# Clinical trial results:
# A Randomized, Double-Blind, Parallel Group, Multicenter 24 Week Study to Assess the Efficacy and Safety of Budesonide and Formoterol Fumarate Metered Dose Inhaler Relative to Budesonide Metered Dose Inhaler and Open-Label Symbicort® Turbuhaler® in Participants with Inadequately Controlled Asthma (VATHOS)

## Summary

| | |
|---|---|
| EudraCT number | 2021-002026-24 |
| Trial protocol | IT DE ES |
| Global end of trial date | 26 February 2025 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 16 July 2025 |
| First version publication date | 16 July 2025 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | D5982C00006 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05202262 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | AstraZeneca |
| Sponsor organisation address | Forskargatan 18, Södertälje, Sweden, |
| Public contact | Global Clinical Lead, AstraZeneca, +1 18772409479, information.center@astrazeneca.com |
| Scientific contact | Global Clinical Lead, AstraZeneca, +1 18772409479, information.center@astrazeneca.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 11 April 2025 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 February 2025 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 February 2025 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of Budesonide and Formoterol Fumarate Metered Dose Inhaler (BFF MDI) 320/9.6 µg BID compared with Budesonide MDI 320 µg and open-label Symbicort TBH 320/9 µg over 24 weeks. BFF MDI 160/9.6 µg BID is included to evaluate dose response by comparing to BFF MDI 320/9.6 µg BID.

Protection of trial subjects:

The conduct of this study met all the local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and was consistent with the ICH guidelines on GCP. Participating participants signed the informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 12 January 2022 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 37 |
| Country: Number of subjects enrolled | Germany: 129 |
| Country: Number of subjects enrolled | Italy: 15 |
| Country: Number of subjects enrolled | Japan: 33 |
| Country: Number of subjects enrolled | Spain: 22 |
| Country: Number of subjects enrolled | United States: 323 |
| Country: Number of subjects enrolled | Viet Nam: 22 |
| Worldwide total number of subjects | 581 |
| EEA total number of subjects | 166 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

| | |
|---|---|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 21 |
| Adults (18-64 years) | 448 |
| From 65 to 84 years | 112 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Subjects with inadequately controlled asthma (ACQ-7 total score ≥ 1.5) despite treatment with medium dose ICS or ICS/LABA were recruited at 147 sites across 7 countries. Participants were randomized in a 1:2:2:2 scheme to BFF MDI 160/9.6 µg, BFF MDI 320/9.6 µg, BD MDI 320 µg, or open-label Symbicort.

### Pre-assignment

Screening details:

All participants had to be taking a stable daily medium dose ICS or ICS/LABA for at least 8 weeks prior to Visit 1.
Of the 645 randomized participants, all populations exclude 60 participants from 11 sites due GCP violation and 4 participants due to not receiving therapy.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | BFF MDI 160/9.6 µg |

Arm description:

Budesonide/ Formoterol Fumarate (BFF) metered-dose inhaler (MDI), 160/9.6 µg

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Budesonide/formoterol fumarate pressurized inhalation suspension, desiccated flow path device |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |

Dosage and administration details:

Two inhalations BID of 80/4.8 µg per actuation. Total daily dose: 320/19.2 µg.

| | |
|---|---|
| **Arm title** | BFF MDI 320/9.6 µg |

Arm description:

Budesonide/ Formoterol Fumarate (BFF) metered-dose inhaler (MDI), 320/9.6 µg

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Budesonide/formoterol fumarate pressurized inhalation suspension, desiccated flow path device |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |

Dosage and administration details:

Two inhalations BID of 160/4.8 µg per actuation. Total daily dose: 640/19.2 µg.

| | |
|---|---|
| **Arm title** | BD MDI 320 µg |

Arm description:

Budesonide MDI (BD MDI), 320 µg

| | |
|---|---|
| Arm type | Active comparator |

| | |
|---|---|
| Investigational medicinal product name | Budesonide pressurized inhalation suspension, desiccated flow path device |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |

Dosage and administration details:

