A 24-week Randomised Exploratory Open-Label Study Aiming To Characterise Changes In Airway Inflammation, Symptoms, Lung Function, And Reliever Use In Asthma Patients Using SABA (Salbutamol) Or Anti-Inflammatory Reliever (SYMBICORT®1) As Rescue Medication In Addition To SYMBICORT As Daily Asthma Controller

Original Clinical Study Report: 22 Nov 2023 (Version 1.0, Final)

Clinical Study Report Synopsis

Drug Substance	Budesonide/formoterol
Study Code	D589BC00018
Edition Number	1.0
Date	22 November 2023
EudraCT Number	2018-003467-64
NCT Number	NCT03924635

A 24-week Randomised Exploratory Open-Label Study Aiming to Characterise Changes in Airway Inflammation, Symptoms, Lung Function, and Reliever Use in Asthma Patients Using SABA (Salbutamol) or Anti-Inflammatory Reliever (SYMBICORT®) as Rescue Medication in Addition to SYMBICORT as Daily Asthma Controller

Study dates: First subject enrolled: 01 August 2019
Last subject last visit: 16 December 2022
The analyses presented in this report are based on a clinical data lock date of 01 June 2023

Phase of development: Therapeutic use (IV)

International Co-ordinating Investigator: PPD
City campus of Nottingham University Hospital
University of Nottingham
Hucknall Road
Nottingham, NG5 1PB, United Kingdom

Sponsor's Responsible Medical Officer: PPD
AstraZeneca Academy House
136 Hills Road
Cambridge, CB2 8PA, UK

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The study was conducted by 7 investigators at 6 sites in the United Kingdom.

Publications

None at the time of writing this report.

Objectives and endpoints

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• Descriptively characterise the relationship between inflammation, asthma symptoms, lung function, and reliever use measured daily over 24 weeks of treatment in the 2 treatment arms.	• Individual patient profiles of daily variations over time in FeNO (morning), asthma symptom scores (morning and evening), PEF and FEV_1 (morning and evening), and occasions of reliever medication use for the 24 weeks of treatment.
Secondary	
• Descriptively characterise the inflammatory, asthma symptoms, lung function, and reliever use profile surrounding an event in the 2 treatment arms.	• Individual patient profiles of daily variations over time in FeNO (morning), asthma symptom scores (morning and evening), PEF and FEV_1 (morning and evening), and occasions of reliever medication use between 14 days prior and 28 days after an event. Events of interest are SevEx, CompEx (full criteria), a single day (in 24 hours) with 6 or more occasions of reliever medication use, and FeNO > 50 ppb.
Exploratory	
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

Abbreviations: CompEx = composite surrogate endpoint for severe exacerbations of asthma; CCI [redacted]; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; PEF = peak expiratory flow; ppb = parts per billion; SevEx = severe exacerbation.

Study design

This was a randomised, active-comparator, open-label, parallel-group, multicentre phase IV exploratory study to characterise temporal changes in airway inflammation, symptoms, lung function, and reliever use in asthma patients using short-acting β2-agonist (SABA or salbutamol) or anti-inflammatory reliever (SYMBICORT) as reliever medication in addition to SYMBICORT as daily asthma controller. Eligible patients diagnosed with asthma at least 6 months prior to the Screening Visit (Visit 1) and fulfilling all of the inclusion criteria and none of the exclusion criteria could continue into the Run-in Period. At Visit 2, patients were assessed for randomisation criteria and, if met, were randomised to receive either SYMBICORT as maintenance and reliever treatment or SYMBICORT as maintenance treatment and salbutamol as reliever treatment in a 1:1 ratio. Randomisation was stratified by the patient's ongoing dose of inhaled corticosteroids (ICS) [low or medium]/long-acting β2-agonist (LABA) at study entry.

