



## Clinical trial results:

### A Randomized, Double-Blind, Parallel Group, Multicenter 12 Week Study to Assess the Efficacy and Safety of Budesonide and Formoterol Fumarate Metered Dose Inhaler Relative to Budesonide Metered Dose Inhaler in Participants with Inadequately Controlled Asthma (LITHOS) Summary

EudraCT number	2021-003334-36
Trial protocol	DE CZ
Global end of trial date	19 November 2024

#### Results information

Result version number	v1 (current)
This version publication date	31 May 2025
First version publication date	31 May 2025

#### Trial information

##### Trial identification

Sponsor protocol code	D5982C00005
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05755906
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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	27 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 November 2024
Global end of trial reached?	Yes
Global end of trial date	19 November 2024
Was the trial ended prematurely?	No

Notes:

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**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) 160/9.6 µg BID compared with Budesonide MDI 160 µg, over 12 weeks.

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	27 February 2023
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Czechia: 82
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Philippines: 22
Country: Number of subjects enrolled	South Africa: 26
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	United States: 176
Worldwide total number of subjects	353
EEA total number of subjects	82

Notes:

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**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)	11
Adults (18-64 years)	276
From 65 to 84 years	66
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects with inadequately controlled asthma (ACQ-7 total score  $\geq 1.5$ ) despite treatment with low dose ICS or ICS/LABA were recruited at 106 sites across 7 countries. Participants were randomized in a 1:1 scheme to BFF MDI 160/9.6  $\mu\text{g}$  or BD MDI 160  $\mu\text{g}$ . The treatment period was 12 weeks in duration.

### Pre-assignment

Screening details:

All participants had to be taking a stable daily low dose ICS or ICS/LABA for at least 8 weeks prior to Visit 1.

Of the 374 randomized participants, all populations exclude 17 participants from 4 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
<b>Arm title</b>	BFF MDI 160/9.6 $\mu\text{g}$

Arm description:

Budesonide/ Formoterol Fumarate (BFF) metered-dose inhaler (MDI), 160/9.6  $\mu\text{g}$  BID (320/19.2 $\mu\text{g}$ /day)

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  $\mu\text{g}$  per actuation. Total daily dose: 320/19.2  $\mu\text{g}$ .

<b>Arm title</b>	BD MDI 160 $\mu\text{g}$
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Arm description:

Budesonide (BD) metered-dose inhaler (MDI), 160  $\mu\text{g}$  BID (320  $\mu\text{g}$ /day)

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 80  $\mu\text{g}$  per actuation. Total daily dose: 320  $\mu\text{g}$ .

<b>Number of subjects in period 1</b>	BFF MDI 160/9.6 µg	BD MDI 160 µg
Started	179	174
Completed	176	165
Not completed	3	9
Physician decision	-	1
Failure to meet randomization criteria	1	1
Withdrawal by Subject	2	6
Lost to follow-up	-	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 BID (320/19.2µg/day)	
Reporting group title	BD MDI 160 µg
Reporting group description:	
Budesonide (BD) metered-dose inhaler (MDI), 160 µg BID (320 µg/day)	

Reporting group values	BFF MDI 160/9.6 µg	BD MDI 160 µg	Total
Number of subjects	179	174	353
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	6	5	11
Adults (18-64 years)	141	135	276
From 65-84 years	32	34	66
Age Continuous			
Units: Years			
arithmetic mean	48.7	47.8	
standard deviation	± 16.6	± 16.1	-
Sex: Female, Male			
Units: Participants			
Female	114	131	245
Male	65	43	108
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	15	22	37
Asian	27	33	60
White	125	112	237
Other	10	5	15
Multiple	2	2	4
Prior asthma medication			
Units: Subjects			
ICS	43	44	87
ICS/LABA	136	130	266
Region of Enrollment			
Units: Subjects			
Canada	19	13	32
Czech Republic	40	42	82
Malaysia	4	5	9
Philippines	11	11	22
South Africa	11	15	26
South Korea	3	3	6
United States	91	85	176
Baseline pre-bronchodilator FEV1 (L)			
Units: Litre			
arithmetic mean	2.100	2.050	
standard deviation	± 0.627	± 0.603	-

Baseline reversibility (%)			
Reversibility (%) is calculated as (Post-Albuterol FEV1 - Pre-Albuterol FEV1)/Pre-Albuterol FEV1 x100			
Units: Percentage			
arithmetic mean	21.7	21.3	
standard deviation	± 14.5	± 15.0	-

## 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 BID (320/19.2µg/day)	
Reporting group title	BD MDI 160 µg
Reporting group description: Budesonide (BD) metered-dose inhaler (MDI), 160 µg BID (320 µg/day)	

### Primary: Change from baseline in morning pre-dose trough FEV1 over 12 Weeks

End point title	Change from baseline in morning pre-dose trough FEV1 over 12 Weeks
End point description: Change from baseline in morning pre-dose trough FEV1 over 12 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 12 Weeks	

End point values	BFF MDI 160/9.6 µg	BD MDI 160 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	169		
Units: Litre				
least squares mean (standard error)	0.135 (± 0.0174)	0.073 (± 0.0178)		

### 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 160/9.6 µg v BD MDI 160 µg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.0133
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.062



Confidence interval	
level	95 %
sides	2-sided
lower limit	0.013
upper limit	0.111
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