Two inhalations BID of 160 µg per actuation. Total daily dose: 640 µg.

| | |
|---|---|
| **Arm title** | Symbicort TBH 320/9 µg |

Arm description:

Open-Label Comparator Symbicort Turbuhaler 320/9 µg

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Symbicort® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |

Dosage and administration details:

Two inhalations BID of 160/4.5 µg per actuation. Total daily dose: 640/18 µg.

| **Number of subjects in period 1** | BFF MDI 160/9.6 µg | BFF MDI 320/9.6 µg | BD MDI 320 µg |
|---|---|---|---|
| Started | 88 | 163 | 168 |
| Completed | 81 | 150 | 155 |
| Not completed | 7 | 13 | 13 |
| Physician decision | 3 | 3 | - |
| Failure to meet randomization criteria | - | 1 | - |
| Adverse event, non-fatal | - | 1 | - |
| Pregnancy | - | - | - |
| Various Reasons | 2 | 5 | 3 |
| Lost to follow-up | - | - | 4 |
| Withdrawal by subject | 2 | 3 | 5 |
| Development of withdrawal Criteria | - | - | 1 |

| **Number of subjects in period 1** | Symbicort TBH 320/9 µg |
|---|---|
| Started | 162 |
| Completed | 151 |
| Not completed | 11 |
| Physician decision | - |
| Failure to meet randomization criteria | 1 |
| Adverse event, non-fatal | - |
| Pregnancy | 1 |
| Various Reasons | 4 |

| | |
|---|---|
| Lost to follow-up | - |
| Withdrawal by subject | 4 |
| Development of withdrawal Criteria | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | BFF MDI 160/9.6 µg |
| Reporting group description: | |
| Budesonide/ Formoterol Fumarate (BFF) metered-dose inhaler (MDI), 160/9.6 µg | |
| Reporting group title | BFF MDI 320/9.6 µg |
| Reporting group description: | |
| Budesonide/ Formoterol Fumarate (BFF) metered-dose inhaler (MDI), 320/9.6 µg | |
| Reporting group title | BD MDI 320 µg |
| Reporting group description: | |
| Budesonide MDI (BD MDI), 320 µg | |
| Reporting group title | Symbicort TBH 320/9 µg |
| Reporting group description: | |
| Open-Label Comparator Symbicort Turbuhaler 320/9 µg | |

| Reporting group values | BFF MDI 160/9.6 µg | BFF MDI 320/9.6 µg | BD MDI 320 µg |
|---|---|---|---|
| Number of subjects | 88 | 163 | 168 |
| Age Categorical<br>Units: Subjects | | | |
| Adolescents (12-17 years) | 3 | 6 | 7 |
| Adults (18-64 years) | 68 | 124 | 132 |
| From 65-84 years | 17 | 33 | 29 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 49.5 | 49.6 | 49.0 |
| standard deviation | ± 17.1 | ± 15.9 | ± 15.1 |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 48 | 102 | 109 |
| Male | 40 | 61 | 59 |
| Race<br>Units: Subjects | | | |
| Black or African American | 10 | 16 | 18 |
| Asian | 9 | 22 | 18 |
| White | 64 | 120 | 123 |
| Other | 5 | 5 | 9 |
| Prior asthma medication<br>Units: Subjects | | | |
| ICS | 12 | 17 | 20 |
| ICS/LABA | 76 | 146 | 147 |
| ICS/LAMA/LABA | 0 | 0 | 1 |
| Region of enrollment<br>Units: Subjects | | | |
| Canada | 6 | 13 | 10 |
| Germany | 27 | 33 | 39 |
| Italy | 4 | 4 | 1 |
| Japan | 4 | 12 | 8 |
| Spain | 3 | 6 | 7 |

| | | | |
|---|---|---|---|
| United States | 41 | 89 | 99 |
| Vietnam | 3 | 6 | 4 |

