An anti-inflammatory reliever algorithm approach to asthma management in adults: an open-label, single-arm trial

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eClinicalMedicine
2025;89: 103570
Published Online 21 October 2025
https://doi.org/10.1016/j.eclinm.2025.103570

Summary

Background The stepwise approach to asthma management is a key feature of guidelines, yet knowledge of its implementation in clinical practice is limited. Our objective was to evaluate the implementation of an anti-inflammatory reliever (AIR) stepwise algorithm.

Methods Between December 2020 and July 2022, we conducted a 52-week, open-label, single-arm trial of 100 adults aged 18–75 with asthma, with 25 patients each on Global Initiative for Asthma 2018 treatment steps 1, 2, 3 and 4 at baseline. Patients were assigned to an AIR algorithm, with budesonide-formoterol 200/6 μg, one actuation as-needed (Step 1), one actuation twice-daily plus as-needed (Step 2), or two actuations twice-daily plus one as-needed (Step 3), depending on baseline treatment. Treatment steps were adjusted in response to participant reported reliever use and asthma attacks, according to the AIR algorithm. The primary outcome was Treatment Satisfaction Questionnaire for Medication (TSQM-II) Global Satisfaction score. Secondary outcomes assessed the TSQM-II Global Satisfaction minimal clinically important difference (MCID), efficacy, safety, patterns of medication use, and patient flow through treatment steps. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12620001010987).

Findings 100 participants were assigned an AIR treatment step, 68 were female and the mean age was 48 (range 19–75). There was a significant increase in TSQM-II Global Satisfaction at week 52 compared with baseline, mean (SD) 84.3 (18.6) compared to 78.1 (14.7); difference 6.3 (95% CI 1.7–10.9), p = 0.007. The estimated MCID for this variable was 3.0 (95% CI 0.2–5.7). There was a transition to lower treatment steps, with 60% (56/94), 31% (29/94), and 10% (9/94) on Steps 1, 2, and 3 at week 52 compared with 25% (25/100), 50% (50/100), and 25% (25/100) at baseline, respectively. There was a reduction in Asthma Control Questionnaire-5 at week 52 compared with baseline, mean (SD) 0.8 (0.7) compared to 1.0 (0.8); difference –0.22 (95% CI –0.39 to –0.05). There were four serious adverse events unrelated to treatment, including one death due to an acute cardiac event.

Interpretation The adoption of the AIR Algorithm in adults with asthma was associated with enhanced patient satisfaction and asthma control.

Funding Medical Research Institute of New Zealand (Independent Research Organisation funding from the Health Research Council of New Zealand [IRO grant 18/002]) and AstraZeneca.

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Registration: ACTRN12620001010987.

Keywords: Asthma; Anti-Inflammatory reliever therapy; Clinical trial; Patient satisfaction; Stepwise algorithm

Research in context

Evidence before this study

We searched PubMed on 9th December 2024 for studies of a stepwise algorithm approach to asthma in adults using an anti-inflammatory reliever treatment regimen. We used the search terms (asthma) AND ((step*) OR (track) OR (algorithm)). There were no language or date restrictions. We also reviewed the recent Global Initiative for Asthma (GINA) guidelines to identify reference to studies on which the stepwise treatment algorithms were based. We identified one single arm feasibility study which utilised a stepwise algorithm based on budesonide-formoterol reliever ± maintenance therapy in 313 patients with chronic respiratory disease, including both asthma and chronic obstructive pulmonary disease, in a rural setting in Vietnam. Whilst demonstrating the feasibility of the algorithm, and the real-world pragmatism of single inhaler budesonide-formoterol therapy, the undifferentiated population used in this study limits any conclusions that can be drawn for patients diagnosed with asthma.

Added value of this study

Whereas there is substantial evidence of the efficacy and safety of inhaled corticosteroid (ICS)-formoterol reliever ± maintenance therapy in mild, moderate and severe asthma, this is the first study to demonstrate that an anti-inflammatory reliever (AIR) therapy algorithm is a practical stepwise approach to asthma management and quality of life across the range of asthma severity.

Implications of all the available evidence

This study shows how ICS-formoterol reliever ± maintenance therapy may be implemented in clinical practice, through a practical stepwise algorithm, in which treatment steps are adjusted in response to reliever use and asthma attacks. Further studies are warranted to confirm the efficacy and safety of this regimen.

Introduction

The stepwise approach to the pharmacological treatment of asthma is a key feature of asthma guidelines.[1] Through this approach, treatment intensity is increased in discrete steps to obtain symptom control and reduce exacerbation risk, and decreased after periods of prolonged control. This approach is usually represented by algorithms, typically comprising a five-step treatment track with guidance on transitioning between steps.

Traditionally, asthma treatment algorithms include short-acting beta$_2$-agonist (SABA) reliever therapy at each step. However, in 2019, the Global Initiative for Asthma (GINA) recommended inhaled corticosteroid (ICS)-formoterol as the preferred reliever for adolescents and adults across all asthma severities. In 2020, the New Zealand asthma guidelines recommended two separate 3-step tracks based on ICS-formoterol and SABA reliever therapies, with the ICS-formoterol 'anti-inflammatory reliever' (AIR) therapy track the preferred approach.[2] In 2021, GINA also adopted two separate tracks and currently recommends both a 5-step and simplified 3-step AIR 'Track 1' algorithm, designated as preferred.[1]

Substantial evidence supports the efficacy and safety of treatment at each step of the different tracks. However, there is limited evidence of the risks and benefits of implementing specific algorithms. The AIR Algorithm is a simple and pragmatic formula for transitioning between the three AIR 'Track 1' treatment steps, which encourages patient self-management and provides clear guidance based on asthma attacks and reliever medication use.[3]

This trial investigates the 3-step AIR Algorithm approach to the treatment of asthma in adults across all levels of asthma severity. The primary objective was to assess patient satisfaction, a key factor in treatment adherence and continuation.[4,5] We hypothesised that the AIR Algorithm would improve patient satisfaction compared to pre-trial SABA reliever-based therapies. Secondary objectives were to assess transitions between treatment steps, patterns of medication use, efficacy, and safety.

Methods

Trial design

This investigator-initiated, 52-week, single-site (Wellington, New Zealand), open-label, single-arm trial assessed patient satisfaction with the AIR Algorithm approach to asthma treatment (Fig. 1). The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12620001010987).

Ethics

The study was approved by the Central Health and Disability Ethics Committee (20/CEN/154). Written informed consent was obtained from all participants before any trial-specific procedures were performed. An independent Data Safety Monitoring Committee

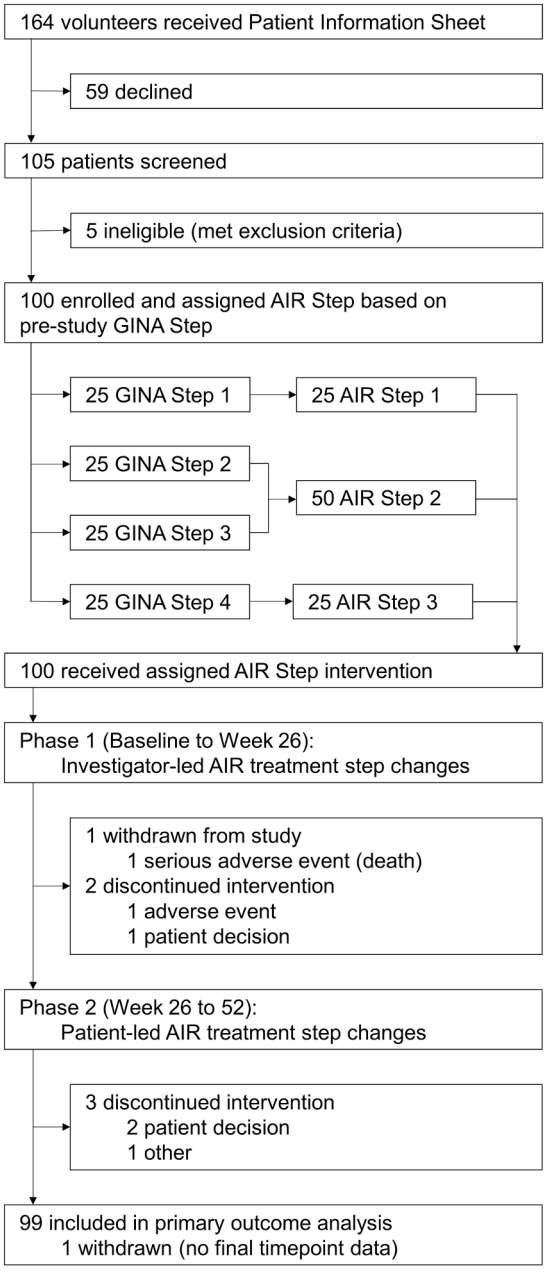

Fig. 1: **Flow chart of participants**. AIR, Anti-Inflammatory Reliever; GINA, Global Initiative for Asthma. GINA treatment steps were based on the 2018 strategy.[1] Patients received budesonide-formoterol via dry powder inhaler (Symbicort Turbuhaler, AstraZeneca), 200/6 μg; AIR Step 1 patients were assigned one actuation as needed for symptom relief; AIR Step 2 patients were assigned one actuation twice-daily plus as-needed; AIR Step 3 patients were assigned two actuations twice-daily plus one as-needed. Phase 1 is defined as the period between baseline (week 0) to week 26; Phase 2 is the period between week 26 and week 52. Baseline is defined as the point of enrolment and assignment to trial intervention (week 0).

(DSMC) reviewed monthly reports of all adverse events and could recommend termination of the trial if deemed necessary. The full trial protocol has been published.[6]

Patients

Eligible patients were aged 18–75 years with a self-reported doctor's diagnosis of asthma and current use (within last three months) of either SABA reliever monotherapy, ICS maintenance plus SABA reliever therapy, or ICS-long-acting beta$_2$-agonist (LABA) maintenance plus SABA reliever therapy. Patients were required to be willing and able to give informed consent, willing to allow their General Practitioner and/or consultant to be notified of participation in the trial, and in the investigator's opinion, able and willing to comply with all trial requirements. Exclusion criteria were: (1) current use (within last three months) of other asthma medications including budesonide-formoterol Single Maintenance and Reliever Therapy (SMART), leukotriene receptor antagonists, long-acting muscarinic antagonists, theophylline, regular oral corticosteroids, sodium cromoglycate or nedocromil sodium, or monoclonal antibody therapy; (2) self-reported urgent medical review for asthma, or treatment with systemic corticosteroids such as oral prednisone, in the two weeks before potential study entry; (3) Intensive Care Unit (ICU) admission for asthma (ever); (4) self-reported diagnosis of chronic obstructive pulmonary disease (COPD), bronchiectasis, vocal cord dysfunction or interstitial lung disease; (5) self-reported greater than 20 pack year smoking history, or onset of respiratory symptoms after the age of 40 years in current or ex-smokers with $\geq$10 pack year history; (6) self-reported current pregnancy or breast feeding at the time of enrolment or planned pregnancy within the study period; (7) self-reported congestive heart failure, atrial fibrillation, unstable coronary artery disease, or other clinically significant cardiac disease; (8) patient is unwilling or unable to switch from current asthma treatment regimen; (9) self-report of participation in another research trial involving an unapproved investigational medicinal product, in the past three months; (10) a Body Mass Index (BMI) of $\geq$40; (11) any known or suspected contraindications to the medications prescribed for the study or their respective excipients; (12) any other condition which, at the investigator's discretion, is believed may present a safety risk or impact the feasibility of the study or the study results. A total of 25 patients were recruited from each of the first four GINA 2018 treatment steps as follows: Step 1: SABA reliever alone; Step 2: low dose maintenance ICS plus SABA; Step 3: medium or high dose ICS plus SABA or low dose ICS-LABA plus SABA; Step 4: medium or high dose ICS-LABA plus SABA reliever.

Treatment

Based on their pre-enrolment GINA 2018 treatment, eligible patients were assigned to one of three AIR treatment steps (Fig. 2A; Table S1).

AIR step 1

ICS-LABA reliever: budesonide-formoterol 200/6 µg dry powder inhaler (DPI) (Symbicort Turbuhaler, AstraZeneca) one actuation as required to relieve symptoms.

AIR step 2

Low dose ICS-LABA SMART: budesonide-formoterol 200/6 µg DPI, one actuation twice daily plus one actuation as required.

AIR step 3

Medium dose ICS-LABA SMART: budesonide-formoterol 200/6 µg DPI, two actuations twice daily plus one actuation as required.

Patients received personalised asthma action plans (Figure S1) and used inhalers fitted with electronic monitor devices (Turbu+, Adherium, Auckland) to record actuations and timings. From enrolment to week 26 (Phase 1), investigators re-assessed treatment steps at weeks 13 and 26 based on reliever use and asthma attacks, defined as a deterioration in asthma symptoms severe enough to warrant the use or prescription of systemic corticosteroids, such as a course of prednisone.

A cut point of ≤2 budesonide-formoterol actuations for symptom relief per week and no recent asthma attack (<3 months) indicated that the patient should step down a level, and a cut point of >7 budesonide-formoterol actuations for symptom relief per week or an asthma attack indicated a step up in level; budesonide-formoterol actuation use between three and seven per week and no recent asthma attacks indicated no change in the step level of treatment. During weeks 26–52 (Phase 2), patients were provided with an updated action plan outlining how to self-adjust their treatment step using the AIR algorithm (Fig. 2B, Figure S1).

Trial procedures

Patients attended five in-person visits over 52 weeks (Table S3). Treatment satisfaction was assessed at each visit by the electronically administered Treatment Satisfaction Questionnaire for Medication (TSQM-II).[4] The Asthma Control Questionnaire (ACQ-5),[7,8] Asthma Quality of Life Questionnaire (AQLQ-S),[9] Asthma Control Test (ACT),[10] as measures of asthma control and quality of life. The Beliefs about Medicines Questionnaires (BMQ-AIR and BMQ-SABA),[11,12] were administered at baseline, week 26, and week 52 to assess participant beliefs and attitudes on treatment. At

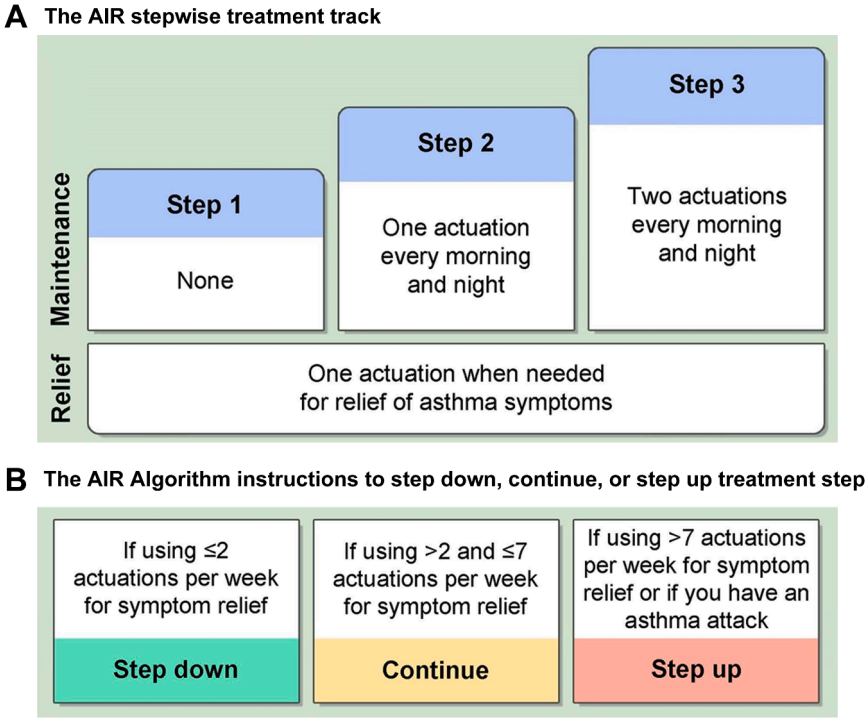

Fig. 2: **The Anti-Inflammatory Reliever (AIR) Algorithm**. The AIR Algorithm stepwise treatment track (A) is based on budesonide-formoterol via dry powder inhaler (Symbicort Turbuhaler, AstraZeneca), 200/6 µg. Participants were instructed to step down, continue, or step up treatment step in response to the frequency of reliever inhaler use (B). An asthma attack was defined as a deterioration in asthma symptoms severe enough to warrant the use or prescription of systemic corticosteroids.

weeks 26 and 52, patients were asked to rate *"How did you find your study treatment relative to your previous treatment*?" on a 5-point Likert scale. At baseline, week 26, and week 52, the Forced Expiratory Volume in 1 s (FEV_1) and Fractional exhaled Nitric Oxide (FeNO) were recorded, key measures of airway function and inflammation, respectively. (Full description of trial procedures and patient reported outcomes are provided in the study Protocol).

Outcome measures

The primary outcome was patient satisfaction, measured by the Global Satisfaction score of the TSQM-II at week 52. The TSQM-II consists of 11 questions representing four domains (Effectiveness, Side Effects, Convenience, Global Satisfaction), with the Global Satisfaction score the most predictive indicator of continued use of treatment.[4] Each domain is scored out of 100; higher scores indicate higher levels of patient satisfaction. A secondary analysis of this outcome variable was to estimate the minimal clinically important difference (MCID) by comparison with the ACQ-5 score.

Secondary outcome measures assessed treatment preference, patterns of medication use, patient flow through the treatment steps, safety, and efficacy, including asthma exacerbations, FEV_1, FeNO, ACQ-5, ACT, AQLQ-S and BMQ scores (Table S4).

A moderate asthma exacerbation was defined by any of the following criteria:

a) Worsening asthma resulting in unplanned medical review (primary care or ED visit) but not severe enough to warrant systemic corticosteroid use, such as a course of oral prednisone, and/or hospital admission, or,
b) Worsening asthma resulting in the use of systemic corticosteroids for fewer than 3 days

A severe asthma exacerbation was defined as based on the American Thoracic Society and European Respiratory Society statement:[13]

a) The use of systemic corticosteroids for at least 3 days because of asthma, or,
b) Hospitalisation, emergency department (ED) or primary care visit because of asthma, requiring systemic corticosteroids.

For an exacerbation to be counted as a separate event, it must have been preceded by at least 7 days during which neither of the above criteria were fulfilled.

Sample size

Twenty-five patients were recruited from each of the first four GINA 2018 steps for a total sample size of 100. This provides a 95% confidence interval (CI) for the estimation of a mean change from baseline of a continuous variable of plus or minus 0.2 standard deviations (SD), based on the Cohen t size framework representing a 'small' effect. Patient dropout was expected to be minimal.

Statistics

Categorical data were summarised by counts and proportions expressed as percentages. Continuous data were summarised by mean, standard deviation, median, interquartile range (IQR), and range (minimum to maximum). The proportion of patients on each treatment step and the proportion of patients that changed treatment step were displayed by alluvial plots, including an initial node for GINA 2018 Step at baseline followed by AIR Step at baseline and subsequent visits.