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

The number of subjects analyzed is based on the Efficacy Set, which excludes 7 participants who were randomized multiple times at sites or studies. 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 12 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 12 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 12 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 12 Weeks

<b>End point values</b>	BFF MDI 160/9.6 µg	BD MDI 160 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	169		
Units: Litre				
least squares mean (standard error)	0.299 (± 0.0173)	0.121 (± 0.0177)		

### **Statistical analyses**

<b>Statistical analysis title</b>	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 160/9.6 µg v BD MDI 160 µg
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.179

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.227
Variability estimate	Standard error of the mean
Dispersion value	0.0248

Notes:

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

The number of subjects analyzed is based on the Efficacy Set, which excludes 7 participants who were randomized multiple times at sites or studies. 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	BD MDI 160 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	157		
Units: Litre				
least squares mean (standard error)	0.179 (± 0.0138)	0.026 (± 0.0142)		

## 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 160/9.6 µg v BD MDI 160 µg
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.153

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.114
upper limit	0.192
Variability estimate	Standard error of the mean
Dispersion value	0.0198

Notes:

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

The number of subjects analyzed is based on the Efficacy Set, which excludes 7 participants who were randomized multiple times at sites or studies. 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 12 Weeks

End point title	Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 12 Weeks
End point description:	
Change from baseline in the mean number of puffs of rescue medication use (puffs/day) over 12 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 12 Weeks	

End point values	BFF MDI 160/9.6 µg	BD MDI 160 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	167		
Units: Puffs				
least squares mean (standard error)	-0.589 (± 0.0708)	-0.309 (± 0.0721)		

### 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 160/9.6 µg v BD MDI 160 µg
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority <sup>[4]</sup>
P-value	= 0.0058
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.478
upper limit	-0.082
Variability estimate	Standard error of the mean
Dispersion value	0.1008

Notes:

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

The number of subjects analyzed is based on the Efficacy Set, which excludes 7 participants who were randomized multiple times at sites or studies. 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 ( $\geq 0.5$ decrease equals response) over 12 Weeks

End point title	Percentage of responders in ACQ-7 ( $\geq 0.5$ decrease equals response) over 12 Weeks
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End point description:

Percentage of responders in ACQ-7 ( $\geq 0.5$  decrease equals response) over 12 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 12 Weeks

End point values	BFF MDI 160/9.6 $\mu$ g	BD MDI 160 $\mu$ g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	169		
Units: Responders	127	107		

### 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 160/9.6 $\mu$ g v BD MDI 160 $\mu$ g
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority <sup>[5]</sup>
P-value	= 0.0768
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.512

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.956
upper limit	2.391

Notes:

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

The number of subjects analyzed is based on the Efficacy Set, which excludes 7 participants who were randomized multiple times at sites or studies. 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 ( $\geq 0.5$ decrease equals response) over 12 Weeks

End point title	Percentage of responders in ACQ-5 ( $\geq 0.5$ decrease equals response) over 12 Weeks
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End point description:

Percentage of responders in ACQ-5 ( $\geq 0.5$  decrease equals response) over 12 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 12 Weeks

End point values	BFF MDI 160/9.6 $\mu$ g	BD MDI 160 $\mu$ g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	169		
Units: Responders	134	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 160/9.6 $\mu$ g v BD MDI 160 $\mu$ g
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority <sup>[6]</sup>
P-value	= 0.119
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.465

Confidence interval

level	95 %
sides	2-sided
lower limit	0.906
upper limit	2.367

Notes:

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

The number of subjects analyzed is based on the Efficacy Set, which excludes 7 participants who were randomized multiple times at sites or studies. 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) ( $\geq 0.5$ increase equals response) over 12 Weeks**

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

End point values	BFF MDI 160/9.6 $\mu$ g	BD MDI 160 $\mu$ g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	163		
Units: Responders	103	82		

### **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 160/9.6 $\mu$ g v BD MDI 160 $\mu$ g
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority <sup>[7]</sup>
P-value	= 0.0951
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.488
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.933
upper limit	2.374

Notes:

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

The number of subjects analyzed is based on the Efficacy Set, which excludes 7 participants who were

randomized multiple times at sites or studies. 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 160 µg
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Reporting group description:

Budesonide (BD) metered-dose inhaler (MDI), 160 µg BID (320 µg/day)

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

Budesonide/ Formoterol Fumarate (BFF) metered-dose inhaler (MDI), BDI (320/19.2µg/day)

Serious adverse events	BD MDI 160 µg	BFF MDI 160/9.6 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 174 (0.00%)	0 / 179 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	BD MDI 160 µg	BFF MDI 160/9.6 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 174 (5.17%)	9 / 179 (5.03%)	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 174 (2.87%)	6 / 179 (3.35%)	
occurrences (all)	7	6	
Nasopharyngitis			
subjects affected / exposed	4 / 174 (2.30%)	3 / 179 (1.68%)	
occurrences (all)	4	4	





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2022	Home-coached spirometry removed from study to reduce participant and clinical study site burden as well as reduce the study operational complexity; clarifications/additions to the statistical analysis; and required wording from the updated AstraZeneca protocol standard template added.
05 December 2023	An amendment was required to update statistical methodology, including changes to estimands, the Type 1 error control procedure, covariates in the analysis models, and analysis sets and to add updated wording from the new AstraZeneca protocol standard template.
15 October 2024	An amendment was required to update the statistical methodological approaches to handling intercurrent events and the Type 1 error control procedure for EU/RoW health authorities.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported