



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
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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, Data analyst, Carer, 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
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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
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Arm description:

Budesonide MDI (BD MDI), 320 μg

Arm type	Active comparator
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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
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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			
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			
Units: years			
arithmetic mean	49.5	49.6	49.0
standard deviation	± 17.1	± 15.9	± 15.1
Gender Categorical			
Units: Subjects			
Female	48	102	109
Male	40	61	59
Race			
Units: Subjects			
Black or African American	10	16	18
Asian	9	22	18
White	64	120	123
Other	5	5	9
Prior asthma medication			
Units: Subjects			
ICS	12	17	20
ICS/LABA	76	146	147
ICS/LAMA/LABA	0	0	1
Region of enrollment			
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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.1
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Reporting groups

Reporting group title	BD MDI 320 µg
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Reporting group description:

Budesonide MDI (BD MDI), 320 µg

Reporting group title	BFF MDI 320/9.6 µg
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Reporting group description:

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

Reporting group title	BFF MDI 160/9.6 µg
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Reporting group description:

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

Reporting group title	Symbicort TBH 320/9 µg
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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 occurrences (all)	3 / 168 (1.79%) 3	1 / 163 (0.61%) 1	3 / 88 (3.41%) 3
General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all)	0 / 168 (0.00%) 0	0 / 163 (0.00%) 0	2 / 88 (2.27%) 2
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 168 (0.60%) 1	0 / 163 (0.00%) 0	2 / 88 (2.27%) 2
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 168 (0.60%) 1 0 / 168 (0.00%) 0	3 / 163 (1.84%) 3 4 / 163 (2.45%) 4	2 / 88 (2.27%) 2 1 / 88 (1.14%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 168 (0.60%) 1	1 / 163 (0.61%) 1	3 / 88 (3.41%) 3
Infections and infestations Viral upper respiratory tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis bacterial subjects affected / exposed occurrences (all) COVID-19	3 / 168 (1.79%) 3 12 / 168 (7.14%) 15 15 / 168 (8.93%) 20 2 / 168 (1.19%) 2	3 / 163 (1.84%) 3 8 / 163 (4.91%) 12 15 / 163 (9.20%) 17 2 / 163 (1.23%) 2	1 / 88 (1.14%) 1 3 / 88 (3.41%) 3 12 / 88 (13.64%) 13 2 / 88 (2.27%) 2

subjects affected / exposed occurrences (all)	8 / 168 (4.76%) 8	15 / 163 (9.20%) 15	3 / 88 (3.41%) 3
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	0 / 168 (0.00%) 0	1 / 163 (0.61%) 2	2 / 88 (2.27%) 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 occurrences (all)	1 / 162 (0.62%) 1		
General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all)	0 / 162 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 162 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 162 (0.00%) 0 1 / 162 (0.62%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 162 (1.23%) 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