Description of a randomised controlled trial of inhaled corticosteroid/fast-onset LABA reliever therapy in mild asthma

To the Editor:

This paper describes the rationale and design of the Novel START (Symbicort Turbuhaler Asthma Reliever Therapy) randomised controlled trial of inhaled corticosteroid (ICS)/fast-onset long-acting β-agonist (LABA) reliever therapy in mild asthma.

The main focus of clinical research and management in asthma is on patients with moderate or severe asthma. There is little attention paid to the "silent majority" with asthma who experience so-called intermittent and mild persistent asthma. These patients are often taking inhaled short-acting β-agonist (SABA) therapy alone, to provide symptom relief. However, while use of SABA therapy alone does provide symptom relief, there is little robust evidence supporting the long-term efficacy and safety of treating mild asthma with a SABA alone, or to guide clinicians and patients when to initiate regular low-dose ICS therapy. Further, doctors and patients find it difficult to recognise the need for ICS therapy when symptoms are infrequent and in this situation poor adherence to ICS is common. This has led to consideration of alternative regimens to regular ICS prescription for intermittent or mild asthma.

A combination inhaler containing both an ICS and fast-onset LABA, which is used solely as reliever therapy, may be superior to SABA reliever therapy alone, and might be an alternative to regular ICS with SABA reliever therapy in patients with intermittent or mild asthma [1–4]. Combination ICS/fast-onset LABA reliever therapy allows titration of ICS therapy according to symptoms. This may increase ICS use in patients who over-rely on their SABA and are otherwise poorly adherent to maintenance ICS therapy, and may actually represent what patients, prescribed regular combination ICS/fast-onset LABA treatment, take in the "real world" [5, 6].

The Novel START trial will investigate the efficacy and safety of ICS/fast-onset LABA as sole reliever therapy in patients with intermittent or mild persistent asthma. The study hypothesis is that ICS/fast-onset LABA reliever therapy is more effective than SABA reliever therapy and maintenance ICS and SABA reliever therapy, in adult patients with intermittent or mild asthma. The primary objective is to compare the efficacy of ICS/fast-onset LABA reliever therapy with two other treatment strategies: SABA reliever therapy only and maintenance ICS combined with SABA reliever therapy. Participants will be adult patients using only SABA monotherapy and no other asthma medication. The secondary objectives are to compare the safety of each regimen, examine patterns of inhaler use with the randomised regimens, and to explore whether baseline clinical characteristics such as T-helper cell (Th) 2 profile predict preferential response to randomised treatments.

The study design is a 52-week, open-label, parallel-group, multicentre, phase III, randomised controlled trial (RCT) to be performed in sites in New Zealand, the UK, Italy and Australia. The experimental treatment will be budesonide, formoterol fumarate dihydrate (Symbicort Turbuhaler; AstraZeneca, Sodertalje, Sweden) 200 μg/6 μg one inhalation for relief of symptoms as required. The two comparator treatments, representing current clinical practice, will be firstly salbutamol pressurised metered dose inhaler (pMDI) (Ventolin; GlaxoSmithKline, London, UK) 100 μg, two inhalations for relief of symptoms as required; and secondly budesonide (Pulmicort Turbuhaler; AstraZeneca) 200 μg, one inhalation twice daily, and salbutamol pMDI (Ventolin) 100 μg, two inhalations for relief of symptoms as required. Participants will be provided with asthma action plans, which include when to seek medical review for worsening asthma. All study inhalers will have electronic monitoring devices that record use, enabling the identification of patterns of medication use, as previously described [5].

The study aims to recruit 675 participants with doctor-diagnosed asthma receiving SABA reliever therapy only. Potential participants will be recruited if 1) they report a severe exacerbation that occurred with the last 12 months and self-report SABA use on average $\leqslant$2 occasions per day in the previous 4 weeks; or 2) they have not had a severe exacerbation in the last 12 months, self-report SABA use on average $\geqslant$2 occasions in the previous 4 weeks [7], but do so on average $\leqslant$2 occasions per day in the previous 4 weeks. The number of actuations the patient usually takes on each occasion will be documented. Details of the inclusion and exclusion criteria, study procedures and protocol, including the statistical analysis plan, can be found on the Australian New Zealand Clinical Trials Registry (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369311&isReview=true); the trial design is summarised in figure 1.

