent on step and age of participant	100/6mcg one inhalation as required; 100/6mcg one inhalation once daily + one inhalation as required; 100/6mcg one inhalation twice daily + one inhalation as required 100/6mcg two inhalations twice daily	500mcg one inhalation as required	100mcg one inhalation twice daily 100mcg two inhalations twice daily
Route of Administration	Oral inhalation	Oral inhalation	Oral inhalation

Use	Experimental (reliever)/ Active comparator (maintenance)	Active comparator	Active comparator
IMP and NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor, via supply from AstraZeneca, manufacturer	Provided centrally by the sponsor, via supply from AstraZeneca, manufacturer	Provided centrally by the sponsor, via supply from AstraZeneca, manufacturer
Packaging and Labelling	Study intervention will be provided as a dry powder inhaler in the original marketed package. Each inhaler will be over-labelled with a study specific label, according to Good Manufacturing Practices	Study intervention will be provided as a dry powder inhaler in the original marketed package. Each inhaler will be over-labelled with a study specific label, according to Good Manufacturing Practices	Study intervention will be provided as a dry powder inhaler in the original marketed package. Each inhaler will be over-labelled with a study specific label, according to Good Manufacturing Practices

10.6.2 Post-Study Inhalers

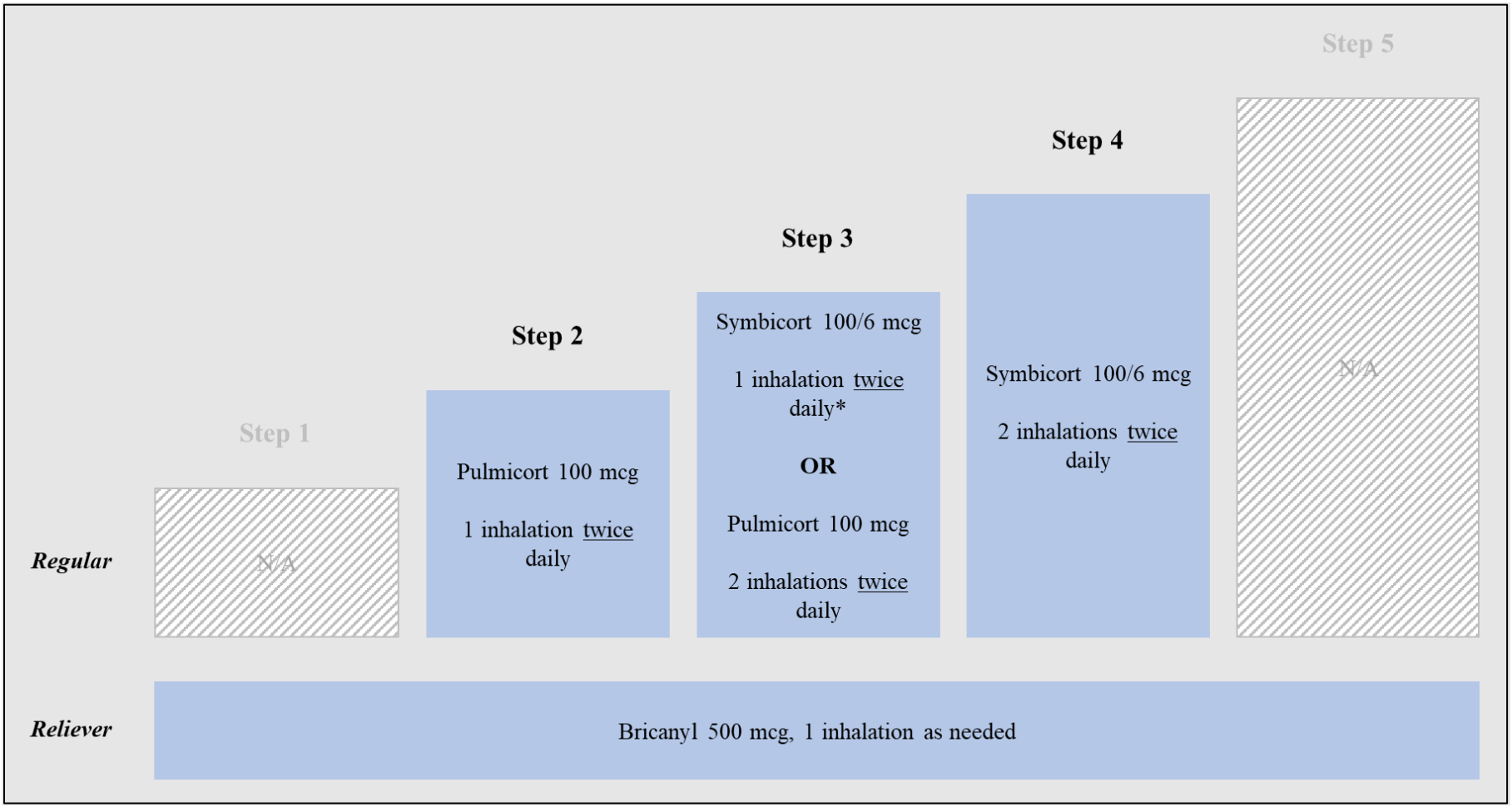
Intervention Label	**Symbicort Turbuhaler® (Post Study)**	**Respigen® (Post Study)**
Intervention Name	Budesonide-formoterol (Symbicort Turbuhaler®) DPI	Salbutamol (Respigen®) pMDI
Intervention Description	100/6mcg one inhalation as required (MART regimen only) 200/6mcg one inhalation as required For use post study only as interim treatment prior to obtaining prescribed medication	100mcg, two inhalations as required For use post study only as interim treatment prior to obtaining prescribed medication

Type	Drug	Drug
Dose Formulation	Dry Powder	Aerosol
Unit Dose Strength(s)	100/6mcg 200/6mcg	100mcg
Dosage Level(s)	One inhalation as required (200/6mcg only) One inhalation twice daily and one inhalation as required Two inhalations twice daily and one inhalation as required	Two inhalations as required
Route of Administration	Oral inhalation	Oral inhalation
Use	Other: post study medication	Other: post study medication
IMP and NIMP/AxMP.	AxIMP	AxIMP
Sourcing	Provided centrally by the sponsor, via supply from AstraZeneca, manufacturer	Provided centrally by the sponsor, via purchase of commercial stock
Packaging and Labelling	Post-study medication will be provided as a dry powder inhaler in the original marketed package. Each inhaler will be over-labelled with a specific post-study label, according to Good Manufacturing Practices	Post-study medication will be provided as a pressurised metered-dose inhaler in the original marketed package. Each inhaler will be over-labelled with a specific post-study label, according to Good Manufacturing Practices

See Section 6.6 for details on prescribing post-trial maintenance treatment.

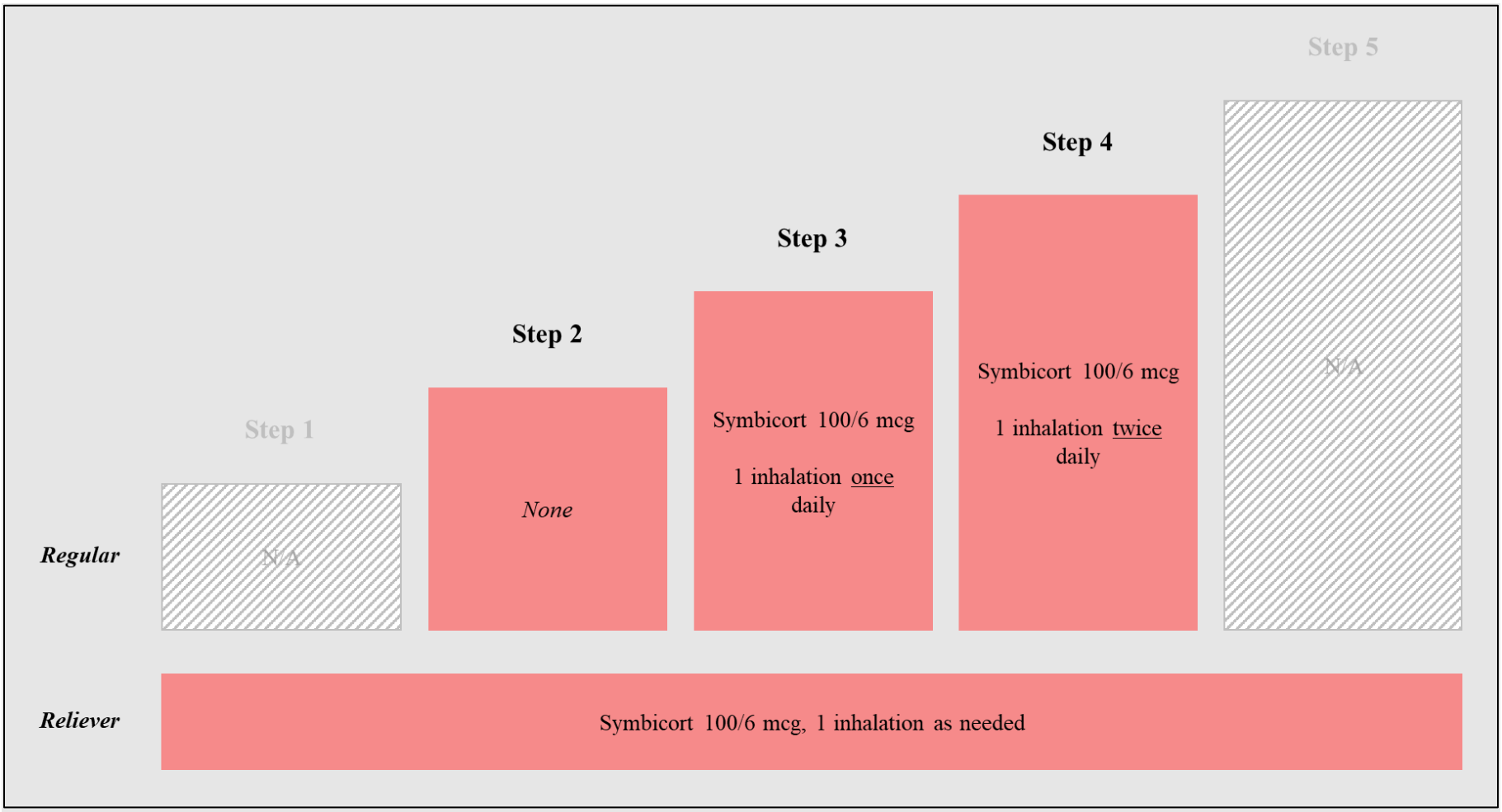
10.7 Appendix 7: START CARE Stepwise treatment tracks

10.7.1 Control arm (Terbutaline reliever)



*Symbicort 100/6, 1 inhalation twice daily is the preferred maintenance treatment option at Step 3 in the control arm.

10.7.2 Intervention arm (Budesonide-formoterol reliever)



10.8 Appendix 8: Asthma Action Plans

10.8.1 Control arm (Terbutaline reliever):

START CARE

ASTHMA ACTION PLAN | BLUE PLAN

Name: Date of plan:

GP: GP phone:

Know your asthma symptoms | Know when and how to take your inhalers

Feeling well

Your asthma is under control when...

- You do not have asthma symptoms most days (wheeze, tight chest, cough, or find it hard to breathe)
- You can play just like other children
- Most days you do not need your reliever

Remember...

Preventer: _____	___ inhalation(s) every morning ___ inhalation(s) every night
Reliever: **Bricanyl**	1 inhalation when needed to relieve symptoms

Getting worse

Your asthma is getting worse when...

- You coughing or wheezing more
- **OR** you wake up at night because of your asthma
- **OR** You are using more than 4 inhalations of your reliever a day, for one week

Let's take action...

- You need to see your doctor within the next week to change your preventer
- Take **1 inhalation** of your **reliever** as often as needed to relieve symptoms

Feeling worried

Your asthma is a worry when...

- You are breathing fast or find it hard to breathe
- **OR** your reliever is only helping for 2-3 hours
- **OR** you are using more than 6 inhalations of your reliever a day
- **OR** you feel you need to see your doctor

Let's get help...

- **You need to see your doctor or go to the hospital today**
- Take **1 inhalation** of your **reliever** as often as needed to relieve symptoms

Emergency

Your asthma is an emergency when...

- Your symptoms are getting more severe quickly
- **OR** you are finding it hard to speak or breathe
- **OR** you look pale or blue
- **OR** your reliever is not helping
- **OR** you are using your reliever every 1-2 hours
- **OR** you are using more than 8 inhalations of your reliever a day

Let's keep calm...

- **Dial 111 for an ambulance and tell them you're having a severe asthma attack**
- Sit upright and try to stay calm
- Take **1 inhalation** of your **reliever** as often as needed until help arrives
- Even if you seem to get better, seek medical help right away

Preventer inhaler...

Your preventer is _____

You take this every day even when you are well.

Reliever inhaler...

Your reliever is **Bricanyl**

You take this only when you need it.

You should carry your reliever with you at all times

Next appointment dates

Visit 2 _____

Visit 3 _____

Visit 4 _____

Visit 5 _____

Visit 6 _____

Study contact

Name _____

Phone _____

Email _____

Medical help

If you need medical help for your asthma, please contact your GP, After Hours service, or 111 as appropriate. This is important to make sure you get treated quickly.

How to use your inhaler

1. Hold the inhaler upright and remove the cover
2. Check the dose counter just below the mouthpiece. Use a different inhaler if it is red.
3. Twist the red grip as far as it will go in one direction and then back again until you hear a click. Your inhaler is now ready to use.
4. Place the mouthpiece between your lips and suck in deeply and forcefully through your inhaler. (You may not taste or feel the medication.)
5. Remove the inhaler from your mouth and breathe out. Do not breathe back into the mouthpiece as you will make it damp inside.
6. If you need more, repeat the steps above.
7. When you are finished, place the cover back on the inhaler and twist shut.

Caring for your inhaler

1. Do not wash your inhaler as it will not work properly if it gets wet
2. Wipe the mouthpiece with a dry tissue or cloth

Since your last visit...

Have you taken any days off school or work due to asthma?

Start date	End date	How many days off school?	Did someone take time off work due to your asthma?	How many people took time off work due to your asthma? Who were they?	How many days did each person take off work?
e.g. 01/03/2023	*e.g. 03/03/2023*	*e.g. 3*	*e.g. Yes*	*e.g. 2 - me and mum*	*e.g. Me 2 days, Mum 1 day*

Have you started any new medication (other than prednisone) **OR** changed any existing medication?

Medication started/changed	Dose	How many times a day?	How long for?	Date started/ changed	Date stopped	Reason for medication
e.g. Amoxicillin	*e.g. 500mg*	*e.g. 3*	*e.g. 5 days*	*e.g. ••/09/202••*	*e.g. ••/09/202••*	*e.g. Sore throat*

Have you visited your doctor (e.g. GP) or been admitted to hospital due to asthma?

Date	Service used?	Prednisone given?	Prednisolone dose?	How long for?	Start date	Stop date	Comments
e.g. 15/09/202•	*e.g. ED visit*	*e.g. Yes*	*e.g. 40mg*	*e.g. •• days*	*e.g. 15/09/2020*	*e.g. 1•/09/202•*	*e.g. Admitted*

10.8.2 Intervention arm (Budesonide-formoterol reliever):

START CARE

ASTHMA ACTION PLAN | RED PLAN

Name: *Date of plan:*

GP: *GP phone:*

Know your asthma symptoms **Know when and how to take your inhaler**

Feeling well

Your asthma is under control when...

- You do not have asthma symptoms most days (wheeze, tight chest, cough, or find it hard to breathe)
- You can play just like other children
- Most days you do not need to use your Symbicort as a reliever

Remember...

Preventer and reliever: **Symbicort**	___ *inhalation(s) every morning*
	___ *inhalation(s) every night*
	1 *inhalation when needed to relieve symptoms*

Getting worse

Your asthma is getting worse when...

- You coughing or wheezing more
- **OR** you wake up at night because of your asthma
- **OR** You are using more than 4 reliever inhalations a day, for one week

Let's take action...

- You need to see your doctor within the next week to change the way you use your inhaler
- Take **1 inhalation** of your **Symbicort** as often as needed to relieve symptoms

Feeling worried

Your asthma is a worry when...

- You are breathing fast or find it hard to breathe
- **OR** your Symbicort is only helping for 2-3 hours
- **OR** you are using more than 6 reliever inhalations a day
- **OR** you feel you need to see your doctor

Let's get help...

- **You need to see your doctor or go to the hospital today**
- Take **1 inhalation** of your **Symbicort** as often as needed to relieve symptoms

Emergency

Your asthma is an emergency when...

- Your symptoms are getting more severe quickly
- **OR** you are finding it hard to speak or breathe
- **OR** you look pale or blue
- **OR** your Symbicort is not helping
- **OR** you are using your Symbicort every 1-2 hours
- **OR** you are using more than 8 reliever inhalations a day

Let's keep calm...

- **Dial 111 for an ambulance and tell them you're having a severe asthma attack**
- Sit upright and try to stay calm
- Take **1 inhalation** of **Symbicort** as often as needed until help arrives
- Even if you seem to get better, seek medical help right away

Your inhaler...

Your inhaler is **Symbicort**

Symbicort is a preventer and a reliever inhaler

You do not need an extra inhaler as a reliever

You should **carry your Symbicort** with you at all times

Next appointment dates

Visit 2 _____

Visit 3 _____

Visit 4 _____

Visit 5 _____

Visit 6 _____

Study contact

Name _____

Phone _____

Email _____

Medical help

If you need medical help for your asthma, please contact your GP, After Hours service, or 111 as appropriate. This is important to make sure you get treated quickly.

How to use your inhaler

1. Hold the inhaler upright and remove the cover
2. Check the dose counter just below the mouthpiece. Use a different inhaler if it is red.
3. Twist the red grip as far as it will go in one direction and then back again until you hear a click. Your inhaler is now ready to use.
4. Place the mouthpiece between your lips and suck in deeply and forcefully through your inhaler. (You may not taste or feel the medication.)
5. Remove the inhaler from your mouth and breathe out. Do not breathe back into the mouthpiece as you will make it damp inside.
6. If you need more, repeat the steps above.
7. When you are finished, place the cover back on the inhaler and twist shut.

Caring for your inhaler

1. Do not wash your inhaler as it will not work properly if it gets wet
2. Wipe the mouthpiece with a dry tissue or cloth

Since your last visit...

Have you taken any days off school or work due to asthma?

Start date	End date	How many days off school?	Did someone take time off work due to your asthma?	How many people took time off work due to your asthma? Who were they?	How many days did each person take off work?
e.g. 01/03/2023	*e.g. 03/03/2023*	*e.g. 3*	*e.g. Yes*	*e.g. 2 - me and mum*	*e.g. Me 2 days, Mum 1 day*

Have you started any new medication (other than prednisone) **OR** changed any existing medication?

Medication started/changed	Dose	How many times a day?	How long for?	Date started/ changed	Date stopped	Reason for medication
e.g. Amoxicillin	*e.g. 500mg*	*e.g. 3*	*e.g. 5 days*	*e.g. 05/09/2023*	*e.g. 09/09/2023*	*e.g. Sore throat*

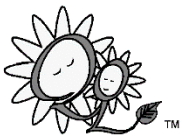
Have you visited your doctor (e.g. GP) or been admitted to hospital due to asthma?

Date	Service used?	Prednisone given?	Prednisolone dose?	How long for?	Start date	Stop date	Comments
e.g. 15/09/2022	*e.g. ED visit*	*e.g. Yes*	*e.g. 40mg*	*e.g. 3 days*	*e.g. 15/09/2020*	*e.g. 18/09/2023*	*e.g. Admitted*

10.9 Appendix 9: ACQ-5 questionnaire

ASTHMA CONTROL QUESTIONNAIRE (ACQ-IA)

INTERVIEWER-ADMINISTERED
(for children 6-10 years)
UK ENGLISH VERSION



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Web: http://www.qoltech.co.uk

JULY 2011

Revised 07 February 2012
ACQ-IA - UK English Version

ASTHMA CONTROL QUESTIONNAIRE (for children 6-10 years)

Please read these instructions carefully before administering the questionnaire

Parents may be present during the interview but you should encourage the child to respond and only ask the parent to help if the child is having difficulties.

Some younger children may have difficulty understanding the meaning of some questions. First, you should read each question to the child exactly as written in the text. If the child doesn't understand, read the question again using the secondary wording (marked with 'a'). Try not to place your own interpretation on the question.

The questionnaire will ask how the child's asthma has been during the last week (7 days). Check that the child understands this time frame. If in doubt, ask the parent to identify an event that occurred a week previously (e.g. a football match) and then ask the child to tell you how she/he has been since that event. Make sure that the child understands that we want to know how their asthma has been **on average** during the week, not about one specific asthma event.

Show the child the response card and explain the options. Explain the concept of the 7 responses. Explain that 0 means that they have not had any asthma symptoms and have not been limited at all in their daily activities and that 6 means that their symptoms and activity limitations have been really, really bad. Explain that the other numbers (1-5) represent levels in between. For children who can read, we suggest that you ask them to read aloud each of the responses. For younger children, start by reading to them just the 7 responses to question one (both number and words) and check that they understand the meaning of the words (then repeat at the beginning of each question).

Reassure the child that there are no right or wrong answers.

ASTHMA CONTROL QUESTIONNAIRE©
(ENGLISH FOR THE UK)
INTERVIEWER-ADMINISTERED

Participant ID: _____

Participant initials: _____

Participant DOB: _____

Visit date: _____

First, read each question to the child using the primary wording. If the child does not fully understand the question, read it again using the secondary wording marked with 'a' (e.g. 2a, 3a, etc.)

1. During the past week, how often were you **woken by your asthma** during the night?

2. During the past week, how **bad were your asthma symptoms when you woke up** in the morning?

2a During the past week, how **bad were your asthma symptoms (for instance, hard to breathe, wheeze, cough) when you woke up** in the morning?)

3. During the past week, how **limited were you in your activities** because of your asthma?

3a During the past week, how **bothered were you in the things you do every day** because of your asthma?)

4. During the past week, how much **shortness of breath** did you experience because of your asthma?

4a During the past week, how much **shortness of breath (hard or difficult to breathe, breathless)** did you have because of your asthma?)

5. During the past week, how much of the time did you **wheeze?**

ASTHMA CONTROL QUESTIONNAIRE©
(ENGLISH FOR THE UK)
INTERVIEWER-ADMINISTERED

Participant ID: _____

Participant initials: _____

Participant DOB: _____

Visit date: _____

RESPONSE SHEET

Question	Response (0-6)
1. Woken by asthma	.....
2. Asthma symptoms on waking	.....
3. Activity limitation	.....
4. Short of breath	.....
5. Wheeze	.....

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ACQ-IA - UK English Version

ASTHMA CONTROL QUESTIONNAIRE©
(ENGLISH FOR THE UK)
INTERVIEWER-ADMINISTERED

Participant ID: _____

Participant initials: _____

Participant DOB: _____

Visit date: _____

RESPONSE CARD

QUESTION 1
0 Never
1 Hardly ever
2 A few times
3 Several times
4 Many times
5 A great many times
6 Unable to sleep because of asthma

QUESTION 2
0 No symptoms
1 Very mild symptoms
2 Mild symptoms
3 Moderate symptoms
4 Quite severe symptoms
5 Severe symptoms
6 Very severe symptoms

QUESTION 3
0 Not limited at all
1 Very slightly limited
2 Slightly limited
3 Moderately limited
4 Very limited
5 Extremely limited
6 Totally limited

QUESTION 4
0 None
1 A very little
2 A little
3 A moderate amount
4 Quite a lot
5 A great deal
6 A very great deal

QUESTION 5
0 Never
1 Hardly any of the time
2 A little of the time
3 A moderate amount of the time
4 A lot of the time
5 Most of the time
6 All the time

Revised 07 February 2012
ACQ-IA - UK English Version

10.10 Appendix 10: Inhaler Education

Inhaler education and (re-)training will be provided at all visits. In between visits, participants will have access to the study portal, which will include videos for correct Turbuhaler technique.

At visit 6/treatment discontinuation/withdrawal, inhaler education and assessment of technique will be for the post-study inhaler dispensed, with the type of device determined by the participant's age at study completion rather than on-study randomised treatment regimen.

10.10.1 Turbuhaler technique

1. Unscrew and remove the cover	
2. Check the dose counter	
3. Hold the inhaler upright	
4. Turn the grip as far as it will go in one direction, then turn it as far as it will go in the other direction (it does not matter which way you turn it first). You should hear a click sound. It does not matter whether the click comes on the first or the second twist. Your Turbuhaler is now ready to use.	
5. Breathe out, away from the Turbuhaler.	
6. Place the mouthpiece in your mouth to form a seal with you lips.	
7. Breathe in strongly and deeply. Remove the Turbuhaler and hold your breath for up to 10 seconds.	
8. Replace the cover and twist to close.	
9. If water is on hand, rinse your mouth with water after each dose, and spit it out.	

10.10.2 Turbuhaler maintenance

1. Wipe the mouthpiece with a dry tissue or cloth	
2. Do not wash your inhaler as it will not work properly if it gets wet.	

10.10.3 pMDI (with spacer) Technique

1. Check the dose counter (if applicable).	
2. Take off the cap.	
3. Hold the inhaler upright and shake for 5 seconds.	
4. Fit the inhaler upright into the spacer.	
5. Put the mouthpiece between your teeth without biting and close your lips to form a good seal.	