This study included a minimum of 3 site visits. Patients could also attend up to 4 additional visits during the randomised Treatment Period if they met one of the 3 criteria for Event Visits. The duration of participation in the study was 26 to 28 weeks (maximum) for each individual patient, including a 2-week Run-in Period, followed by a 24-week randomised Treatment Period, and an additional follow-up period if the Event Visits fell within the final 2 weeks of the Treatment Period.

Target subject population and sample size

The key inclusion criteria were as follows: male and female patients aged 18 years and over with physician diagnosis of asthma a minimum ≥ 6 months prior to Visit 1, ≥ 3 months of use of ICS (low or medium dose)/LABA for asthma prior to Visit 1, and an episode of asthma symptom worsening requiring overuse of reliever at least once during the last 30 days prior to Visit 1. Randomisation criteria included symptoms requiring reliever medication use for a minimum of 2 to a maximum 8 days out of the last 10 days of the Run-in Period and at least 80% overall compliance rate for performing fractional exhaled nitric oxide (FeNO) and spirometry assessments and completing the asthma symptom diary during the Run-in Period.

The study planned to randomise a minimum of 60 patients to a maximum of 80 patients to achieve at least 54 patients completing the study. CCI [redacted]

It was an inclusion criterion of the study that patients were to be 'Able to perform home FeNO and spirometry assessments and complete the asthma symptom diary on a regular basis during the conduct of the study', and it was assumed that patients had these data collected regularly to provide adequate data for the analyses of the primary and secondary objectives with regards to the aforementioned numbers of patients.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Patients were provided commercially available SYMBICORT and salbutamol and both treatments were used according to their approved indication during the study.

Table S2 Study Treatments

	SYMBICORT (budesonide/formoterol)		VENTOLIN (salbutamol)
	Low Dose	**Medium Dose**	
Study treatment name:	SYMBICORT TURBOHALER 100/6, inhalation powder	SYMBICORT TURBOHALER 200/6, inhalation powder	VENTOLIN pMDI
Dosage formulation:	Budesonide 100 µg/formoterol fumarate 6 µg per inhalation	Budesonide 200 µg/formoterol fumarate 6 µg per inhalation	Salbutamol sulfate 100 µg per inhalation
Route of administration:	Oral inhalation	Oral inhalation	Oral inhalation
Batch numbers, Vendor or AstraZeneca Lot ID:	CCI [redacted]	CCI [redacted]	CCI [redacted]
Dosing instructions:	Maintenance: 2 inhalations twice per day, once in the morning and once in the evening Reliever use: Inhalation as needed		Reliever use: Inhalation as needed
Packaging and labelling:	Commercially available SYMBICORT (budesonide/formoterol) were provided by AstraZeneca or designee in a TURBOHALER.		Commercially available VENTOLIN (salbutamol) were provided by AstraZeneca or designee in a pMDI.
	All treatments were labelled according to Annex 13 and per UK country regulatory requirements with a reduced label on the secondary container only.		

Abbreviations: ID = identification; pMDI = pressurised metered dose inhaler; UK = United Kingdom.

Duration of treatment

During the Run-in Period, patients stopped their ongoing ICS/LABA asthma treatment (low or medium dose) and for 2 weeks, they received SYMBICORT as maintenance treatment and salbutamol as reliever treatment at the following doses:

- Patients on ICS (low dose)/LABA prior to study entry (per Global Initiative for Asthma guidelines): SYMBICORT (budesonide/formoterol 100/6 µg) × 2 twice daily (BID) + salbutamol (100 µg) as needed (PRN; pro re nata).
- Patients on ICS (medium dose)/LABA prior to study entry (per Global Initiative for Asthma guidelines): SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID + salbutamol (100 µg) PRN.

During the randomised Treatment Period, patients were randomly assigned in a 1:1 ratio to one of the following groups and received treatments for 24 weeks:

- SYMBICORT as maintenance and reliever treatment:
  - Patients on ICS (low dose)/LABA prior to study entry (per Global Initiative for Asthma guidelines): SYMBICORT (budesonide/formoterol 100/6 µg) × 2 BID for maintenance and PRN for relief.
  - Patients on ICS (medium dose)/LABA prior to study entry (per Global Initiative for Asthma guidelines): SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID for maintenance and PRN for relief.
- SYMBICORT as maintenance treatment and salbutamol as reliever treatment:
  - Patients on ICS (low dose)/LABA prior to study entry (per Global Initiative for Asthma guidelines): SYMBICORT (budesonide/formoterol 100/6 µg) × 2 BID for maintenance + salbutamol (100 µg) PRN for relief.
  - Patients on ICS (medium dose)/LABA prior to study entry (per Global Initiative for Asthma guidelines): SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID for maintenance + salbutamol (100 µg) PRN for relief.

Statistical methods

This study was exploratory in nature with no formal hypotheses pre-specified. This exploratory study was not designed or powered to test for significant differences between treatment arms; findings will be used to generate hypotheses for future research.

Continuous data were summarised in terms of the number of non-missing observations, mean, standard deviation (SD), two-sided 95% confidence interval (CI) of the mean (except safety data), median, 1st and 3rd quartile, minimum and maximum unless otherwise stated.

Baseline was defined as the last 10 days of the Run-in Period prior to randomisation, during which all patients were on the same run-in treatment (ie, maintenance SYMBICORT [100/6 or 200/6 µg, × 2 BID] and reliever salbutamol [100 µg, PRN]).

For FeNO, CCI [redacted], CCI [redacted], and CCI [redacted], data were summarised using arithmetic mean, SD, median, minimum and maximum, along with geometric mean, geometric coefficient of variation, and the associated

two-sided 95% CI, 1st and 3rd quartile, in order to describe the lognormal distribution of the skewed data. For patients collecting multiple FeNO measurements at a given time, means were used for the analyses.

Categorical data were summarised in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages, as well as a two-sided 95% CI for proportions computed using exact Clopper-Pearson method, where necessary.

Analysis sets:

- All Patients Analysis Set: The All Patients Analysis Set was defined as all patients screened for the study who signed the informed consent form. All disposition and screening failure analyses were based on the All Patients Analysis Set.
- Full Analysis Set (FAS): The FAS was defined as all patients randomised who had at least 1 post baseline measurement, irrespective of their protocol adherence and continued participation in the study. Patients were analysed as randomised, irrespective of whether or not they had prematurely discontinued, according to the intent-to-treat principle. Patients who withdrew consent to participate in the study were included up to the date of their study termination. All study intervention analyses were based on the FAS.
- The following subsets of the FAS were defined to assess the secondary and exploratory objectives:
  - FAS – Secondary Objective: Patient population who had reported at least 1 of the secondary objective events was defined as FAS – Secondary Objective.
  - CCI [redacted]
  - CCI [redacted]
- Safety Analysis Set (SS): The SS was defined as all patients who received at least 1 dose of the investigational product. Patients were classified according to the treatment they actually received.

Study population

- A total of 59 patients entered the Run-in Period of the study, and 42 were randomised.
- A total of 42 patients were included in the FAS (Symbicort + Symbicort PRN: 18 [42.9%] patients; Symbicort + Salbutamol PRN: 24 [57.1%] patients).
- A total of 35 patients were included in the FAS – Secondary Objective (Symbicort + Symbicort PRN: 14 [77.8%] patients; Symbicort + Salbutamol PRN: 21 [87.5%] patients).
- CCI [redacted]
- CCI [redacted]
- All 42 randomised patients were included in the SS.

- A total of 4 (22.2%) and 7 (29.2%) patients were receiving ICS (Low)/LABA at randomisation, while 14 (77.8%) and 17 (70.8%) patients were receiving ICS (medium)/LABA at randomisation in the Symbicort + Symbicort PRN and in the Symbicort + Salbutamol PRN treatment arms, respectively. For 3 patients, the information was initially reported as missing. This was due to the type of ICS they were administered (ie, fluticasone furoate), which did not fall under either of the 2 categories reported in the "Estimated Clinical Comparability for Low, Medium and High Doses of Inhaled Corticosteroids" table. For stratification purposes, two of these patients initially reported on medium dose ICS, were later reclassified on high dose. The 3rd patient was initially considered on low dose ICS, and later reclassified on medium dose.
- A total of 10 (23.8%) patients had at least one important protocol deviation (IPD). No coronavirus disease-2019 related IPD were reported.
- The demographic and other patient characteristics were consistent with the target populations intended per the clinical study protocol.
- The most commonly reported previous disease-related treatments prior to Visit 1 were SABA (36 [85.7%] patients), medium-dose ICS (24 [57.1%] patients), and a combination of medium dose ICS+LABA (23 [54.8%] patients).
- Of the 42 randomised patients, 17 (40.5%) patients in the FAS received concomitant medications during the Treatment Period.
- Median overall compliance for the Symbicort + Symbicort PRN treatment arm ranged from 84.836% (evening FEV_1) to 92.34% (FeNO). Median overall compliance for the Symbicort + Salbutamol PRN treatment arm ranged from 86.44% (evening peak expiratory flow) to 90.03% (morning asthma symptom diary).

Summary of evaluation of response to study intervention

For the primary endpoint, below data are presented for all patients in the FAS:

- Overall, less variability in inflammation and outcome measures was observed in the Symbicort + Symbicort PRN treatment arm than in the Symbicort + Salbutamol PRN treatment arm.
- At the individual patient level, the relationship between inflammation and outcome measures was found to be variable between patients, with few patients showing simultaneous variation in all parameters. Simultaneous variation was most often observed in asthma symptom scores and total reliever medication use.
- A lower symptom score and smaller range of extreme observations for each outcome measure was observed in the Symbicort + Symbicort PRN treatment arm than in the Symbicort + Salbutamol PRN treatment arm.

For the secondary endpoint, below data are presented for all patients in the FAS:

- No specific pattern was observed for the outcome variables surrounding the events.
- Overall, less severe exacerbations (SevEx), composite endpoint for severe exacerbations in asthma (CompEx), and occasions of reliever medication use events were observed in

the Symbicort + Symbicort PRN treatment arm than in the Symbicort + Salbutamol PRN treatment arm.
- The duration of these events was shorter in the Symbicort + Symbicort PRN treatment arm than in the Symbicort + Salbutamol PRN treatment arm.
- Among the Symbicort + Salbutamol PRN treatment arm, a smaller proportion of patients reporting CompEx events had concurrent SevEx events.

For the exploratory endpoints, below data are presented for all patients in the FAS:

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

Summary of safety results

The study collected only serious adverse events (SAEs) and adverse events of discontinuation. No new safety findings were observed during the study.

All 42 randomised patients were included in the SS; of these, only one (4.2%) patient in the Symbicort + Salbutamol PRN treatment arm experienced one SAE. The SAE was judged to be unrelated to either Symbicort or Salbutamol and was reported as resolved.

Conclusions

- Of the 42 randomised patients who were included in the FAS, 18 (42.9%) patients were in the Symbicort + Symbicort PRN treatment arm, and 24 (57.1%) patients were in the Symbicort + Salbutamol PRN treatment arm.
- The demographic and other patient characteristics were consistent with the target populations intended per the clinical study protocol.
- Less variation in inflammation and a smaller range of values for each outcome measure was observed in the Symbicort + Symbicort PRN treatment arm than in the Symbicort + Salbutamol PRN treatment arm.
- Less SevEx, CompEx and a shorter duration of these events were observed in the Symbicort + Symbicort PRN treatment arm than in the Symbicort + Salbutamol PRN treatment arm.
- CCI [redacted]
- No new safety findings were observed during the study.