The primary outcome, TSQM-II Global Satisfaction Score, was analysed by paired t-test, with associated confidence interval. The MCID for the TSQM-II Global Satisfaction score was estimated in relation to ACQ-5 using a simple linear regression approach; the predicted mean change in TSQM-II from baseline in relation to the MCID of 0.5 units for ACQ-5 was used to estimate the equivalent change.[7,8] A regression approach was used to explore if key baseline variables predicted change from baseline TSQM Global Satisfaction Score.

Differences in ACQ-5, ACT, and AQLQ-S scores, FEV_1, FeNO, and inhaler use between visits were estimated using paired t-tests. FeNO was reported on the logarithm-transformed scale due to the skewed distribution of this variable, and normality assumptions were better met on the logarithm-transformed scale. The widths of confidence intervals were not adjusted for multiplicity and inferences drawn may not be reproducible. The proportion of days of no inhaler use was analysed by McNemar's test. Severe exacerbations, and moderate and severe exacerbations were analysed by Poisson regression with an offset for number of days in the trial.

It was anticipated that there would be very little missing data, and the planned approach was to only report participants with data.

SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.3.3 were used.

Role of funding source

The trial was funded by the Medical Research Institute of New Zealand (MRINZ) which receives Independent Research Organisation funding from the Health Research Council of New Zealand (IRO grant [18/002]). The Medical Research Institute of New Zealand (MRINZ) takes full responsibility for trial design and writing the protocol, data collection, analysis and interpretation, and writing the report and decision to submit the manuscript for publication. AstraZeneca Ltd

provided support through a grant-in-aid, and the supply of the trial medication, electronic monitors, and electronic monitor data collection. AstraZeneca had no role in designing the trial, writing the protocol, data collection, analysis, interpretation, writing the manuscript, or in the decision to submit the manuscript for publication.

Results

Between December 2020 and July 2022, 99 patients completed the study (Fig. 1). The mean age was 48 years; 68% were female, and the mean FEV_1 was 96% predicted, ranging from 39 to 134%. The mean (SD) prescribed dose of maintenance ICS at baseline was 454.5 µg/d (388) budesonide equivalent (Table 1, Table. S5A–E). Five patients discontinued the trial intervention, and there were four serious adverse events unrelated to treatment, including one death due to an acute cardiac event (Tables S6 and S7).

Overall, there was a transition to lower treatment steps during the trial, with 56/94 (59.6%), 29/94 (30.9%), and 9/94 (9.6%) patients on steps 1, 2, and 3 at week 52, compared with 25%, 50%, and 25% at baseline, respectively (Fig. 3; Tables S8A and B). A similar number of treatment step changes were undertaken by investigators in Phase 1 and by patients in Phase 2 (Table S8C).

Primary outcome

The mean (SD) TSQM-II Global Satisfaction score at week 52 was 84.3 (18.6) compared to 78.1 (14.7) at baseline; mean difference 6.3 (95% CI 1.7–10.9), p = 0.007 (Table 2). The TSQM-II Global Satisfaction scores were similar across the treatment step levels throughout the trial period (Table S9).

Secondary outcomes

TSQM-II Global Satisfaction score change from baseline per the 0.5 MCID in ACQ-5 score was 3.0 (95% CI 0.2–5.7) and 4.0 (95% CI –1.4 to 9.3) at weeks 26 and 52, respectively.[7,8] The receiver operating characteristic (ROC) plot for ACQ-5 change from baseline of < –0.5 versus TSQM-II Global Satisfaction score showed modest discriminative ability at weeks 26 and 52, with area under the curve (AUC)-ROC of 0.67 and 0.62, respectively (Figure S2A–D).

There was no evidence of an association between TSQM-II Global Satisfaction score at baseline and: ethnicity, sex, exacerbation status, age, BMQ variables, FeNO, FEV_1, or GINA treatment step at enrolment. There was evidence of an association between TSQM-II Global Satisfaction score at baseline and ACQ-5, ACT, and AQLQ-S scores, although correlation coefficients were low for these associations and ranged from 0.19 to 0.24 (Table S10A and B).

	AIR algorithm intervention (N = 100)
Age—yr	
Mean (SD)	47.6 (16.2)
Range	19–75
Female sex—no. (%)	68 (68)
Ethnicity—no. (%)	
Asian	10 (10)
European	83 (83)
MELAA	2 (2)
Māori	4 (4)
Pacific	1 (1)
Mean BMI-kg/m^2 (SD)	27.8 (4.9)
Smoking status—no. (%)	
Current	0 (0)
Ex-smoker	25 (25)
Never	75 (75)
Mean pack years (among ever smokers) (SD)	3.2 (5.1)
Mean age at asthma diagnosis—yr (SD)	14.5 (13.1)
GINA treatment step at baseline—no. (%)[b]	
1	25 (25)
2	25 (25)
3	25 (25)
4	25 (25)
Pre-trial asthma medication—no. (%)	
SABA monotherapy	25 (25)
SABA plus ICS only maintenance therapy	31 (31)
SABA plus ICS-LABA maintenance therapy	44 (44)
Mean pre-trial prescribed ICS dose—µg/d (SD)	455 (388)
Count of severe exacerbations in the past 12 months—no. (%)[c]	
0	93 (93)
1	5 (5)
≥2	2 (2)
Mean ACQ-5 score (SD)	1.0 (0.8)
On-treatment FEV_1—% of predicted value (SD)[d]	96.2 (18.5)
Median FeNO—ppb (IQR)[e]	25 (13–41.5)

SD, standard deviation; the range refers to the minimum and maximum values; IQR, inter-quartile range; AIR, Anti-Inflammatory Reliever; MELAA, Middle Eastern/Latin American/African; BMI, body-mass index; Pack years, packs of cigarettes smoked per day multiplied by the number of years the person has smoked; GINA, Global Initiative for Asthma; SABA, short-acting $beta_2$-agonist; ICS, inhaled corticosteroid; LABA; long-acting $beta_2$-agonist; ACQ-5, Asthma Control Questionnaire-5; FEV1, forced expiratory volume in 1 s; FeNO, fractional exhaled nitric oxide; ppb, parts per billion. [a]Baseline is defined as the assessment at enrolment and assignment to trial intervention (week 0). [b]GINA treatment steps based on the 2018 strategy.[1] [c]Asthma exacerbations were defined as per the American Thoracic Society (ATS) and European Respiratory Society (ERS) statement.[13] [d]Patients received no specific instruction to withhold use of their bronchodilator before measurement of FEV_1. [e]Data on the FeNO at baseline was missing for one patient.

Table 1: **Demographic and clinical characteristics of patients at baseline.**[a]

At weeks 26 and 52, mean (SD) scores across all TSQM-II domains were higher compared to baseline: Global Satisfaction scores increased from 78.1 (14.7) at baseline to 81.1 (18.1) at week 26; Effectiveness scores rose from 71.4 (16.0) at baseline to 77.0 (19.7) at week

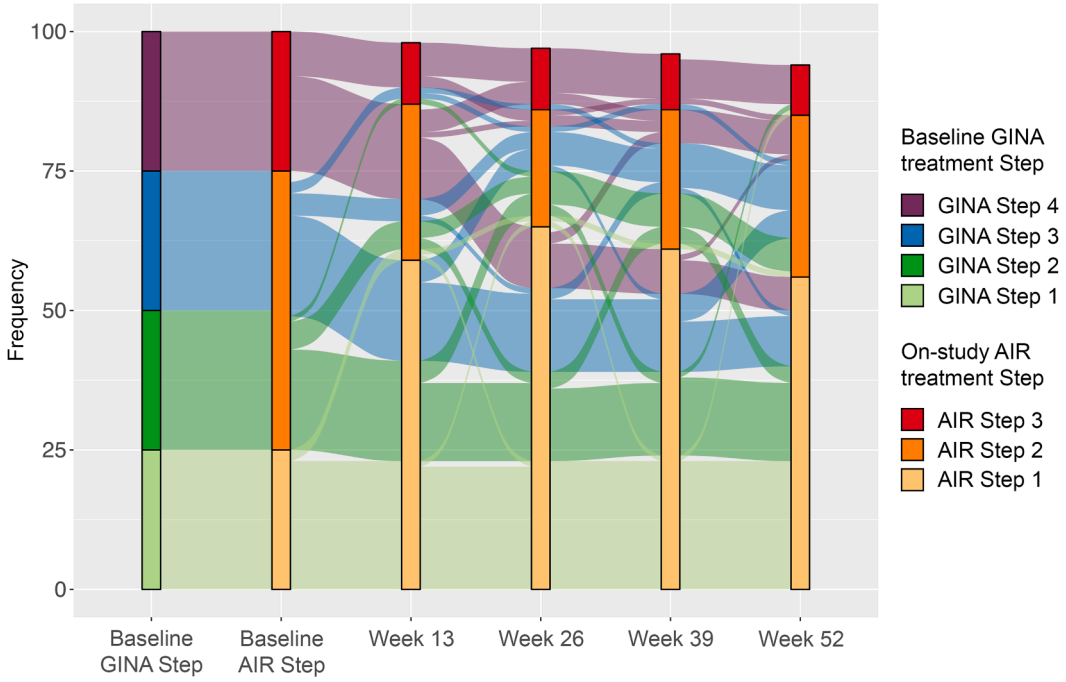

Fig. 3: **Alluvial plot of the number of patients on each of the treatment steps at each timepoint, including the initial GINA step at baseline, followed by the AIR step at baseline and subsequent visits**.*. GINA, Global Initiative for Asthma; AIR, Anti-Inflammatory Reliever. *Treatment step at timepoint is defined as the treatment step at the completion of the clinic visit, including any investigator-led treatment step changes during the visit. GINA treatment steps were based on the 2018 strategy.[1] Baseline is defined as the point of enrolment and assignment to trial intervention (week 0). During the trial, patients received budesonide-formoterol via dry powder inhaler (Symbicort Turbuhaler, AstraZeneca), 200/6 μg; AIR Step 1 patients were assigned one actuation as needed for symptom relief; AIR Step 2 patients were assigned one actuation twice-daily plus as-needed; AIR Step 3 patients were assigned two actuations twice-daily plus one as-needed. Baseline to week 26 (Phase 1) includes all investigator-led treatment step changes; week 26 to week 52 (Phase 2) covers self-reported patient-led treatment step changes.

26 and 80.5 (20.8) at week 52; Convenience scores improved from 73.8 (14.3) at baseline to 81.8 (16.0) at week 26 and 84.2 (17.3) at week 52 and; Side Effects scores remained high, increasing slightly from 97.6 (10.0) at baseline to 98.5 (8.4) at week 26 and 98.2 (9.2) at week 52 (Tables S9, S11A–C).

At weeks 26 and 52, 74.7% and 80.8% of patients considered that their AIR treatment was somewhat better or much better than their previous treatment, respectively (Figure S3; Table S12). The change in outcome variables from baseline at weeks 26 and 52 are shown in Table 2. There was a significant reduction in

Outcome	Week 26			Week 52		
	N	Mean difference (SD)	95% CI	N	Mean difference (SD)	95% CI
TSQM-II Global satisfaction score	99	3.2 (23)	−1.4 to 7.8	99	6.3 (22.9)	1.7–10.9
ACQ-5 score	99	−0.21 (0.82)	−0.37 to −0.05	99	−0.22 (0.85)	−0.39 to −0.05
ACT score	99	0.76 (3.61)	−0.04 to 1.48	99	0.35 (3.57)	−0.36 to 1.07
AQLQ score	99	0.27 (0.7)	0.13–0.41	99	0.32 (0.69)	0.18–0.45
FEV_1–ml	99	20 (240)	−29 to 68	97	−15 (200)	−54 to 25
Log FeNO–ppb[b]	98	−0.25 (0.59)	−0.37 to −0.13	97	−0.02 (0.62)	−0.15 to 0.10

SD, standard deviation; CI, confidence interval; TSQM-II, Treatment Satisfaction Questionnaire for Medication; ACQ-5, Asthma Control Questionnaire-5; AQLQ-S, Asthma Quality of Life with Standardised Activities Questionnaire; ACT, Asthma Control Test Questionnaire; FEV_1: Forced Expiratory Volume in 1s; FeNO, Fractional exhaled Nitric Oxide; ppb, parts per billion. Note a negative change from baseline ACQ-5 and FeNO is 'better' and a positive change from baseline is 'worse'. For the other variables a positive change is 'better'. [a]Baseline is defined as the point of enrolment and assignment to trial intervention (week 0). [b]FeNO was reported on the logarithm-transformed scale due to the skewed distribution of this variable, and normality assumptions were better met on the logarithm-transformed scale.

Table 2: **Change in Treatment Satisfaction with Medication (TSQM-II) Global Satisfaction and secondary outcomes by variable paired comparison with baseline.**[a]

ACQ-5 at week 52 compared with baseline, mean (SD) 0.8 (0.7) compared to 1.0 (0.8), with a paired mean (SD) difference of −0.22 (0.85); estimated difference −0.22 (95% CI −0.39 to −0.05). The reduction in ACQ-5 was similar across the AIR steps, with a mean (SD) of 0.8 (0.7), 0.9 (0.7), 1.5 (0.8) at baseline and 0.6 (0.6), 0.8 (0.7), 1.4 (0.8) at week 52 for AIR steps 1, 2 and 3, respectively (Figure S4; Table S13); 60/99 (60.6%) patients achieved an ACQ-5 $\leq$0.75 at week 52. A significant increase in AQLQ-S was observed at weeks 26 and 52 (Figure S5; Table S14) and in ACT at week 26 (Figure S6; Table S15). The FEV_1 remained stable throughout the trial (Figure S7; Table S16). The median (IQR) difference in FeNO from baseline at weeks 26 and 52 was −3.5 ppb (−12 to 0) and −1.0 ppb (−9.0 to 5.5), respectively (Figures S8 and S9; Tables S17 and S18).

There were nine severe asthma exacerbations during the trial, of which five and four occurred in the trial's first and second phases, respectively (Table S19A and B). In Phase 1, three severe exacerbations occurred during Step 2 treatment, and two during Step 3 treatment. One patient had been changed from Step 3 to Step 2 prior to the exacerbation. Amongst the four patients who experienced an asthma attack during Phase 2, in the 14 days before and after the attack, one patient stepped up from Step 1 to Step 2; one patient stepped up from Step 1 to Step 3, and then stepped down to Step 2 and then Step 1; one patient stepped up from Step 1 to Step 2 and then to Step 3; and one patient remained on Step 3; these four patients enrolled on Steps 2, 1, 2, and 3 respectively.

Different patterns of ICS use were observed depending on the treatment step (Table 3; Figure S10). The mean (SD) daily budesonide dose was 343 µg/d (243) and 267 µg/d (235) in Phase 1 and 2, respectively. The mean (SD) daily budesonide dose for the last 13 weeks leading up to week 52 was 271 µg/d (233). The

ICS dose per day	N	Mean (SD)	Median (IQR)	Range
Overall[b]	100	307 (227)	280 (128–382)	2–937
AIR Step 1 at visit 1[c]	25	93 (107)	49 (32–99)	2–389
AIR Step 2 at visit 1	50	290 (125)	291 (227–352)	74–769
AIR Step 3 at visit 1	25	556 (236)	589 (313–732)	177–937
Phase 1[d]	100	343 (243)	324 (193–455)	5–1004
AIR Step 1 at visit 1	25	90 (108)	38 (22–129)	5–380
AIR Step 2 at visit 1	50	323 (116)	324 (252–369)	61–696
AIR Step 3 at visit 1	25	639 (212)	614 (473–844)	255–1004
Phase 2	97	267 (235)	219 (80–376)	0–1043
AIR Step 1 at visit 3	65	149 (126)	133 (40–224)	0–589
AIR Step 2 at visit 3	21	381 (127)	384 (281–438)	153–689
AIR Step 3 at visit 3	11	753 (136)	758 (645–821)	558–1043
Baseline to week 13[e]	100	394 (260)	373 (226–518)	0–1036
AIR Step 1 at visit 1	25	93 (110)	49 (22–123)	0–467
AIR Step 2 at visit 1	50	377 (101)	373 (345–410)	87–716
AIR Step 3 at visit 1	25	730 (184)	781 (596–863)	391–1036
Week 13–26	97	295 (255)	253 (76–434)	0–979
AIR Step 1 at visit 2	59	141 (115)	106 (36–250)	0–387
AIR Step 2 at visit 2	27	423 (137)	434 (351–540)	77–642
AIR Step 3 at visit 2	11	806 (156)	866 (697–921)	445–979
Week 26–39	97	263 (252)	187 (56–380)	0–1031
AIR Step 1 at visit 3	65	134 (124)	114 (22–196)	0–586
AIR Step 2 at visit 3	21	392 (149)	387 (295–449)	126–800
AIR Step 3 at visit 3	11	781 (169)	783 (668–943)	518–1031
Week 39–52	95	271 (233)	229 (84–378)	0–1062
AIR Step 1 at visit 4	61	150 (125)	119 (38–236)	0–474
AIR Step 2 at visit 4	25	411 (179)	381 (273–520)	180–989
AIR Step 3 at visit 4	9	699 (219)	726 (596–812)	261–1062

SD, standard deviation; IQR, inter-quartile range; the range refers to the minimum and maximum values; AIR, Anti-Inflammatory Reliever; ICS, inhaled corticosteroid. [a]Patients received budesonide-formoterol via dry powder inhaler (Symbicort Turbuhaler, AstraZeneca), 200/6 µg; Step 1 patients were assigned one actuation as needed for symptom relief; Step 2 patients were assigned one actuation twice-daily plus as-needed; Step 3 patients were assigned two actuations twice-daily plus one as-needed. [b]Overall data covers the entirety of the trial period from week 0 to week 52. [c]AIR Step at Visit is defined as the treatment step at the completion of the clinic visit, including any investigator-led treatment step changes during the visit. [d]Phase 1 is defined as the period between baseline (week 0) to week 26; Phase 2 is the period between week 26 and week 52. [e]Baseline is defined as the point of enrolment and assignment to trial intervention (week 0).

Table 3: **Daily inhaled corticosteroid (ICS) dose (budesonide—µg/d) by Anti-Inflammatory Reliever (AIR) treatment step.**[a]

longest duration of no inhaler use increased progressively during the trial, from 16 days in Phase 1 to 22 days in Phase 2 (Figure S11; Table S20). The proportion of days of no inhaler use increased progressively during the trial, from 29% in Phase 1–40% in Phase 2 (Figure S12; Table S21).

The mean number of days of high inhaler use (>8 actuations) and marked inhaler overuse (>12 actuations) was 0.93 and 0.29 days, respectively. Patients at higher steps had a relatively higher number of high inhaler use and marked inhaler overuse days (Figures S13 and S14; Tables S22 and S23). The number of high inhaler use days without medical review within 48 h was 92 (out of a total 93 high inhaler use days); in all 29 marked inhaler overuse days, medical review was not obtained within 48 h (Tables S24 and S25).

In Phase 2, the mean number of actuations (including reliever and maintenance doses) in the seven days prior to stepping up from Step 1 was seven actuations, and 18 actuations in the seven days prior to stepping up from Step 2 (Table S26). In Phase 2, patients took, on average, 11 actuations in the seven days prior to stepping down from Step 2 and 25 actuations in the seven days prior to stepping down from Step 3 (Table S27).

At baseline, the BMQ showed patients were well-aligned with the AIR concept and had significantly stronger beliefs in their need for AIR than SABA. Concerns were low for both SABA and AIR with no significant differences. BMQ-AIR and BMQ-SABA Necessity belief scores at weeks 26 and 52 indicate that patients' beliefs in the importance of AIR relative to SABA were maintained throughout the trial. Patients' concerns about AIR diminished with treatment experience and were significantly lower than their concerns about SABA at weeks 26 and 52 (Table S28).

The findings for the main clinical outcomes in subgroups defined by sex and age are shown in Table S29.

Discussion

In this trial, the AIR Algorithm was a practical stepwise approach to asthma management that resulted in a clinically important increase in patient satisfaction. There was a transition to lower treatment steps during the trial, with 60% of patients on budesonide-formoterol reliever therapy alone (Step 1) at the end of the trial, compared with 25% who started the trial at this step. Despite this down-titration, there was a significant improvement in asthma symptom control and quality of life, though the magnitude of these changes did not meet the established cut points for an MCID. There was no deterioration in lung function or change in FeNO from baseline.

The intervention was based on budesonide-formoterol 200/6 μg per actuation Symbicort Turbuhaler, being the only ICS-formoterol product approved and available for use in New Zealand as reliever therapy alone and in combination with ICS-formoterol maintenance therapy. In addition, it is the only ICS-formoterol product in which efficacy and safety have been established across the range of asthma severity.[14–16]

The trial was designed in two phases, with patients' allocation to treatment steps determined at 3-monthly clinic reviews in Phase 1 and then patients self-transitioning between the different steps in Phase 2. This approach enhanced the generalisability of the findings to routine clinical practice in which patients may receive clinic-based supervision with the initiation of a new treatment strategy and are then responsible for their self-management with infrequent reviews. It was relevant that the increase in patient satisfaction continued during the second phase, with a clinically important improvement similar in magnitude to that observed in Phase 1.

The TSQM-II was selected for the primary outcome due to its validation and use in assessing patient-reported satisfaction with inhaled medications across respiratory diseases including asthma.[5,17] Among its domains, the Global Satisfaction score was prioritized as the indicator that best predicted medication adherence and persistence with treatment.[4] A measure of asthma control was considered most appropriate for calculating the primary outcome MCID, given the strong correlation between Satisfaction and Effectiveness (path coefficient of 0.96).[4] Of the asthma control measures assessed, the ACQ-5 is entirely symptom-based and least likely to be influenced by factors linked to the AIR Algorithm, such as reliever use.

We also assessed patients' perceptions of AIR and SABA reliever therapy using the BMQ. These findings indicate that patients aligned well with the AIR concept at baseline and were not overly reliant on SABA. Their experience of the AIR Algorithm throughout the trial positively affected their perceptions of treatment, with a significant increase in their beliefs about the importance of AIR relative to SABA and a significant reduction in concerns about AIR relative to SABA.

The AIR Algorithm incorporated both reliever use and asthma attacks as markers of risk to guide treatment adjustments.[18–20] The threshold of ≤2 budesonide-formoterol 200/6 μg actuations for symptom relief per week aligns with the GINA criterion of ≤2 occasions of reliever use per week to identify well-controlled asthma.[1] The threshold of >7 actuations per week for stepping up treatment was based on the association between SABA reliever use and the risk of both severe asthma exacerbations and poor asthma control.[21,22] The use of three to five SABA canisters annually (versus ≤2)

increases the risk of an asthma exacerbation by 26%; assuming two SABA actuations per use, four SABA canisters containing 200 actuations equate to just over seven occasions per week.[21] It is recognised that interpretation of these calculations are limited as increasing SABA use is associated with a higher risk of severe exacerbations compared to increasing ICS-formoterol reliever use.[23,24]

The progressive reduction in mean ICS dose during the trial contrasts with the GOAL trial that investigated a prototype GINA 'Track 2' stepwise approach in which ICS or ICS-LABA maintenance doses are progressively increased to achieve optimal control.[25] In GOAL, across all baseline strata of severity (GINA Step 1–4), 41% and 28% of patients in the ICS-LABA (fluticasone propionate [FP]-salmeterol) and ICS (FP) arms achieved total control at the end of 12 months, respectively, despite 68% and 76% being up-titrated to the highest dose of FP (1,000 μg/d). By comparison, we observed that 61% of patients achieved well-controlled asthma with a mean budesonide dose of 271 μg/d (169 μg/d FP equivalent), down from a prescribed dose of 455 μg/d (284 μg/d FP equivalent) pre-trial. As ICS doses above 800 μg/d budesonide (500 μg/d FP equivalent) are associated with significant risks of adverse systemic effects, such as cataracts, adrenal insufficiency, fractures, pneumonia, and diabetes,[26,27] these findings suggest major safety benefits with the AIR 'Track 1' compared with the SABA-based 'Track 2'. They also support the concept that the timing of ICS-formoterol therapy, titrated through the vehicle of bronchodilator reliever use, may be more important for efficacy than total daily maintenance dose.[28]

Interpreting the alignment of reliever use and patient-led step changes was challenging due to the inability to distinguish between symptom relief and maintenance inhaler use, variable adherence to maintenance treatment, and potential undocumented step changes. As a result, we were unable to analyse in a standardised manner the extent to which, during Phase 2, patients adhered to the algorithm's instructions to step up or step down treatment in response to >7 or ≤2 reliever actuations per week, respectively. However, documented patient-led treatment step changes generally aligned with guidance provided to step up or step down the treatment step in accordance with asthma attacks and reliever use. On average, patients took seven actuations in the seven days prior to stepping up from Step 1 and 18 actuations when stepping up from Step 2 (recommended 14 maintenance doses in a week), and patients took 11 actuations in the seven days prior to stepping down from Step 2, and 25 actuations stepping down from Step 3 (recommended 28 maintenance doses in a week). Similarly, in the four patients who experienced an asthma attack during Phase 2, three stepped up their level of treatment around the time of the exacerbation, and one remained at Step 3. However, most patients with high or marked inhaler use did not record changing their treatment step, indicating poor alignment to the guidance provided.

A key finding was that on 92 of 93 days of high budesonide-formoterol use (>8 actuations per day, including maintenance and reliever doses), patients did not seek medical review within the 48-h window recommended in their asthma action plan. This is consistent with observations in high-risk asthma, in which 93% of days of high budesonide-formoterol use (>8 actuations per day in excess of the prescribed 4 maintenance doses) occurred without medical review within 48 h.[29] Such behaviour was also observed with high salbutamol use in high-risk asthma, in which 92% of days of high salbutamol use (>16 actuations in addition to maintenance budesonide-formoterol use) occurred without medical review within 48 h.[29] Similarly, in mild asthma, although there were lower rates of beta$_2$-agonist overuse days, there were no occasions in either the budesonide-formoterol or terbutaline reliever groups (>8 and > 16 actuations, respectively) in which medical review was sought within 48 h.[30] These findings indicate that even in the setting of a clinical trial, with repeat clinic visits during which an asthma action plan is introduced and reinforced, most patients do not follow this written advice to obtain medical review when beta$_2$-agonist use exceeds predefined levels. This behaviour may reflect patient experience that most episodes of worsening asthma requiring high doses of beta$_2$-agonist are self-limiting and eventually resolve without medical review. Closing this gap between recommended self-management and actual patient behaviour should be a key priority for asthma education.

Limitations of the current trial include the relatively small sample size which limits the extent to which the study group can be considered fully representative of the wider asthma population. The broad inclusion criteria, including patients with mild to severe asthma across the adult population, however, helps mitigate this effect on generalisability and enhances the external validity of the findings. A further limitation is the absence of a control group, making causal inference and accounting for confounding factors challenging, particularly in light of the potential influence of COVID-19 restrictions on patient behaviour and asthma control. The absence of blinding may also have introduced bias for patient-reported outcomes. The pre-post analysis however, assessed changes in patient satisfaction and asthma outcomes, accounting for baseline variability, and providing valuable insights into the AIR Algorithm's impact. The study was also not powered to investigate exacerbation rates, although their documentation allowed assessment of the step changes in the 14 days before and after the exacerbation. Large studies comparing the 'Track 1' and 'Track 2' algorithms are now needed to validate these findings.

In conclusion, this single-arm, open-label trial has shown that adopting the AIR Algorithm approach to asthma management in adults is associated with enhanced patient satisfaction at lower treatment steps without compromising asthma control, airways inflammation, or lung function.

Contributors

Conceptualisation, funding acquisition and methodology: PB, LH, CK, MH, JM, AS, IP, TH, AP, RH, RB; Data curation: PB, MH, AE, JM, JS; Formal analysis: CB, AE, MW; Investigation/data collection: PB, CH, LH, CK, MP; Project administration: PB, CH, MH, JM, JS; Software: AA, CB, AE, JM; Supervision: PB, MH, JS, RB; Validation: PB, CH, MH, AA, JM, JS have verified the underlying data; Writing—original draft: RB, PB; Writing—review & editing: all authors. All authors read and approved the final version of the manuscript.

Data sharing statement

Individual participant data for this trial (including data dictionaries) will be made available, upon request, one year after publication until a minimum of 5 years after publication. Researchers must provide a methodologically sound proposal for consideration by the AIR Algorithm steering committee.

Declaration of interests

PB, CH, LH, CK, MH, AA, MP, CB, AE, JM, JS, AS and MW have no conflicts of interests to declare.

IP reports consulting fees from GlaxoSmithKline, Sanofi/Regeneron, AstraZeneca, Circassia, Aretriea and Upstream Bio, outside the submitted work; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from GlaxoSmithKline, Sanofi/Regeneron, AstraZeneca and Circasia, outside the submitted work; support for attending meetings and/or travel from GlaxoSmithKline, Sanofi/Regeneron and AstraZeneca, outside the submitted work; and stock or stock options in Upstream Bio and Mybiometry.

TH reports grants or contracts from AstraZeneca, outside the submitted work; and stock or stock options in AstraZeneca.

AP reports grants or contracts from Chiesi, AstraZeneca, GlaxoSmithKline, and Sanofi, outside the submitted work; consulting fees from Chiesi, AstraZeneca, GlaxoSmithKline, Sanofi, Avillion, Moderna, and Roche, outside the submitted work; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Chiesi, AstraZeneca, GlaxoSmithKline, Menarini, Zambon, Mundipharma, Sanofi, IQVIA, Avillion, and Regeneron, outside the submitted work; and participation on a Data Safety Monitoring Board or Advisory Board for Chiesi, AstraZeneca, GlaxoSmithKline, Sanofi, IQVIA, Avillion, and Moderna, outside the submitted work.

RH reports royalties or licences from GSK, AstraZeneca, TEVA, Novartis, UCB, EliLilly, Sanofi, Pfizer and Gilead, outside the submitted work; consulting fees from AstraZeneca, UCB, Daiichi, Sciencus, Esai and Vertex, outside the submitted work; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Abbott, Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, Biogen, Gilead Sciences, GlaxoSmithKline, Janssen, Merck Sharp Dohme, Merck, Novartis, Pfizer, Procter & Gamble, Roche, Sanofi, Shire, TEVA and UCB, outside the submitted work; participation on advisory boards for AstraZeneca, UCB, Abbott and Novartis, outside the submitted work; and stock or stock options as Founding Director of a UCL-Business company (Spoonful of Sugar Ltd) providing consultancy on treatment engagement and patient support programmes to healthcare policy makers, providers and pharmaceutical industry.

RB reports support for the present manuscript from HRC (NZ) through Independent Research Organisation (IRO) funding; and AstraZeneca through a grant-in-aid, and supply of the study medication, electronic monitors, and electronic monitor data collection. RB reports research grants from AstraZeneca, Teva, HRC NZ, Curekids NZ, and Perpetual Guardian outside the submitted work; consulting fees from AstraZeneca, Avillion, and Teva; honoraria for Advisory Board membership from AstraZeneca; writing support for unrelated NOVELTY study manuscripts from AstraZeneca; medications for other clinical trials outside the submitted work from AstraZeneca; Chair of the Asthma and Respiratory Foundation NZ adolescent and adult asthma guidelines group, reviewer for the GINA guidelines, and ex-member of the Board of GOLD.

Acknowledgements

The authors would like to thank all participants in this study, and the Data and Safety Monitoring Committee: Andrew Harrison (Chair), and Andrew Corin. This work was supported by Medical Research Institute of New Zealand (Independent Research Organisation funding from the Health Research Council of New Zealand [IRO grant 18/002]) and AstraZeneca.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103570.

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