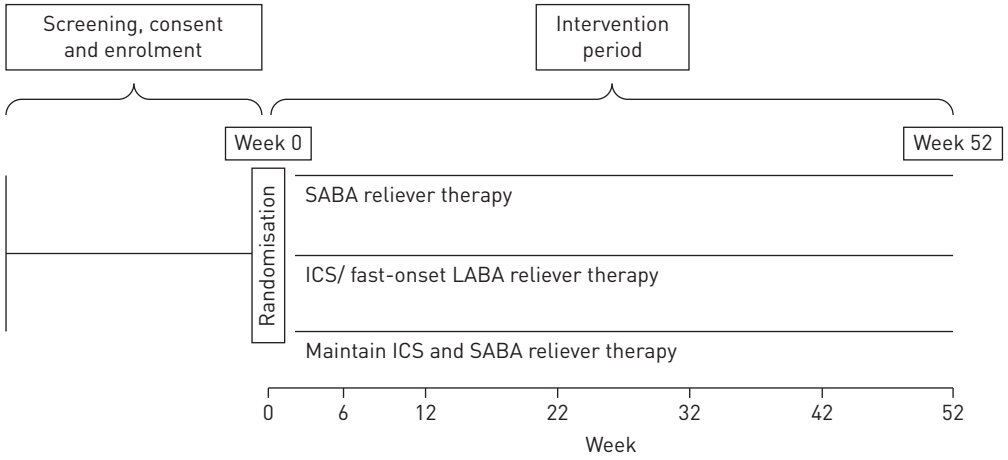

FIGURE 1 Study design. SABA: short-acting β-agonist; ICS: inhaled corticosteroid; LABA: long-acting β-agonist.

The primary outcome will be the asthma exacerbation rate expressed as number of exacerbations per patient per year.

The study definition of an asthma exacerbation is: 1) worsening asthma resulting in urgent medical review (primary care visit, emergency department (ED) visit or hospital admission); and/or 2) worsening asthma, resulting in the use of systemic corticosteroids, such as prednisone, for any duration; and/or 3) worsening asthma resulting in a high β-agonist use episode, defined as >16 actuations of salbutamol or >8 actuations of budesonide/formoterol within 24 h.

Key secondary outcomes include:

1) Clinical outcomes:
   a) The proportion of exacerbations defined by each of the three criteria, the proportion of patients with at least one exacerbation and the time to the first exacerbation.
   b) Rate of severe exacerbations and time to first severe exacerbation as defined by American Thoracic Society/European Respiratory Society criteria [8].
      - Use of systemic corticosteroids for at least 3 days.
      - Hospitalisation or ED visit because of asthma, requiring systemic corticosteroids.
   c) Proportion of patients withdrawn due to treatment failure, defined as:
      - One severe exacerbation.
      - Three exacerbations, separated by at least 7 days.
      - Unstable asthma resulting in change in randomised treatment.
   d) Asthma Control Questionnaire (ACQ-5 score).
   e) Forced expiratory volume in 1 s (FEV_1) % predicted.
   f) Fraction of exhaled nitric oxide.

2) Study medication use:
   a) Mean ICS dose per day (budesonide $\mu g \cdot day^{-1}$); number of days of no ICS use, longest duration of no ICS use.
   b) Total oral corticosteroid dose. Number of courses of oral corticosteroid per year; composite systemic corticosteroid exposure per year in which the total ICS dose per year converted to oral prednisone-equivalent dose for systemic effects on adrenal function [9] is added to the oral prednisone dose per year, as previously defined [5].
   c) High β-agonist-use episodes including proportion of participants with at least one episode of high use; proportion of high use episodes without medical review within 48 h, 7 days and 14 days.
   d) Maximum number of β-agonist actuations in a 24 h period.
   e) Use of study medications in the 14 days prior to severe exacerbations, as previously defined [10].

3) Adverse events:
   a) Adverse events.
   b) Serious adverse events.

4) Cost-effectiveness. The medical costs (medications, emergency medical and emergency department visits, and hospital admissions), and non-medical costs (days off work). The cost-effectiveness data collected will allow extrapolation to future pricing models.

5) Patient attitudes:

a) ASK-12 questionnaire [11].
b) Qualitative interviews in a subset of 120 participants to assess the acceptability and utility of medications and the impact of the medications on patient beliefs. This will be undertaken in groups of 10 participants, selected by randomised treatment and country.

The statistical analysis will be by "intention-to-treat". The primary analysis is comparison of the rate of exacerbations per patient per year by Poisson regression with an offset for the days of observation and a fixed effect for SABA use and number of prior severe exacerbations before recruitment. Over dispersion will be evaluated prior to analysis and a corrected analysis applied if necessary. Two sensitivity analyses will be undertaken to account for different distributions of potentially important predictors of response. Survival analysis with Kaplan–Meier plots and Cox's proportional hazards will be used to calculate the hazard ratio for time to first exacerbation.

For the secondary outcome variables based on medication use, counts of events will be analysed by Poisson regression with an offset for time of observation and correction for over-dispersion if necessary. Proportions of events will be analysed by calculation of relative risks or odds ratios and appropriate confidence intervals. Continuous variables, such as the ACQ-5 scores, and FEV_1 will be compared by t-tests and mixed linear models to account for repeated measurements and to examine patterns of change with time. Pre-specified subgroup analyses will be performed to evaluate if specific characteristics influence treatment response.

A sample size of 225 in each treatment arm, which accounts for a 20% drop-out, has 80% power, α 5%, for a relative rate of exacerbation of 0.75, from 1.2 to 0.9 per patient per year.

A Data Safety Monitoring Committee will review all serious adverse events with a masked interim safety statistical analysis after 400 patients have been randomised.

This study is the first independent investigator-initiated and managed RCT into the use of an ICS/fast-onset LABA inhaler, as sole reliever therapy in asthma patients with mild asthma, and will provide robust data about the safety and efficacy of all three treatment strategies. The study has a pragmatic open-label design so that two of the potential "real world" advantages of the ICS/fast-onset LABA reliever therapy regimen, *i.e.* the use of a single inhaler and no requirement for regular inhaler use, would occur as in clinical practice. The avoidance of a double-dummy, double-blind design, and the broad inclusion criteria, will ensure that the findings can be generalised to clinical practice. The subgroup analyses to determine if specific characteristics, such as Th2 profile influence response to the randomised treatment will provide data on which individualised treatments might be based.

We will address the clinical question: "In patients with intermittent or mild asthma who are treated with SABA reliever therapy alone, what is the comparative efficacy of SABA reliever therapy (continuation of their current treatment) *versus* maintenance ICS and SABA reliever therapy (as recommended by guidelines)[7] *versus* ICS/fast-onset LABA reliever therapy (novel treatment regimen)?". While the study has not been designed to validate the guidelines, it will enable an assessment of the recommendation that patients using their SABA on at least two occasions in the previous 4 weeks should receive regular ICS therapy, in addition to those with a severe exacerbation in the past 12 months regardless of infrequency of SABA use [7].

The primary outcome, the asthma exacerbation rate, is a composite measure that includes high β-agonist use episodes as previously defined [5], with thresholds based on levels of β-agonist use requiring medical review in standard action plans, and supported by the short-term bronchodilator equivalence of 6 μg formoterol to 200 μg salbutamol with repeat dosing in acute asthma [12, 13]. Validated electronic monitoring devices that record inhaler use to identify otherwise unrecorded exacerbations, and use of action plans which provide written instructions on how to recognise exacerbations and what actions to take, allow robust identification of exacerbations. The primary outcome measure corresponds to "moderate-to-severe exacerbations"; severe exacerbations will also be analysed as an important secondary outcome.

The assumed exacerbation rate of 1.2 per patient per year in the as-needed SABA group is conservative and is derived from two placebo-controlled RCTs, which report placebo maintenance and SABA reliever therapy exacerbation rates of 0.77–1.63 per patient per year [1, 14]. Definitions of exacerbations differ between studies but the most important difference, our inclusion of periods of high β-agonist use, identified by electronic monitoring of study medication use, should improve identification of exacerbations [5]. The nominated clinically meaningful treatment effect of a relative exacerbation rate of 0.75 is also conservative.

In conclusion, the Novel START study will provide data on the efficacy and safety of the ICS/fast-onset LABA reliever therapy regimen, compared with SABA reliever therapy and with maintenance ICS and SABA reliever therapy regimens in adult patients with mild asthma.

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Description of a real world study of the novel ICS/fast-onset LABA reliever therapy regimen in mild asthma http://ow.ly/WE3Yp

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