| Baseline reversibility (%) | | | |
|---|---|---|---|
| Reversibility (%) is calculated as (Post-Albuterol FEV1 - Pre-Albuterol FEV1)/Pre-Albuterol FEV1 x100 | | | |
| Units: Percentage | | | |
| arithmetic mean | 18.3 | 17.7 | 19.9 |
| standard deviation | ± 11.4 | ± 13.0 | ± 10.9 |
| Baseline pre-bronchodilator FEV1 (L) | | | |
| Units: Litre | | | |
| arithmetic mean | 2.313 | 2.160 | 2.130 |
| standard deviation | ± 0.663 | ± 0.664 | ± 0.558 |

| **Reporting group values** | Symbicort TBH 320/9 µg | Total | |
|---|---|---|---|
| Number of subjects | 162 | 581 | |
| Age Categorical | | | |
| Units: Subjects | | | |
| Adolescents (12-17 years) | 5 | 21 | |
| Adults (18-64 years) | 124 | 448 | |
| From 65-84 years | 33 | 112 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 51.2 | | |
| standard deviation | ± 15.4 | - | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 103 | 362 | |
| Male | 59 | 219 | |
| Race | | | |
| Units: Subjects | | | |
| Black or African American | 24 | 68 | |
| Asian | 19 | 68 | |
| White | 114 | 421 | |
| Other | 5 | 24 | |
| Prior asthma medication | | | |
| Units: Subjects | | | |
| ICS | 19 | 68 | |
| ICS/LABA | 143 | 512 | |
| ICS/LAMA/LABA | 0 | 1 | |
| Region of enrollment | | | |
| Units: Subjects | | | |
| Canada | 8 | 37 | |
| Germany | 30 | 129 | |
| Italy | 6 | 15 | |
| Japan | 9 | 33 | |
| Spain | 6 | 22 | |
| United States | 94 | 323 | |
| Vietnam | 9 | 22 | |

| | | | |
|---|---|---|---|
| Baseline reversibility (%) | | | |
| Reversibility (%) is calculated as (Post-Albuterol FEV1 - Pre-Albuterol FEV1)/Pre-Albuterol FEV1 x100 | | | |
| Units: Percentage | | | |
| arithmetic mean | 20.0 | | |
| standard deviation | ± 15.8 | - | |
| Baseline pre-bronchodilator FEV1 (L) | | | |
| Units: Litre | | | |
| arithmetic mean | 2.099 | | |
| standard deviation | ± 0.586 | - | |

## End points

| End points reporting groups | |
|---|---|
| Reporting group title | BFF MDI 160/9.6 µg |
| Reporting group description: | |
| Budesonide/ Formoterol Fumarate (BFF) metered-dose inhaler (MDI), 160/9.6 µg | |
| Reporting group title | BFF MDI 320/9.6 µg |
| Reporting group description: | |
| Budesonide/ Formoterol Fumarate (BFF) metered-dose inhaler (MDI), 320/9.6 µg | |
| Reporting group title | BD MDI 320 µg |
| Reporting group description: | |
| Budesonide MDI (BD MDI), 320 µg | |
| Reporting group title | Symbicort TBH 320/9 µg |
| Reporting group description: | |
| Open-Label Comparator Symbicort Turbuhaler 320/9 µg | |

| Primary: Change from baseline in morning pre-dose trough FEV1 over 24 Weeks | |
|---|---|
| End point title | Change from baseline in morning pre-dose trough FEV1 over 24 Weeks |
| End point description: | |
| Change from baseline in morning pre-dose trough FEV1 over 24 Weeks. Treatment policy is implemented to handle all intercurrent events with the exception of initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of randomised study intervention, for which the composite strategy is implemented. | |
| End point type | Primary |
| End point timeframe: | |
| Over 24 Weeks | |

| End point values | BFF MDI 160/9.6 µg | BFF MDI 320/9.6 µg | BD MDI 320 µg | Symbicort TBH 320/9 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 86 | 161 | 166 | 158 |
| Units: Litre | | | | |
| least squares mean (standard error) | 0.140 (± 0.0222) | 0.106 (± 0.0162) | 0.025 (± 0.0159) | 0.123 (± 0.0163) |

### Statistical analyses

| Statistical analysis title | Primary analysis |
|---|---|
| Statistical analysis description: | |
| The ANCOVA model includes treatment, visit, prior maintenance medication, treatment-by-visit interaction, baseline trough FEV1, and percent Albuterol reversibility. | |
| Comparison groups | BFF MDI 320/9.6 µg v BD MDI 320 µg |

| | |
|---|---|
| Number of subjects included in analysis | 327 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.0004 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.036 |
| upper limit | 0.125 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0227 |

Notes:

[1] - An increase in estimate favors study drug.

The number of subjects analyzed is based on the Efficacy Set, which excludes 6 participants who were randomized multiple times at sites or studies within the program. Additionally, only subjects with non-missing baseline covariates used in the analysis model are included in the analysis.

## Secondary: Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve 0 to 3 hours (AUC0-3) over 24 Weeks

| | |
|---|---|
| End point title | Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve 0 to 3 hours (AUC0-3) over 24 Weeks |

End point description:

Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve 0 to 3 hours (AUC0-3) over 24 Weeks. Treatment policy is implemented to handle all intercurrent events with the exception of initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of randomised study intervention, for which the composite strategy is implemented.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Over 24 Weeks

| End point values | BFF MDI 160/9.6 µg | BFF MDI 320/9.6 µg | BD MDI 320 µg | Symbicort TBH 320/9 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 87 | 161 | 166 | 159 |
| Units: Litre | | | | |
| least squares mean (standard error) | 0.294 (± 0.0221) | 0.267 (± 0.0162) | 0.078 (± 0.0159) | 0.245 (± 0.0163) |

## Statistical analyses

| Statistical analysis title | Primary analysis |
|---|---|

Statistical analysis description:

The ANCOVA model includes treatment, visit, prior maintenance medication, treatment-by-visit interaction, baseline trough FEV1, and percent Albuterol reversibility.

| | |
|---|---|
| Comparison groups | BFF MDI 320/9.6 µg v BD MDI 320 µg |

| | |
|---|---|
| Number of subjects included in analysis | 327 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.145 |
| upper limit | 0.234 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0227 |

Notes:

[2] - An increase in estimate favors study drug.

The number of subjects analyzed is based on the Efficacy Set, which excludes 6 participants who were randomized multiple times at sites or studies within the program. Additionally, only subjects with non-missing baseline covariates used in the analysis model are included in the analysis.

## Secondary: Onset of action on Day 1: Absolute change in FEV1 at 5 minutes on Day 1

| | |
|---|---|
| End point title | Onset of action on Day 1: Absolute change in FEV1 at 5 minutes on Day 1 |

End point description:

Onset of action on Day 1: Absolute change in FEV1 at 5 minutes on Day 1. Treatment policy is implemented to handle all intercurrent events with the exception of initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of randomised study intervention, for which the composite strategy is implemented.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

On Day 1

| **End point values** | BFF MDI 160/9.6 µg | BFF MDI 320/9.6 µg | BD MDI 320 µg | Symbicort TBH 320/9 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 84 | 159 | 158 | 156 |
| Units: Litre | | | | |
| least squares mean (standard error) | 0.236 (± 0.0167) | 0.184 (± 0.0122) | 0.041 (± 0.0121) | 0.161 (± 0.0123) |

## Statistical analyses

| **Statistical analysis title** | Primary analysis |
|---|---|

Statistical analysis description:

The ANCOVA model includes treatment, timepoint, prior maintenance medication, treatment-by-timepoints interaction, baseline tFEV1, and % Albuterol reversibility.

| | |
|---|---|
| Comparison groups | BFF MDI 320/9.6 µg v BD MDI 320 µg |

| | |
|---|---|
| Number of subjects included in analysis | 317 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.144 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.11 |
| upper limit | 0.177 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0172 |

Notes:

[3] - An increase in estimate favors study drug.

The number of subjects analyzed is based on the Efficacy Set, which excludes 6 participants who were randomized multiple times at sites or studies within the program. Additionally, only subjects with non-missing baseline covariates used in the analysis model are included in the analysis.