6. Hold spacer level and press down firmly on inhaler canister once.	
7. Take 6 slow breaths in and out through your mouth. Do not remove the spacer from your mouth between breaths.	
8. Repeat steps 5 to 7 for each extra dose needed.	
9. Remove the spacer from your mouth.	
10. Remove the inhaler from the spacer and replace the cap.	
11. Rinse your mouth with water or clean your teeth after using a preventer inhaler or Symbicort to help prevent side effects.	

10.11 Appendix 11: Maintenance treatment GINA steps at trial entry

The following inhalers are commercially available in New Zealand for the treatment of asthma.

Drug and brand	Inhaler type	Daily maintenance dose	GINA step
Budesonide • *Pulmicort (100, 200, 400mcg/dose)*	Inhaled corticosteroid (ICS)	≥100 to 200mcg	2
		>200 to 400mcg	3
		>400mcg	4
Budesonide-formoterol • *DuoResp Spiromax* • *Symbicort* • *Vannair* *(100/6, 200/6mcg/dose)*	Inhaled corticosteroid with Long-Acting Beta$_2$-Agonist (ICS-LABA)	≥100/6 to 200/12mcg	3
		>200/12 to 400/24mcg	4
		>400/24mcg	5
Beclomethasone dipropionate • *Beclazone (50, 100, 250mcg/dose)*	Inhaled corticosteroid (ICS)	≥100 to 200mcg	2
		>200 to 500mcg	3*
		>500mcg	4*
Beclomethasone dipropionate ultrafine • *QVar (50, 100mcg/dose)*	Inhaled corticosteroid (ICS)	≥50 to 100mcg	2
		>100 to 200mcg	3
		>200mcg	4
Fluticasone propionate • *Flixotide (50, 125, 250mcg/dose)*	Inhaled corticosteroid (ICS)	≥50 to 100mcg	2
		>100 to 250 mcg	3*
		>250 mcg	4*
Fluticasone propionate-salmeterol • *Seretide (50/25, 125/25, 250/25mcg/dose)*	Inhaled corticosteroid with Long-Acting Beta$_2$-Agonist (ICS-LABA)	≥50/25 to 100/50 mcg	3
		>100/50 to 250/100 mcg	4*
		>250/100 mcg	5*

*Adjusted to reflect Asthma And Respiratory Foundation NZ New Zealand Child Asthma Guidelines.

10.12 Appendix 12: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

Amendment 02 (16-March-2023)

This amendment is considered to be substantial by the Trial Management Group based on the Health and Disability Ethics Committee Guidance on amendments to approved studies, contained within their standard operating procedures.

Overall Rationale for the Amendment:

- Exclusion criteria have been adjusted:
  - to allow for patients in the same household to be able to take part in the study (if otherwise eligible)
  - to clarify that there may be milk protein in the excipient of the study medications, therefore those with a known or suspected milk protein hypersensitivity should be excluded.
  - to ensure that those who have received intravenous therapy for asthma in the year prior to Visit 1 will be excluded.
- The Expenses and Inducements section has been amended to allow for a stipend/ honorarium to be paid per visit to reflect the time and commitment participants/ parents/ guardians have to make for study visits, in addition to reimbursing the costs of attending the study site.
- Appendix 11 has been adjusted to reflect the New Zealand Child Asthma Guidelines (in addition to the Global Initiative for Asthma Guidelines) in regard to the total daily inhaled steroid doses at each asthma treatment step, to better reflect local practice.
- Additional guidance has been added for dispensing of IMP outside of visits, to confirm that this is possible to do without an in-person visit, when re-supply is only required for lost, damaged or expired inhalers.
- The requirement to collect pre-study reliever inhaler use data has been removed.
- An additional secondary outcome has been added to report on the proportion of participants with at least one asthma exacerbation or step-up.
- Further minor clarifications and correction of errors have been made, as outlined in the summary of changes below.

Summary of Changes

Section # and Name	Description of Change	Brief Rationale
Protocol Summary 1.1 Synopsis	Added an additional secondary outcome: Proportion of participants with at least one asthma exacerbation (moderate or severe), or step up in	Confirmation that data will be reported as proportion of participants, in addition to the existing outcome for composite of asthma exacerbations

3 Objectives, Endpoints 9.3.3.2 Comparison of proportions by logistic regression	treatment. Time point: Maximum observation time 52 weeks	(moderate and severe), or step up in treatment, as rate per participant per year
2.3.1.2 Reaction to excipient in Bricanyl and Symbicort Turbuhaler devices	Added hypersensitivity to milk protein	Lactose excipient may contain small amounts of milk protein, which may lead to a small risk of hypersensitivity reaction in those with a milk protein allergy. Exclusion criteria clarified to ensure safety.
5.2 Exclusion Criteria	Exclusion 2 modified to reflect New Zealand Child Asthma guidelines step 5 prescribing. Added further text to Exclusion criterion 6: *or cow's milk protein,* in the list of excluded known or suspected hypersensitivities to the excipient. Added new Exclusion 7: Any intravenous therapy for the treatment of asthma, in the last year Exclusion 9 deleted: ~~Any other member of the household currently enrolled or randomised into the START CARE study~~	Prevents participants on Asthma and Respiratory Foundation NZ Step 4 treatment from being excluded from trial. For safety of participants. According to Medsafe datasheets, the lactose excipient in Bricanyl and Symbicort DPIs may contain small amounts of cow's milk protein, therefore there is a small chance of hypersensitivity reaction in those with a milk protein allergy**.** For participant safety, prevents those that have had a potentially life-threatening asthma exacerbation in the past year from being enrolled. Many families manage multiple asthma regimes in the same household. Having multiple members enrolled is similar to having one member a part of the study and others taking non-trial medication.

6.1.2 Intervention period (Visits 2 to 6) Table 4: Intervention period inhalers at each treatment step	Table amended to correct Step 2 intervention arm from LD SMART to VLD SMART	Correction of error
8.1.1.3 Asthma History and Medical History 9.3.5 Sub-group and sensitivity analysis	Deletion of text regarding capture and analysis of reliever inhaler use in the 4 weeks prior to Visit 1: ~~Current reliever inhaler use in the last 4 weeks~~ ~~SABA use at enrolment, measured as the average number of occasions per week of self-reported SABA use in the four weeks before enrolment~~	This data is no longer deemed required.
8.1.2: Run-in Period	Added clarification of maintenance therapy for run-in period for those entering at Step 4	Those entering the study at Step 4 should be on ICS-LABA as maintenance therapy. This has been specified to prevent ICS only maintenance therapy being prescribed to this group.
8.1.3 Randomisation	Added: clarification of maintenance therapy to be prescribed at randomisation to those on control treatment.	Clarified that participants randomised to the control arm should remain on the maintenance therapy that they were prescribed during the run-in period.
8.3.4.2 Unscheduled visit for IMP dispensing and/or training	Added new text to clarify that there is no requirement for an in-person unscheduled visit for simple IMP re-supply: If a participant requires additional inhalers due to losing their existing supply, or due to expiry, then unscheduled dispensing can be performed. This does not require an in-person visit, inhalers may be dispensed and couriered/ supplied to the participant/	To prevent the need for unnecessary visits for straightforward IMP re-supply, in cases where there are no safety concerns or need for inhaler technique (re-)training or assessment of the participant.

	parent(s)/guardian(s) as required. The investigator should ensure that an in-person unscheduled visit is not required (i.e. that re-supply is not required due to high use or any other safety concern).	
10.1.3 Expenses and Inducements	Added: In addition to this reimbursement parent(s)/guardian(s) will be paid a stipend/ honoraria to recognise the time taken out of work/usual activities to attend each visit.	Due to length of visits a stipend has been added to recognise the significant amount of time parent(s)/guardian(s) must take out of work or daily activities to attend visits and the real cost associated. It is hoped that this will improve equity in the study by allowing those on lower incomes to participate.
10.3.8 Site reporting of Serious AEs	Adjusted the contact details for SAE or urgent issue reporting via telephone	To reflect Sponsor internal process.
10.4.2 Definitions	Removed the definition for 24 hour period: ~~24-hour period: From midnight to midnight, at local time to the investigator site.~~	Definition deemed superfluous, potentially confusing
Appendix 11: Maintenance treatment GINA steps at trial entry 11. References	Altered allowable doses of ICS or ICS-LABA: • Beclametasone now >200 to 500mcg at step 3, >500mcg at step 4. • Fluticasone proprionate now >100 to 250mcg at step 3, >250mcg at step 4. • Fluticasone proprionate – salmeterol now >100/50 to 250/100mcg at step 4, >250/100mcg step 5 Added reference to New Zealand Child Asthma Guidelines	This brings the inclusion criteria in line with New Zealand Child Asthma Guidelines. Prevents exclusion of those being treated at Step 4 of these guidelines.

Amendment 01 (10-October-2022)

This amendment is considered to be substantial by the Trial Management Group based on the Health and Disability Ethics Committee Guidance on amendments to approved studies, contained within their standard operating procedures.

Overall Rationale for the Amendment:

- The health economics questionnaire has been removed after advice from the health economist (William Leung, added to list of investigators, page 2) and replaced with specific questions in order to capture data for the health economics outcomes. The outcomes and statistical methods for the health economics analysis has been updated accordingly.
- Escalation of treatment by the Investigator after a second moderate exacerbation (within the same treatment step) has been mandated, to ensure safety of the participant.
- Overdose has been adjusted to extreme overuse to reflect the guidance for continued reliever use during worsening asthma.
- The discrete choice experiment assessment has been added to the Schedule of Activities and section 8.10 (a separate sub-study protocol contains the details of this procedure).
- Trial registration has been completed, per page 1, and membership of the DSMC has been confirmed, per page 3.
- Other minor adjustments have been made for clarity or to remove errors.

Summary of Changes

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Outcomes have been re-arranged to match the order in Section 3, Objectives, and amended to confirm the baseline time point as either enrolment or randomisation Health economics/ cost - effectiveness outcomes have been amended. Course of antibiotics for respiratory tract infections has been added as an outcome	For clarity, ease of understanding Reflective of changes to health economics data capture per health economist advice. It is hypothesized that there may be differences in the no. of courses antibiotics taken in each treatment arm.
Table 2: Schedule of Activities	Errors fixed for GP notifications, asthma review and IMP dispensing. Health economics questionnaire replaced with health economics data collection Addition of Discrete Choice Experiment (DCE) procedure	Removal of errors. Removal of Health Economics Questionnaire.The DCE will be undertaken at selected sites at Visit 6/ early withdrawal

Section # and Name	Description of Change	Brief Rationale
4.2.4 Treatment escalation 8.3.4.1 Unscheduled visit following a severe asthma exacerbation or two moderate exacerbations	Title of section 8.3.4.1 amended and text added/ changed as follows: Participants will be advised to contact their study team for urgent review (unscheduled visit) as soon as possible if they experience an asthma exacerbation (moderate or severe). The study team will arrange for an urgent review (unscheduled visit), within seven days of a severe exacerbation or a second moderate exacerbation occurring within their current treatment step.	In addition to escalating treatment after a severe exacerbation, escalation of treatment by the Investigator after a second moderate exacerbation (within the same treatment step) has been mandated, to ensure safety of the participant.
2.3.1.3 Reliever inhalations 6.7 High use/ Extreme Overuse episodes 6.7.3 Extreme overuse reporting	Text adjusted as follows: Self-reported use of 16~~20~~ or more inhalations within a 24-hour period will be recorded as ~~a~~extreme overuse~~n overdose~~ (Section 6.7.3)	Due to the advice provided to participants to continue to take reliever medication as required during an asthma exacerbation, the terminology for overdose has been amended to extreme overuse. The definition has been amended to 16 inhalations within a 24 hour period (from 20), to reflect taking twice as many inhalations as would require immediate assessment at the emergency department.
6.1 Inclusion Criteria 6.2 Exclusion Criteria	Exclusion 9 made an inclusion criterion: Able and willing to switch from current treatment regimen Exclusion 1 deleted: ~~SABA only use in the 6 months prior to Visit 1~~	For clarity, preventing double negatives on assessment Deemed unnecessary given inclusion criterion 3.
Section 6 Table 3: Run-in period inhalers at each treatment step	Table amended to delete incorrect Step 4 treatment option of Pulmicort Turbuhaler® 200	Removal of error
8.3.2	Reference to FeNO and Spirometry videos removed	Section contains information regarding Turbuhaler technique and training only
8.10	Addition of DCE procedure and reference to sub-study protocol	A DCE will be conducted per a separate sub-study protocol to obtain data on participant and

Section # and Name	Description of Change	Brief Rationale
		parent/ guardian preferences in regard to their asthma treatment
8.1.1.3 Asthma History and Medical History	Adjusted asthma or wheeze attacks to exacerbations Current ~~and previous~~ household exposure to tobacco smoke and e-cigarette fumes	Consistency of terminology Only current exposure is deemed required for the purpose of reporting/ analysis.
8.2.2 9.3.3.1	Amended outcome: Days lost from school and/or usual activities ~~work~~ due to asthma Outcome deleted: Number of days lost from work due to asthma (participant)	Usual activities has replaced work in order ensure the cost effectiveness analysis includes use of non-paid economic resources. Data not being collected therefore analysis section updated.
9.9 Health Economics 10.10 Appendix 10: Health Economics Questionnaire 9.3.6.1	The health economics questionnaire has been removed, with health economics data to be obtained at each visit: • Concomitant medication data used for treatment of asthma • Time taken off school due to asthma • Time taken off usual activities (parent/ guardian) due to participant's asthma • Healthcare visits due to asthma (from asthma exacerbation review) • Expenses incurred due to asthma The economic analysis methods section has been amended	William Leung has joined the team and provided advice regarding collection and analysis of health economic data.
9.3.3.6 Analysis dependent on data distribution	Composite removed from the Total ~~composite~~ inhaled beta$_2$-agonist dose outcome. Addition of no. courses of antibiotics for respiratory tract infections	Removal of error Reflective of the additional outcome measure
9.3.5 Sub group and sensitivity analysis	Amendments made to confirm time of data collection (enrolment or randomisation):	Section updated to clarify collection of data at enrolment (visit 1) or randomisation (visit 2)

Section # and Name	Description of Change	Brief Rationale
	• SABA use at ~~baseline~~ enrolment, measured as the average number of occasions per week of self-reported SABA use in the four weeks before enrolment ~~randomisation~~ • Severe asthma exacerbation in the 12 months prior to ~~randomisation~~ enrolment • Age at ~~baseline~~ enrolment • Sex • Ethnicity • Trial site • Smoking exposure • ~~Baseline~~ ACQ-5 score at randomisation (for asthma exacerbations and severe asthma exacerbations outcomes only) • ~~Baseline~~ FeNO at randomisation • ~~Baseline~~ FEV_1 % predicted at randomisation • Treatment step at randomisation	
9.3.6.5 Individual Patient Data meta-analyses	Included the PRECARE study in the NZ children's studies and NZ portfolio of studies	Removal of error
10.3.8 Site Reporting of Serious AEs	Adjusted wording to refer to reporting via telephone section	Removal of error
10.3.12 Sponsor Review of AEs	Amended reference from Appendix 6 to Appendix 5	Removal of error
10.10.1 Appendix 10: Inhaler Education Turbuhaler technique	Table amended by addition of: 2. Check the dose counter	Removal of error
10.4.2 Definitions	Table updated with asthma exacerbation, study end date and extreme overuse definitions.	For clarity

DOCUMENT HISTORY		
Document	**Protocol Version No.**	**Date**
Amendment 02	3.0	16-Mar-2022
Amendment 01	2.0	26-Oct-2022
Original Protocol	1.0	22-Aug-2022

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