## Secondary: Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 24 Weeks

| | |
|---|---|
| End point title | Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 24 Weeks |

End point description:

Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 24 Weeks. Treatment policy is implemented to handle all intercurrent events with the exception of initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of randomised study intervention, for which the composite strategy is implemented.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Over 24 Weeks

| End point values | BFF MDI 160/9.6 µg | BFF MDI 320/9.6 µg | BD MDI 320 µg | Symbicort TBH 320/9 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 157 | 163 | 153 |
| Units: Puffs | | | | |
| least squares mean (standard error) | -0.350 (± 0.1061) | -0.481 (± 0.0781) | -0.213 (± 0.0764) | -0.443 (± 0.0791) |

## Statistical analyses

| Statistical analysis title | Primary analysis |
|---|---|

Statistical analysis description:

The ANCOVA model includes treatment, 4-week interval, their interaction, prior maintenance medication, severe asthma exacerbation history, baseline daily rescue use, baseline tFEV1, and % Albuterol reversibility.

| | |
|---|---|
| Comparison groups | BFF MDI 320/9.6 µg v BD MDI 320 µg |

| | |
|---|---|
| Number of subjects included in analysis | 320 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | = 0.0146 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.268 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.482 |
| upper limit | -0.053 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1092 |

Notes:

[4] - A decrease in estimate favors study drug.

The number of subjects analyzed is based on the Efficacy Set, which excludes 6 participants who were randomized multiple times at sites or studies within the program. Additionally, only subjects with non-missing baseline covariates used in the analysis model are included in the analysis.

## Secondary: Percentage of responders in ACQ-7 (≥ 0.5 decrease equals response) over 24 Weeks

| | |
|---|---|
| End point title | Percentage of responders in ACQ-7 (≥ 0.5 decrease equals response) over 24 Weeks |

End point description:

Percentage of responders in ACQ-7 (≥ 0.5 decrease equals response) over 24 Weeks. Treatment policy is implemented to handle all intercurrent events with the exception of initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of randomised study intervention, for which the composite strategy is implemented.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Over 24 Weeks

| **End point values** | BFF MDI 160/9.6 µg | BFF MDI 320/9.6 µg | BD MDI 320 µg | Symbicort TBH 320/9 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 86 | 162 | 166 | 158 |
| Units: Responders | 66 | 111 | 99 | 116 |

## Statistical analyses

| **Statistical analysis title** | Primary analysis |
|---|---|

Statistical analysis description:

The logistic regression model includes treatment, prior maintenance medication, baseline instrument score, baseline tFEV1, and % Albuterol reversibility.

| | |
|---|---|
| Comparison groups | BFF MDI 320/9.6 µg v BD MDI 320 µg |

| | |
|---|---|
| Number of subjects included in analysis | 328 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[5] |
| P-value | = 0.0634 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.549 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.976 |
| upper limit | 2.46 |

Notes:

[5] - An odds ratio greater than 1 favors study drug.

The number of subjects analyzed is based on the Efficacy Set, which excludes 6 participants who were randomized multiple times at sites or studies within the program. Additionally, only subjects with non-missing baseline covariates used in the analysis model are included in the analysis.

## Secondary: Percentage of responders in ACQ-5 (≥ 0.5 decrease equals response) over 24 Weeks

| | |
|---|---|
| End point title | Percentage of responders in ACQ-5 (≥ 0.5 decrease equals response) over 24 Weeks |

End point description:

Percentage of responders in ACQ-5 (≥ 0.5 decrease equals response) over 24 Weeks. Treatment policy is implemented to handle all intercurrent events with the exception of initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of randomised study intervention, for which the composite strategy is implemented.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Over 24 Weeks

| End point values | BFF MDI 160/9.6 µg | BFF MDI 320/9.6 µg | BD MDI 320 µg | Symbicort TBH 320/9 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 86 | 162 | 166 | 158 |
| Units: Responders | 67 | 120 | 109 | 116 |

## Statistical analyses

| Statistical analysis title | Primary analysis |
|---|---|

Statistical analysis description:

The logistic regression model includes treatment, prior maintenance medication, baseline instrument score, baseline tFEV1, and % Albuterol reversibility.

| | |
|---|---|
| Comparison groups | BFF MDI 320/9.6 µg v BD MDI 320 µg |

| | |
|---|---|
| Number of subjects included in analysis | 328 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[6] |
| P-value | = 0.0731 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.557 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.959 |
| upper limit | 2.526 |

Notes:

[6] - An odds ratio greater than 1 favors study drug.

The number of subjects analyzed is based on the Efficacy Set, which excludes 6 participants who were randomized multiple times at sites or studies within the program. Additionally, only subjects with non-missing baseline covariates used in the analysis model are included in the analysis.

## Secondary: Percentage of responders in the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(s) +12) (≥ 0.5 increase equals response) over 24 Weeks

| | |
|---|---|
| End point title | Percentage of responders in the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(s) +12) (≥ 0.5 increase equals response) over 24 Weeks |

End point description:

Percentage of responders in the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(s) +12) (≥ 0.5 increase equals response) over 24 Weeks. Treatment policy is implemented to handle all intercurrent events with the exception of initiation of new asthma therapy or administration of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of randomised study intervention, for which the composite strategy is implemented.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Over 24 Weeks

| End point values | BFF MDI 160/9.6 µg | BFF MDI 320/9.6 µg | BD MDI 320 µg | Symbicort TBH 320/9 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 83 | 153 | 162 | 150 |
| Units: Responders | 44 | 91 | 81 | 77 |

### Statistical analyses

| Statistical analysis title | Primary analysis |
|---|---|

Statistical analysis description:

The logistic regression model includes treatment, prior maintenance medication, baseline instrument score, baseline tFEV1, and % Albuterol reversibility.

| | |
|---|---|
| Comparison groups | BFF MDI 320/9.6 µg v BD MDI 320 µg |

| | |
|---|---|
| Number of subjects included in analysis | 315 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[7] |
| P-value | = 0.0233 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.732 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.077 |
| upper limit | 2.784 |

Notes:

[7] - An odds ratio greater than 1 favors study drug.

The number of subjects analyzed is based on the Efficacy Set, which excludes 6 participants who were randomized multiple times at sites or studies within the program. Additionally, only subjects with non-missing baseline covariates used in the analysis model are included in the analysis.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the date of first dose of IP up to and including 1 day following the date of last IP dose.

Adverse event reporting additional description:

Adverse events were reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The Investigator and any designees were responsible for detecting, documenting, and recording events that meet the definition of an AE.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 27.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | BD MDI 320 µg |

Reporting group description:

Budesonide MDI (BD MDI), 320 µg

| | |
|---|---|
| Reporting group title | BFF MDI 320/9.6 µg |

Reporting group description:

Budesonide/ Formoterol Fumarate (BFF) metered-dose inhaler (MDI), 320/9.6 µg

| | |
|---|---|
| Reporting group title | BFF MDI 160/9.6 µg |

Reporting group description:

Budesonide/ Formoterol Fumarate (BFF) metered-dose inhaler (MDI), 160/9.6 µg

| | |
|---|---|
| Reporting group title | Symbicort TBH 320/9 µg |

Reporting group description:

Open-Label Comparator Symbicort Turbuhaler 320/9 µg

| Serious adverse events | BD MDI 320 µg | BFF MDI 320/9.6 µg | BFF MDI 160/9.6 µg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 168 (0.60%) | 3 / 163 (1.84%) | 3 / 88 (3.41%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 0 / 163 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 168 (0.60%) | 0 / 163 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 0 / 163 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 0 / 163 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 0 / 163 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 0 / 163 (0.00%) | 1 / 88 (1.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 168 (0.60%) | 0 / 163 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 1 / 163 (0.61%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 0 / 163 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Skin ulcer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 168 (0.00%) | 1 / 163 (0.61%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 1 / 163 (0.61%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 0 / 163 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 0 / 163 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 0 / 163 (0.00%) | 0 / 88 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Symbicort TBH 320/9 µg | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 162 (4.32%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Myocardial ischaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 162 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 162 (0.62%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 162 (0.62%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 162 (0.62%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 162 (0.62%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 162 (0.62%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Localised infection | | | |
| subjects affected / exposed | 1 / 162 (0.62%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 162 (0.62%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| **Non-serious adverse events** | BD MDI 320 µg | BFF MDI 320/9.6 µg | BFF MDI 160/9.6 µg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 40 / 168 (23.81%) | 45 / 163 (27.61%) | 31 / 88 (35.23%) |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 168 (1.79%) | 1 / 163 (0.61%) | 3 / 88 (3.41%) |
| occurrences (all) | 3 | 1 | 3 |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 0 / 163 (0.00%) | 2 / 88 (2.27%) |
| occurrences (all) | 0 | 0 | 2 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 168 (0.60%) | 0 / 163 (0.00%) | 2 / 88 (2.27%) |
| occurrences (all) | 1 | 0 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 168 (0.60%) | 3 / 163 (1.84%) | 2 / 88 (2.27%) |
| occurrences (all) | 1 | 3 | 2 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 4 / 163 (2.45%) | 1 / 88 (1.14%) |
| occurrences (all) | 0 | 4 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 168 (0.60%) | 1 / 163 (0.61%) | 3 / 88 (3.41%) |
| occurrences (all) | 1 | 1 | 3 |
| Infections and infestations | | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 168 (1.79%) | 3 / 163 (1.84%) | 1 / 88 (1.14%) |
| occurrences (all) | 3 | 3 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 12 / 168 (7.14%) | 8 / 163 (4.91%) | 3 / 88 (3.41%) |
| occurrences (all) | 15 | 12 | 3 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 15 / 168 (8.93%) | 15 / 163 (9.20%) | 12 / 88 (13.64%) |
| occurrences (all) | 20 | 17 | 13 |
| Bronchitis bacterial | | | |
| subjects affected / exposed | 2 / 168 (1.19%) | 2 / 163 (1.23%) | 2 / 88 (2.27%) |
| occurrences (all) | 2 | 2 | 2 |
| COVID-19 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 8 / 168 (4.76%) | 15 / 163 (9.20%) | 3 / 88 (3.41%) |
| occurrences (all) | 8 | 15 | 3 |
| Metabolism and nutrition disorders | | | |
| Gout | | | |
| subjects affected / exposed | 0 / 168 (0.00%) | 1 / 163 (0.61%) | 2 / 88 (2.27%) |
| occurrences (all) | 0 | 2 | 4 |

| **Non-serious adverse events** | Symbicort TBH 320/9 µg | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 162 (24.07%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 162 (0.62%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 162 (0.62%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 162 (1.23%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Viral upper respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 162 (3.09%) | | |
| occurrences (all) | 5 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 162 (5.56%) | | |
| occurrences (all) | 10 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 13 / 162 (8.02%) | | |
| occurrences (all) | 19 | | |
| Bronchitis bacterial | | | |
| subjects affected / exposed | 2 / 162 (1.23%) | | |
| occurrences (all) | 2 | | |
| COVID-19 | | | |
| subjects affected / exposed | 11 / 162 (6.79%) | | |
| occurrences (all) | 11 | | |
| Metabolism and nutrition disorders | | | |
| Gout | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | | |
| occurrences (all) | 0 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 October 2021 | Clarity added for telemedicine visit conduct, order of assessments, and birth control methods. Additional details added for Treatment Policy estimand and sample size calculations. |
| 05 December 2023 | An amendment was required to update statistical methodology, including changes to estimands, the Type I error control procedure, covariates in the analysis models, and analysis sets and to add updated wording from the new AstraZeneca protocol standard template. |
| 07 November 2024 | An amendment was required due to Health Authority feedback to update statistical methodological approaches to handling intercurrent events and the Type I error control procedure for EU/RoW. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported