Clinical trial results:
A Randomized, Double-Blind, Double Dummy, Parallel Group, Multicenter 24 to 52 Week Variable Length Study to Assess the Efficacy and Safety of Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler (MDI) Relative to Budesonide and Formoterol Fumarate MDI and Symbicort® Pressurized MDI in Adult and Adolescent Participants with Inadequately Controlled Asthma (LOGOS)

Summary

EudraCT number	2020-001521-31
Trial protocol	SK DE CZ PT
Global end of trial date	20 March 2025

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	D5982C00008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04609904
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	1800 Concorde Pike, Wilmington, United States, DE 19803
Public contact	Global Clinical Head, AstraZeneca, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Head, AstraZeneca, +1 8772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002063-PIP01-16
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	15 April 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 March 2025
Global end of trial reached?	Yes
Global end of trial date	20 March 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a randomised, double-blind, double dummy, parallel group, multicenter 24 to 52 week variable length study to assess the efficacy and safety of budesonide, glycopyrronium, and formoterol fumarate metered dose inhaler (MDI) relative to budesonide and formoterol fumarate MDI and Symbicort® pressurized MDI in adult and adolescent participants with inadequately controlled asthma.

Protection of trial subjects:

The protocol, protocol amendments, informed consent form (ICF), and other relevant documents (e.g., advertisements) were submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study was initiated. The Investigator or their representative explained the nature of the study to the participant or their legally authorised representative and answered all questions regarding the study. Participants were informed that their participation was voluntary. Participants or their legally authorised representative were required to sign a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The authorised person obtaining the informed consent must have also signed the ICF. Participants must have been re-consented to the most current version of the ICF(s) during their participation in the study.

Background therapy:

Participants eligible for this study were required to be on a stable regimen of an inhaled asthma maintenance therapy defined as an Inhaled Corticosteroid (ICS)/Long-Acting β2-Agonist (LABA) for at least 4 weeks prior to Visit 1. After meeting all eligibility criteria, participants discontinued their medium or high dose ICS/LABA at Visit 1 and initiated run-in BFF MDI 320/9.6 µg taken BID until the evening prior to Visit 5 (randomisation) when the run-in BFF MDI was discontinued. All participants received albuterol sulfate inhalation aerosol or salbutamol sulfate inhalation aerosol, hereinafter referred to as albuterol, at Visit 1 for rescue use during the study.

Evidence for comparator: -

Actual start date of recruitment	01 March 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 795
Country: Number of subjects enrolled	South Africa: 295
Country: Number of subjects enrolled	Czechia: 127
Country: Number of subjects enrolled	Germany: 196
Country: Number of subjects enrolled	United Kingdom: 5

Country: Number of subjects enrolled	Greece: 41
Country: Number of subjects enrolled	Israel: 82
Country: Number of subjects enrolled	Portugal: 14
Country: Number of subjects enrolled	Russian Federation: 95
Country: Number of subjects enrolled	Slovakia: 70
Country: Number of subjects enrolled	Türkiye: 29
Country: Number of subjects enrolled	Brazil: 81
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Mexico: 123
Country: Number of subjects enrolled	United States: 211
Worldwide total number of subjects	2167
EEA total number of subjects	448

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)	58
Adults (18-64 years)	1687
From 65 to 84 years	422
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 2187 subjects were randomised at 324 study centers in 15 countries from 01 March 2021. The last subject completed their last study visit on 20 March 2025. Of the 2187 randomised subjects, 2167 received treatment; all populations excluded 16 subjects due to GCP violations and 4 subjects due to not receiving study therapy.

Pre-assignment

Screening details:

Adult and adolescent subjects with inadequately controlled moderate to severe asthma were randomised to 1 of 4 groups: BGF MDI 320/28.8/9.6 µg, BGF MDI 320/14.4/9.6 µg, BFF MDI, and Symbicort pMDI. Those who were eligible for the study discontinued their medium or high dose ICS/LABA at Visit 1 and initiated run-in BFF MDI until randomisation.

Period 1

Period 1 title	24 to 52-Wk Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

All participants were centrally assigned to 1 of 4 randomised study interventions using a Randomisation and Trial Supply Management (RTSM). Before the study was initiated, the log-in information and directions for the RTSM were provided to each site.

Arms

Are arms mutually exclusive?	Yes
Arm title	BGF MDI 320/14.4/9.6 µg BID

Arm description:

Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) metered-dose inhaler (MDI), 320/14.4/9.6 µg BID

Arm type	Experimental
Investigational medicinal product name	Budesonide, glycopyrronium, and formoterol fumarate pressurised 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 160/7.2/4.8 µg per actuation. Total daily dose: 640/28.8/19.2 µg.

Arm title	BGF MDI 320/28.8/9.6 µg BID

Arm description:

Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) metered-dose inhaler (MDI), 320/28.8/9.6 µg BID

Arm type	Experimental
Investigational medicinal product name	Budesonide, glycopyrronium, and formoterol fumarate pressurised 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 160/14.4/4.8 µg per actuation. Total daily dose: 640/57.6/19.2 µg.

Arm title	BFF MDI 320/9.6 µg BID
Arm description:	
Budesonide/Formoterol Fumarate (BFF) metered-dose inhaler (MDI), 320/9.6 µg BID	
Arm type	Active comparator
Investigational medicinal product name	Budesonide/formoterol fumarate pressurised 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	Symbicort® pMDI 320/9 µg BID
Arm description:	
Budesonide/Formoterol Fumarate pMDI 320/9 µg BID	
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	BGF MDI 320/14.4/9.6 µg BID	BGF MDI 320/28.8/9.6 µg BID	BFF MDI 320/9.6 µg BID
Started	384	585	604
Completed	360	535	540
Not completed	24	50	64
Physician decision	1	2	2
Consent withdrawn by subject	13	29	36
Death	-	3	3
Not specified	3	4	6
Pregnancy	-	2	-
Adverse event	4	5	2
Non-compliance with study drug	-	1	2
Lost to follow-up	1	2	6
Development of study-specific withdrawal criteria	1	-	-
Withdrawal by parent/guardian	-	-	-
Lack of efficacy	1	2	7

Number of subjects in period 1	Symbicort® pMDI 320/9 µg BID
Started	594

Completed	544
Not completed	50
Physician decision	3
Consent withdrawn by subject	32
Death	1
Not specified	1
Pregnancy	1
Adverse event	1
Non-compliance with study drug	2
Lost to follow-up	7
Development of study-specific withdrawal criteria	-
Withdrawal by parent/guardian	1
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	BGF MDI 320/14.4/9.6 µg BID
Reporting group description:	
Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) metered-dose inhaler (MDI), 320/14.4/9.6 µg BID	
Reporting group title	BGF MDI 320/28.8/9.6 µg BID
Reporting group description:	
Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) metered-dose inhaler (MDI), 320/28.8/9.6 µg BID	
Reporting group title	BFF MDI 320/9.6 µg BID
Reporting group description:	
Budesonide/Formoterol Fumarate (BFF) metered-dose inhaler (MDI), 320/9.6 µg BID	
Reporting group title	Symbicort® pMDI 320/9 µg BID
Reporting group description:	
Budesonide/Formoterol Fumarate pMDI 320/9 µg BID	

Reporting group values	BGF MDI 320/14.4/9.6 µg BID	BGF MDI 320/28.8/9.6 µg BID	BFF MDI 320/9.6 µg BID
Number of subjects	384	585	604
Age Categorical Units: Participants			
Adolescents (12-17 years)	9	14	17
Adults (18-64 years)	312	447	477
From 65-84 years	63	124	110
Age Continuous Units: years			
arithmetic mean	51.7	52.0	51.5
standard deviation	± 14.0	± 14.5	± 14.1
Gender Categorical Units: Participants			
Female	224	341	383
Male	160	244	221
Race Units: Subjects			
White	150	268	270
Asian	170	222	230
Black or African American	11	35	35
American Indian or Alaska Native	9	7	5
Native Hawaiian or Other Pacific Islander	0	0	1
Other	44	53	63
Ethnicity Units: Subjects			
Hispanic or Latino	40	71	68
Not Hispanic or Latino	344	514	536
Baseline Severe Asthma Exacerbation History Within the Prior Year Units: Subjects			
0 exacerbations	170	310	311

1 exacerbation	173	225	234
≥2 exacerbations	40	50	57
Missing	1	0	2
Prior Inhaled Corticosteroid Dose Units: Subjects			
Low	0	3	2
Medium	283	433	440
High	100	149	160
Missing	1	0	2
Baseline Reversibility (%)			
Baseline reversibility (%) calculated as (Post-Albuterol FEV1 - Pre-Albuterol FEV1)/ Pre-Albuterol FEV1 x 100			
Units: Percentage			
arithmetic mean	22.3	21.7	21.6
standard deviation	± 18.1	± 17.9	± 17.2
Baseline Pre-bronchodilator Percent Predicted FEV1 (%) Units: Percentage			
arithmetic mean	58.6	57.9	59.6
standard deviation	± 12.2	± 13.3	± 12.3

Reporting group values	Symbicort® pMDI 320/9 µg BID	Total	
Number of subjects	594	2167	
Age Categorical Units: Participants			
Adolescents (12-17 years)	18	58	
Adults (18-64 years)	451	1687	
From 65-84 years	125	422	
Age Continuous Units: years			
arithmetic mean	51.6		
standard deviation	± 15.0	-	
Gender Categorical Units: Participants			
Female	370	1318	
Male	224	849	
Race Units: Subjects			
White	264	952	
Asian	231	853	
Black or African American	30	111	
American Indian or Alaska Native	9	30	
Native Hawaiian or Other Pacific Islander	0	1	
Other	60	220	
Ethnicity Units: Subjects			
Hispanic or Latino	60	239	
Not Hispanic or Latino	534	1928	
Baseline Severe Asthma Exacerbation History Within the Prior Year Units: Subjects			

0 exacerbations	302	1093	
1 exacerbation	235	867	
≥2 exacerbations	53	200	
Missing	4	7	
Prior Inhaled Corticosteroid Dose Units: Subjects			
Low	3	8	
Medium	428	1584	
High	158	567	
Missing	5	8	
Baseline Reversibility (%)			
Baseline reversibility (%) calculated as (Post-Albuterol FEV1 - Pre-Albuterol FEV1)/ Pre-Albuterol FEV1 x 100			
Units: Percentage			
arithmetic mean	22.1		
standard deviation	± 17.5	-	
Baseline Pre-bronchodilator Percent Predicted FEV1 (%) Units: Percentage			
arithmetic mean	59.3		
standard deviation	± 12.4	-	

End points

End points reporting groups

Reporting group title	BGF MDI 320/14.4/9.6 µg BID

Reporting group description:

Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) metered-dose inhaler (MDI), 320/14.4/9.6 µg BID

Reporting group title	BGF MDI 320/28.8/9.6 µg BID

Reporting group description:

Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) metered-dose inhaler (MDI), 320/28.8/9.6 µg BID

Reporting group title	BFF MDI 320/9.6 µg BID

Reporting group description:

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

Reporting group title	Symbicort® pMDI 320/9 µg BID

Reporting group description:

Budesonide/Formoterol Fumarate pMDI 320/9 µg BID

Subject analysis set title	BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This reporting arm combines the 2 treatment groups BFF MDI 320/9.6 µg and Symbicort pMDI 320/9 µg BID from protocol S5982C00008 (2020-001521-31). In the EU regional multiple testing approach, BGF MDI was compared to these combined treatment groups (with a total of 1192 subjects; 602 in the BFF treatment group and 590 in the Symbicort treatment group).

Subject analysis set title	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This reporting arm contains the pooled population of subjects from protocol D5982C00008 (2020-001521-31) and protocol D5982C00007 (2020-001520-34) who received BGF MDI 320/14.4/9.6 µg BID study intervention. A total of 725 subjects were included in the pooled analysis Efficacy Set comprising 383 subjects from D5982C00008 (LOGOS) and 342 subjects from D5982C00007 (KALOS) who received BGF MDI 320/14.4/9.6 µg BID study intervention.

Subject analysis set title	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This reporting arm contains the pooled population of subjects from protocol D5982C00008 (2020-001521-31) and protocol D5982C00007 (2020-001520-34) who received BGF MDI 320/28.8/9.6 µg BID study intervention. A total of 1179 subjects were included in the pooled analysis Efficacy Set comprising 585 subjects from D5982C00008 (LOGOS) and 594 subjects from D5982C00007 (KALOS) who received BGF MDI 320/28.8/9.6 µg BID study intervention.

Subject analysis set title	Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This reporting arm contains the pooled population of subjects from protocol D5982C00008 (2020-001521-31) and protocol D5982C00007 (2020-001520-34) who received BFF MDI 320/9.6 µg or Symbicort pMDI 320/9 µg BID study intervention. In the EU regional approach of both studies, BGF MDI was compared to subjects who received BFF MDI or Symbicort. A total of 2400 subjects were included in the pooled analysis Efficacy Set comprising 1192 subjects from D5982C00008 (LOGOS) and 1208 subjects from D5982C00007 (KALOS).

Primary: Change from baseline in morning pre-dose trough FEV1 (L) over 24 weeks

End point title	Change from baseline in morning pre-dose trough FEV1 (L) over 24 weeks[1]

End point description:

Change from baseline in morning pre-dose trough forced expiratory volume in 1 second (FEV1) over 24 weeks. Treatment policy was implemented to handle all intercurrent events (ICEs) with the exception of

initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Primary

End point timeframe:

Over 24 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: In the EU regional multiple testing approach, BGF MDI was compared to the combined BFF MDI 320/9.6 µg and Symbicort 320/9 µg reporting groups. Therefore, data for these two reporting groups were presented combined, and not individually for the BFF MDI and Symbicort reporting groups

End point values	BGF MDI 320/14.4/9.6 µg BID	BGF MDI 320/28.8/9.6 µg BID	BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	382	582	1183	
Units: Litres				
least squares mean (standard error)				
Estimate (SE)	0.178 (± 0.015)	0.171 (± 0.013)	0.074 (± 0.010)	

Statistical analyses

Statistical analysis title	Change from BL in Pre-dose Trough FEV1 (L)

Statistical analysis description:

The repeated measures ANCOVA model included treatment, visit, prior ICS dose (medium vs. high), and treatment-by-visit interaction as categorical covariates and baseline trough FEV1 and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/28.8/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1765
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.123
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[2] - An increase in estimate for comparison favors study drug. The number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times at sites or studies within the program. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.

[3] - Statistically significant per the Type I error control procedure.

Statistical analysis title	Change from BL in Pre-dose Trough FEV1 (L)

Statistical analysis description:

The repeated measures ANCOVA model included treatment, visit, prior ICS dose (medium vs. high), and treatment-by-visit interaction as categorical covariates and baseline trough FEV1 and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/14.4/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1565
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.073
upper limit	0.134
Variability estimate	Standard error of the mean
Dispersion value	0.016

Notes:

[4] - An increase in estimate for comparison favors study drug. The number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times at sites or studies within the program. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.
[5] - Statistically significant per the Type I error control procedure.

Primary: Pooled (LOGOS/KALOS): Rate of severe asthma exacerbations

End point title	Pooled (LOGOS/KALOS): Rate of severe asthma exacerbations

End point description:

Rate of severe asthma exacerbations was assessed in a pre-specified pooled analysis across replicate studies D5982C00008 and D5982C00007 (2020-001520-34). An asthma exacerbation was severe if it resulted in at least 1 of the following: a course of systemic corticosteroids for 3 days to treat symptoms of asthma worsening, an ER/urgent care visit that required treatment with systemic corticosteroids, an inpatient hospitalisation, or death related to asthma. Consecutive exacerbations with start/stop days ≤7 days apart were considered the same event of the highest severity. Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Primary

End point timeframe:

Up to 52 Weeks

End point values	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	725	1179	2400[6]	
Units: Exacerbations/Subject Years				
number (not applicable)				
Number of subjects with exacerbations	257	398	914	
Percentage of subjects with exacerbations	35.4	33.8	38.1	
Number of exacerbations	422	612	1444	
Total time at risk (subject-years)	723.6	1077.9	2188.7	
Adjusted exacerbation rate per year	0.533	0.541	0.633	

Notes:

[6] - N=2400; 1192 subjects from D5982C00008 (LOGOS) and 1208 subjects from D5982C00007 (KALOS)

Statistical analyses

Statistical analysis title	Rate of Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, and study.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3125
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.017 [8]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.842
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.731
upper limit	0.97

Notes:

[7] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[8] - Statistically significant per the Type I error control procedure.

Statistical analysis title	Rate of Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, and study.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID

Number of subjects included in analysis	3579
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.012 [10]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.855
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.757
upper limit	0.966

Notes:

[9] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[10] - Statistically significant per the Type I error control procedure.

Secondary: Onset of action on Day 1: Absolute change in FEV1 (L) at 5 minutes on Day 1

End point title	Onset of action on Day 1: Absolute change in FEV1 (L) at 5 minutes on Day 1

End point description:

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

End point type	Secondary

End point timeframe:

On Day 1

End point values	BGF MDI 320/14.4/9.6 µg BID	BGF MDI 320/28.8/9.6 µg BID	BFF MDI 320/9.6 µg BID	Symbicort® pMDI 320/9 µg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	363	553	573	564
Units: Litres				
number (standard deviation)				
Mean change from Baseline (SD)	0.155	0.180	0.134	0.143

Statistical analyses

Statistical analysis title	Absolute Change in FEV1 at 5 Min on Day 1

Statistical analysis description:

The analysis was performed using a within-active-treatment group T-test to demonstrate that the mean change from baseline in FEV1 at 5 minutes post-dose was statistically greater than 0.1 L.

Comparison groups	BFF MDI 320/9.6 µg BID v Symbicort® pMDI 320/9 µg BID v BGF MDI 320/28.8/9.6 µg BID

Number of subjects included in analysis	1690
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.001 [12]
Method	t-test, 1-sided
Parameter estimate	Within BGF MDI group T-test estimate
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.162
upper limit	0.197

Notes:

[11] - Analysis was within the BGF MDI 320/28.8/9.6 µg treatment group. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing value at the visit were included in the analysis.
[12] - Statistically significant per the Type I error control procedure.

Statistical analysis title	Absolute Change in FEV1 at 5 Min on Day 1

Statistical analysis description:

The analysis was performed using a within-active-treatment group T-test to demonstrate that the mean change from baseline in FEV1 at 5 minutes post-dose was statistically greater than 0.1 L.

Comparison groups	BFF MDI 320/9.6 µg BID v Symbicort® pMDI 320/9 µg BID v BGF MDI 320/14.4/9.6 µg BID
Number of subjects included in analysis	1500
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.001 [14]
Method	t-test, 1-sided
Parameter estimate	Within BGF MDI group T-test estimate
Point estimate	0.155
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.133
upper limit	0.177

Notes:

[13] - Analysis was within the BGF MDI 320/14.4/9.6 µg treatment group. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing value at the visit were included in the analysis.
[14] - Statistically significant per the Type I error control procedure.

Secondary: Change from baseline in FEV1 AUC0-3 (L) over 24 weeks

End point title	Change from baseline in FEV1 AUC0-3 (L) over 24 weeks[15]

End point description:

Change from baseline in FEV1 area under the curve 0 to 3 hours (AUC0-3) over 24 weeks. Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Over 24 weeks

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In the EU regional multiple testing approach, BGF MDI was compared to the combined BFF MDI 320/9.6 µg and Symbicort 320/9 µg reporting groups. Therefore, data for these two reporting groups were presented combined, and not individually for the BFF MDI and Symbicort reporting groups

End point values	BGF MDI 320/14.4/9.6 µg BID	BGF MDI 320/28.8/9.6 µg BID	BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	382	582	1186	
Units: Litres				
least squares mean (standard error)				
Estimate (SE)	0.347 (± 0.014)	0.345 (± 0.012)	0.232 (± 0.009)	

Statistical analyses

Statistical analysis title	Change in baseline in FEV1 AUC0-3 (L)

Statistical analysis description:

The repeated measures ANCOVA model included treatment, visit, prior ICS dose (medium vs. high), and treatment-by-visit interaction as categorical covariates and baseline trough FEV1 and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/28.8/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1768
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.001 [17]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.087
upper limit	0.138
Variability estimate	Standard error of the mean
Dispersion value	0.013

Notes:

[16] - An increase in estimate for comparison favors study drug. The number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times at sites or studies within the program. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.
[17] - Statistically significant per the Type I error control procedure.

Statistical analysis title	Change in Baseline in FEV1 AUC0-3 (L)

Statistical analysis description:

The repeated measures ANCOVA model included treatment, visit, prior ICS dose (medium vs. high), and treatment-by-visit interaction as categorical covariates and baseline trough FEV1 and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/14.4/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1568
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	< 0.001 [19]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.085
upper limit	0.145
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[18] - An increase in estimate for comparison favors study drug. The number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times at sites or studies within the program. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.
[19] - Statistically significant per the Type I error control procedure.

Secondary: Rate of severe asthma exacerbations

End point title	Rate of severe asthma exacerbations[20]

End point description:

Rate of severe asthma exacerbations. An asthma exacerbation was severe if it resulted in at least 1 of the following: a course of systemic corticosteroids for 3 days to treat symptoms of asthma worsening, an ER/urgent care visit that required treatment with systemic corticosteroids, an inpatient hospitalisation, or death related to asthma. Consecutive exacerbations with start/stop days ≤7 days apart were considered the same event of the highest severity. Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Up to 52 Weeks

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In the EU regional multiple testing approach, BGF MDI was compared to the combined BFF MDI 320/9.6 µg and Symbicort 320/9 µg reporting groups. Therefore, data for these two reporting groups were presented combined, and not individually for the BFF MDI and Symbicort reporting groups

End point values	BGF MDI 320/14.4/9.6 µg BID	BGF MDI 320/28.8/9.6 µg BID	BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	383	585	1192	
Units: Exacerbations/Subject Years				
number (not applicable)				
Number of subjects with exacerbations	114	180	386	
Percentage of subjects with exacerbations	29.8	30.8	32.4	
Number of exacerbations	180	259	567	

Total time at risk (subject-years)	387.0	537.4	1091.2	
Adjusted exacerbation rate per year	0.44	0.47	0.50	

Statistical analyses

Statistical analysis title	Rate of Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), and region.

Comparison groups	BGF MDI 320/28.8/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1777
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.399
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.923
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.767
upper limit	1.111

Notes:

[21] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

Statistical analysis title	Rate of Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), and region.

Comparison groups	BGF MDI 320/14.4/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1575
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.234
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.879
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.087

Notes:

[22] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were 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[23]

End point description:

Percentage of responders in the Asthma Control Questionnaire (ACQ)-7 (≥0.5 decrease equals response) over 24 weeks. Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Over 24 weeks

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In the EU regional multiple testing approach, BGF MDI was compared to the combined BFF MDI 320/9.6 µg and Symbicort 320/9 µg reporting groups. Therefore, data for these two reporting groups were presented combined, and not individually for the BFF MDI and Symbicort reporting groups

End point values	BGF MDI 320/14.4/9.6 µg BID	BGF MDI 320/28.8/9.6 µg BID	BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	382	581	1180	
Units: Responders				
number (not applicable)				
Number of responders	264	403	757	
Percentage (%)	69.1	69.4	64.2	

Statistical analyses

Statistical analysis title	Percentage of Responders in ACQ-7

Statistical analysis description:

The logistic regression model included treatment and prior ICS dose (medium vs. high) as categorical covariates and baseline ACQ-7 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/14.4/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1562
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.061
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.64

Notes:

[24] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

Statistical analysis title	Percentage of Responders in ACQ-7

Statistical analysis description:

The logistic regression model included treatment and prior ICS dose (medium vs. high) as categorical covariates and baseline ACQ-7 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/28.8/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1761
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.012 [26]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.64

Notes:

[25] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[26] - Nominally significant due to placement in Type I error control for EU submission.

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[27]

End point description:

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

End point type	Secondary

End point timeframe:

Over 24 weeks

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: In the EU regional multiple testing approach, BGF MDI was compared to the combined BFF MDI 320/9.6 µg and Symbicort 320/9 µg reporting groups. Therefore, data for these two reporting groups were presented combined, and not individually for the BFF MDI and Symbicort reporting groups

End point values	BGF MDI 320/14.4/9.6 µg BID	BGF MDI 320/28.8/9.6 µg BID	BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	382	581	1180	
Units: Responders				
number (not applicable)				
Number of responders	283	425	826	
Percentage (%)	74.1	73.1	70.0	

Statistical analyses

Statistical analysis title	Percentage of Responders in ACQ-5

Statistical analysis description:

The logistic regression model included treatment and prior ICS dose (medium vs. high) as categorical covariates and baseline ACQ-5 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/28.8/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1761
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.085
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.53

Notes:

[28] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

Statistical analysis title	Percentage of Responders in ACQ-5

Statistical analysis description:

The logistic regression model included treatment and prior ICS dose (medium vs. high) as categorical covariates and baseline ACQ-5 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/14.4/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1562
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.082
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.65

Notes:

[29] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

Secondary: Percentage of responders in the AQLQ(s)+12 (≥0.5 increase equals response) over 24 weeks

End point title	Percentage of responders in the AQLQ(s)+12 (≥0.5 increase equals response) over 24 weeks[30]

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 was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Over 24 weeks

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In the EU regional multiple testing approach, BGF MDI was compared to the combined BFF MDI 320/9.6 µg and Symbicort 320/9 µg reporting groups. Therefore, data for these two reporting groups were presented combined, and not individually for the BFF MDI and Symbicort reporting groups

End point values	BGF MDI 320/14.4/9.6 µg BID	BGF MDI 320/28.8/9.6 µg BID	BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	372	558	1137	
Units: Responders				
number (not applicable)				
Number of responders	228	321	648	
Percentage (%)	61.3	57.5	57.0	

Statistical analyses

Statistical analysis title	Percentage of Responders in AQLQ(s)+12

Statistical analysis description:

The logistic regression model included treatment and prior ICS dose (medium vs. high) as categorical covariates and baseline AQLQ(s)+12 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/28.8/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID

Number of subjects included in analysis	1695
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.305
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.4

Notes:

[31] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

Statistical analysis title	Percentage of Responders in AQLQ(s)+12

Statistical analysis description:

The logistic regression model included treatment and prior ICS dose (medium vs. high) as categorical covariates and baseline AQLQ(s)+12 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/14.4/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1509
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.111
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.59

Notes:

[32] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

Secondary: Percentage of responders in SGRQ (≥4.0 decrease equals response) over 24 weeks

End point title	Percentage of responders in SGRQ (≥4.0 decrease equals response) over 24 weeks[33]

End point description:

Percentage of responders in the St. George’s Respiratory Questionnaire (SGRQ) (≥0.4 unit decrease equals response) over 24 weeks. Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Over 24 weeks

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: In the EU regional multiple testing approach, BGF MDI was compared to the combined BFF MDI 320/9.6 µg and Symbicort 320/9 µg reporting groups. Therefore, data for these two reporting groups were presented combined, and not individually for the BFF MDI and Symbicort reporting groups

End point values	BGF MDI 320/14.4/9.6 µg BID	BGF MDI 320/28.8/9.6 µg BID	BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	373	565	1140	
Units: Responders				
number (not applicable)				
Number of responders	275	406	836	
Percentage (%)	73.7	71.9	73.3	

Statistical analyses

Statistical analysis title	Percentage of Responders in SGRQ

Statistical analysis description:

The logistic regression model included treatment and prior ICS dose (medium vs. high) as categorical covariates and baseline SGRQ score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/28.8/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1705
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.974
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.27

Notes:

[34] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

Statistical analysis title	Percentage of Responders in SGRQ

Statistical analysis description:

The logistic regression model included treatment and prior ICS dose (medium vs. high) as categorical covariates and baseline SGRQ score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	BGF MDI 320/14.4/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID

Number of subjects included in analysis	1513
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.76
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.38

Notes:

[35] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

Secondary: Pooled (LOGOS/KALOS): Rate of severe asthma exacerbations for participants with percent predicted FEV1 ≤55% at baseline

End point title	Pooled (LOGOS/KALOS): Rate of severe asthma exacerbations for participants with percent predicted FEV1 ≤55% at baseline

End point description:

Rate of severe asthma exacerbations for participants with percent predicted FEV1 ≤55% at baseline was assessed in a pre-specified pooled analysis across replicate studies D5982C00008 and D5982C00007 (2020-001520-34). An asthma exacerbation was considered severe if it resulted in at least 1 of the following: a course of systemic corticosteroids for 3 days to treat symptoms of asthma worsening, an ER/urgent care visit that required treatment with systemic corticosteroids, an inpatient hospitalisation, or death related to asthma. Consecutive exacerbations with start/stop days ≤7 days apart were considered the same event of the highest severity. Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	251	417	814[36]	
Units: Exacerbations/Subject Years				
number (not applicable)				
Number of subjects with exacerbations	106	162	363	
Percentage of subjects with exacerbations	42.2	38.8	44.6	
Number of exacerbations	194	264	605	
Total time at risk (subject-years)	249.1	377.4	739.2	
Adjusted exacerbation rate per year	0.733	0.663	0.797	

Notes:

[36] - N=2400; 1192 subjects from D5982C00008 (LOGOS) and 1208 subjects from D5982C00007 (KALOS)

Statistical analyses

Statistical analysis title	Rate of Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, and study.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	1231
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.058 [38]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.831
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.686
upper limit	1.006

Notes:

[37] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[38] - Statistically significant per the Type I error control procedure.

Statistical analysis title	Rate of Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, and study.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	1065
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.455 [40]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.738
upper limit	1.146

Notes:

[39] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[40] - Statistically significant per the Type I error control procedure.

Secondary: Pooled (LOGOS/KALOS): Rate of severe asthma exacerbations for participants with ≥1 severe exacerbation in the 12 months prior to Visit 1

End point title	Pooled (LOGOS/KALOS): Rate of severe asthma exacerbations for participants with ≥1 severe exacerbation in the 12 months prior to Visit 1

End point description:

Rate of severe asthma exacerbations for participants with ≥1 severe exacerbation in the 12 months prior to Visit 1 was assessed in a pre-specified pooled analysis across replicate studies D5982C00008 and D5982C00007 (2020-001520-34). An asthma exacerbation was severe if it resulted in at least 1 of the following: a course of systemic corticosteroids for 3 days to treat symptoms of asthma worsening, an ER/urgent care visit that required treatment with systemic corticosteroids, an inpatient hospitalisation, or death related to asthma. Consecutive exacerbations with start/stop days ≤7 days apart were considered the same event of the highest severity. Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	481	665	1367[41]	
Units: Exacerbations/Subject Years				
number (not applicable)				
Number of subjects with exacerbations	200	255	590	
Percentage of subjects with exacerbations	41.6	38.3	43.2	
Number of exacerbations	341	419	976	
Total time at risk (subject-years)	478.7	626.3	1279.2	
Adjusted exacerbation rate per year	0.707	0.653	0.757	

Notes:

[41] - N=2400; 1192 subjects from D5982C00008 (LOGOS) and 1208 subjects from D5982C00007 (KALOS)

Statistical analyses

Statistical analysis title	Rate of Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, and study.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID

Number of subjects included in analysis	2032
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.055 [43]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.863
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.741
upper limit	1.003

Notes:

[42] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.
[43] - Statistically significant per the Type I error control procedure.

Statistical analysis title	Rate of Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, and study.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	1848
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.417 [45]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.934
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.791
upper limit	1.102

Notes:

[44] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.
[45] - Statistically significant per the Type I error control procedure.

Secondary: Pooled (LOGOS/KALOS): Time to first severe asthma exacerbation

End point title	Pooled (LOGOS/KALOS): Time to first severe asthma exacerbation

End point description:

Time to first severe asthma exacerbation was assessed in a pre-specified pooled analysis across replicate studies D5982C00008 and D5982C00007 (2020-001520-34). Time to first severe asthma exacerbation was the time from the first dose of study medication to the time of onset of the first severe asthma exacerbation. Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	723	1175	2392[46]	
Units: Weeks				
number (not applicable)				
Number of subjects with exacerbations	257	398	914	
Percentage of subjects with exacerbations	35.5	33.9	38.2	
Kaplan-Meier estimate at 24 weeks (%)	18.9	18.6	21.6	
Kaplan-Meier estimate at 52 weeks (%)	36.0	35.5	40.3	

Notes:

[46] - N=2400; 1192 subjects from D5982C00008 (LOGOS) and 1208 subjects from D5982C00007 (KALOS)

Statistical analyses

Statistical analysis title	Time to First Severe Asthma Exacerbation

Statistical analysis description:

The Cox regression model adjusted for baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, study, baseline trough FEV1, and percent reversibility.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3567
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.005 [48]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.845
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.751
upper limit	0.951

Notes:

[47] - A hazard ratio below 1 value favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[48] - Endpoint not included in the Type I error control procedure.

Statistical analysis title	Time to First Severe Asthma Exacerbation

Statistical analysis description:

The Cox regression model adjusted for baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, study, baseline trough FEV1, and percent reversibility.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID

Number of subjects included in analysis	3115
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.03 [50]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.858
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.747
upper limit	0.986

Notes:

[49] - A hazard ratio below 1 value favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[50] - Endpoint not included in the Type I error control procedure.

Secondary: Pooled (LOGOS/KALOS): Rate of moderate or severe asthma exacerbations

End point title	Pooled (LOGOS/KALOS): Rate of moderate or severe asthma exacerbations

End point description:

Rate of moderate or severe asthma exacerbations was assessed in a pre-specified pooled analysis across replicate studies D5982C00008 and D5982C00007 (2020-001520-34). An asthma exacerbation was severe if it resulted in at least 1 of the following: systemic corticosteroids for 3 days, an ER/urgent care visit that required treatment with systemic corticosteroids, an inpatient hospitalisation, or death related to asthma. A moderate asthma exacerbation was a worsening of symptoms that resulted in an additional ICS for 3 days. Consecutive exacerbations with start/stop days ≤7 days apart were considered the same event of the highest severity. Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	725	1179	2400[51]	
Units: Exacerbations/Subject Years				
number (not applicable)				
Number of subjects with exacerbations	259	406	933	
Percentage of subjects with exacerbations	35.7	34.4	38.9	
Number of exacerbations	429	625	1483	
Total time at risk (subject-years)	723.3	1077.3	2187.0	
Adjusted exacerbation rate per year	0.545	0.555	0.653	

Notes:

[51] - N=2400; 1192 subjects from D5982C00008 (LOGOS) and 1208 subjects from D5982C00007 (KALOS)

Statistical analyses

Statistical analysis title	Rate of Moderate or Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, and study.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3579
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.008 [53]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.754
upper limit	0.959

Notes:

[52] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[53] - Endpoint not included in the Type I error control procedure.

Statistical analysis title	Rate of Moderate or Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression. Treatments were compared adjusting for baseline trough FEV1, percent reversibility, baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, and study.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3125
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.011 [55]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.834
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.725
upper limit	0.96

Notes:

[54] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[55] - Endpoint not included in the Type I error control procedure.

Secondary: Pooled (LOGOS/KALOS): Time to first moderate or severe asthma exacerbation

End point title	Pooled (LOGOS/KALOS): Time to first moderate or severe asthma exacerbation

End point description:

Time to first moderate or severe asthma exacerbation was assessed in a pre-specified pooled analysis across replicate studies D5982C00008 and D5982C00007 (2020-001520-34). Time to first moderate or severe asthma exacerbation was the time from the first dose of study medication to the time of onset of the first moderate or severe asthma exacerbation. Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	723	1175	2392[56]	
Units: Weeks				
number (not applicable)				
Number of subjects with exacerbations	259	406	933	
Kaplan-Meier estimate at 24 weeks (%)	19.1	19.1	22.1	
Kaplan-Meier estimate at 52 weeks (%)	36.3	36.2	41.1	

Notes:

[56] - N=2400; 1192 subjects from D5982C00008 (LOGOS) and 1208 subjects from D5982C00007 (KALOS)

Statistical analyses

Statistical analysis title	Time to First Moderate/Severe Asthma Exacerbation

Statistical analysis description:

The Cox regression model adjusted for baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, study, baseline trough FEV1, and percent reversibility.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3567
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	= 0.004 [58]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.843

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.751
upper limit	0.948

Notes:

[57] - A hazard ratio below 1 value favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.
[58] - Endpoint not included in the Type I error control procedure.

Statistical analysis title	Time to First Moderate/Severe Asthma Exacerbation

Statistical analysis description:

The Cox regression model adjusted for baseline severe asthma exacerbation history (0, 1, ≥2), prior ICS dose (medium vs. high), region, study, baseline trough FEV1, and percent reversibility.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3115
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	= 0.017 [60]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.845
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.736
upper limit	0.97

Notes:

[59] - A hazard ratio below 1 value favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.
[60] - Endpoint not included in the Type I error control procedure.

Secondary: Pooled (LOGOS/KALOS): Percentage of responders in ACQ-5 (≥0.5 decrease equals response) over 24 weeks

End point title	Pooled (LOGOS/KALOS): Percentage of responders in ACQ-5 (≥0.5 decrease equals response) over 24 weeks

End point description:

Percentage responders in the ACQ-5 (≥0.5 decrease equals response) over 24 weeks was assessed in a pre-specified pooled analysis across replicate studies D5982C00008 and D5982C00007 (2020-001520-34). Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Over 24 weeks

End point values	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	722	1173	2383[61]	
Units: Responders				
number (not applicable)				
Number of responders	520	853	1666	
Percentage (%)	72.0	72.7	69.9	

Notes:

[61] - N=2400; 1192 subjects from D5982C00008 (LOGOS) and 1208 subjects from D5982C00007 (KALOS)

Statistical analyses

Statistical analysis title	Pooled Percentage of Responders in ACQ-5

Statistical analysis description:

The logistic regression model included treatment, study, and prior ICS dose (medium vs. high) as categorical covariates and baseline ACQ-5 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3556
Analysis specification	Pre-specified
Analysis type	superiority[62]
P-value	= 0.057 [63]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.37

Notes:

[62] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[63] - Endpoint not included in the Type I error control procedure.

Statistical analysis title	Pooled Percentage of Responders in ACQ-5

Statistical analysis description:

The logistic regression model included treatment, study, and prior ICS dose (medium vs. high) as categorical covariates and baseline ACQ-5 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3105
Analysis specification	Pre-specified
Analysis type	superiority[64]
P-value	= 0.173 [65]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.38

Notes:

[64] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[65] - Endpoint not included in the Type I error control procedure.

Secondary: Pooled (LOGOS/KALOS): Percentage of responders in ACQ-7 (≥0.5 decrease equals response) over 24 weeks

End point title	Pooled (LOGOS/KALOS): Percentage of responders in ACQ-7 (≥0.5 decrease equals response) over 24 weeks

End point description:

Percentage responders in the ACQ-7 (≥0.5 decrease equals response) over 24 weeks was assessed in a pre-specified pooled analysis across replicate studies D5982C00008 and D5982C00007 (2020-001520-34). Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Over 24 weeks

End point values	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	721	1173	2383[66]	
Units: Responders				
number (not applicable)				
Number of responders	486	821	1556	
Percentage (%)	67.4	70.0	65.3	

Notes:

[66] - N=2400; 1192 subjects from D5982C00008 (LOGOS) and 1208 subjects from D5982C00007 (KALOS)

Statistical analyses

Statistical analysis title	Pooled Percentage of Responders in ACQ-7

Statistical analysis description:

The logistic regression model included treatment, study, and prior ICS dose (medium vs. high) as categorical covariates and baseline ACQ-7 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID

Number of subjects included in analysis	3556
Analysis specification	Pre-specified
Analysis type	superiority[67]
P-value	= 0.003 [68]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	1.47

Notes:

[67] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.
[68] - Endpoint not included in the Type I error control procedure.

Statistical analysis title	Pooled Percentage of Responders in ACQ-7

Statistical analysis description:

The logistic regression model included treatment, study, and prior ICS dose (medium vs. high) as categorical covariates and baseline ACQ-7 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3104
Analysis specification	Pre-specified
Analysis type	superiority[69]
P-value	= 0.217 [70]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.34

Notes:

[69] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.
[70] - Endpoint not included in the Type I error control procedure.

Secondary: Pooled (LOGOS/KALOS): Percentage of responders in AQLQ(s)+12 (≥0.5 increase equals response) over 24 weeks

End point title	Pooled (LOGOS/KALOS): Percentage of responders in AQLQ(s)+12 (≥0.5 increase equals response) over 24 weeks

End point description:

Percentage of responders in the AQLQ(s)+12 (≥0.5 increase equals response) over 24 weeks was assessed in a pre-specified pooled analysis across replicate studies D5982C00008 and D5982C00007 (2020-001520-34). Treatment policy was implemented to handle all ICEs with the exception of initiation of new asthma therapy or use of prohibited medications thought to impact efficacy in conjunction with premature discontinuation of study intervention, for which the composite strategy was implemented.

End point type	Secondary

End point timeframe:

Over 24 weeks

End point values	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	695	1124	2290[71]	
Units: Responders				
number (not applicable)				
Number of responders	415	654	1293	
Percentage (%)	59.7	58.2	56.5	

Notes:

[71] - N=2400; 1192 subjects from D5982C00008 (LOGOS) and 1208 subjects from D5982C00007 (KALOS)

Statistical analyses

Statistical analysis title	Pooled Percentage of Responders in AQLQ(s)+12

Statistical analysis description:

The logistic regression model included treatment, study, and prior ICS dose (medium vs. high) as categorical covariates and baseline AQLQ(s)+12 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3414
Analysis specification	Pre-specified
Analysis type	superiority[72]
P-value	= 0.215 [73]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.29

Notes:

[72] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[73] - Endpoint not included in the Type I error control procedure.

Statistical analysis title	Pooled Percentage of Responders in AQLQ(s)+12

Statistical analysis description:

The logistic regression model included treatment, study, and prior ICS dose (medium vs. high) as categorical covariates and baseline AQLQ(s)+12 score, baseline trough FEV1, and percent reversibility as continuous covariates.

Comparison groups	Pooled (LOGOS/KALOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (LOGOS/KALOS) BFF MDI or Symbicort pMDI BID

Number of subjects included in analysis	2985
Analysis specification	Pre-specified
Analysis type	superiority[74]
P-value	= 0.275 [75]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.33

Notes:

[74] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed based on the Efficacy Set, which excluded 7 subjects who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[75] - Endpoint not included in the Type I error control procedure.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first intake of study intervention after Visit 1, during screening, and throughout the Treatment Period and including the follow-up period. Serious adverse events were recorded from the time of signing of the informed consent form.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	BGF MDI 320/14.4/9.6 µg BID
Reporting group description:	
Budesonide, Glycopyrronium, and Formoterol Fumarate MDI, 320/14.4/9.6 µg BID	
Reporting group title	Symbicort pMDI 320/9 µg BID
Reporting group description:	
Symbicort pMDI 320/9 µg BID	
Reporting group title	BFF MDI 320/9.6 µg BID
Reporting group description:	
Budesonide/Formoterol Fumarate MDI, 320/9.6 µg BID	
Reporting group title	BGF MDI 320/28.8/9.6 µg BID
Reporting group description:	
Budesonide, Glycopyrronium, and Formoterol Fumarate MDI, 320/28.8/9.6 µg BID	

Serious adverse events	BGF MDI 320/14.4/9.6 µg BID	Symbicort pMDI 320/9 µg BID	BFF MDI 320/9.6 µg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 384 (8.07%)	36 / 594 (6.06%)	49 / 604 (8.11%)
number of deaths (all causes)	0	1	3
number of deaths resulting from adverse events	0	1	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Bladder cancer			

subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Cholangiocarcinoma			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenoma			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipoma			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Peripheral ischaemia			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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			

Sudden cardiac death			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chest pain			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Immune system disorders			
Eosinophilic granulomatosis with polyangitis			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Nasal polyps			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	3 / 604 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	7 / 384 (1.82%)	13 / 594 (2.19%)	20 / 604 (3.31%)
occurrences causally related to treatment / all	1 / 8	1 / 16	1 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphonia			

subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diaphragmatic paralysis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Chronic rhinosinusitis with nasal polyps			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Bronchiectasis			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Pneumothorax			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Sleep apnoea syndrome			

subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis allergic			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Psychiatric disorders			
Mania			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	1 / 384 (0.26%)	1 / 594 (0.17%)	0 / 604 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Spinal compression fracture			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Rib fracture			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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

Radius fracture			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Patella fracture			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Hand fracture			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Lower limb fracture			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Congenital, familial and genetic disorders			
Myocardial bridging			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 384 (0.00%)	2 / 594 (0.34%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Angina pectoris			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Myocardial injury			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Dilated cardiomyopathy			

subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	3 / 604 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	2 / 604 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain hypoxia			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Status epilepticus			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Monoparesis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Hyperammonaemic encephalopathy			

subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Dizziness			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	2 / 604 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	2 / 604 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Open angle glaucoma			

subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Gastritis erosive			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Gastric polyps			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Colitis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Appendicitis noninfective			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Rectal polyp			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Large intestine polyp			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Irritable bowel syndrome			

subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Intestinal polyp			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 384 (0.00%)	2 / 594 (0.34%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Bile duct stone			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Osteonecrosis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Spinal disorder			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Gouty arthritis			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Bursitis			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Arthritis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Pneumonia			
subjects affected / exposed	4 / 384 (1.04%)	4 / 594 (0.67%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 4	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
COVID-19			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinusitis			
subjects affected / exposed	0 / 384 (0.00%)	2 / 594 (0.34%)	0 / 604 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic inflammatory disease			
subjects affected / exposed	1 / 384 (0.26%)	0 / 594 (0.00%)	0 / 604 (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
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Herpes zoster			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Bronchitis			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	1 / 604 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Pneumonia pneumococcal			
subjects affected / exposed	0 / 384 (0.00%)	0 / 594 (0.00%)	0 / 604 (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
Pneumonia viral			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Urinary tract infection			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 384 (0.00%)	1 / 594 (0.17%)	0 / 604 (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

Serious adverse events	BGF MDI 320/28.8/9.6 µg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 585 (7.01%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangiocarcinoma			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colorectal adenoma			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lipoma			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest discomfort			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Eosinophilic granulomatosis with polyangitis			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Nasal polyps				
subjects affected / exposed	2 / 585 (0.34%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Asthma				
subjects affected / exposed	14 / 585 (2.39%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			
Dysphonia				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diaphragmatic paralysis				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic rhinosinusitis with nasal polyps				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchiectasis				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				

subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sleep apnoea syndrome				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rhinitis allergic				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Mania				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Humerus fracture				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple fractures				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Spinal compression fracture				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Patella fracture				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic intracranial haemorrhage				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Myocardial bridging				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute left ventricular failure			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachyarrhythmia			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			

subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial injury				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dilated cardiomyopathy				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral infarction				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Brain hypoxia				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				

subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Monoparesis				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperammonaemic encephalopathy				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vertebrobasilar insufficiency				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombotic cerebral infarction				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				

subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Open angle glaucoma			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis erosive			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric polyps			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis noninfective			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal polyp			

subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine polyp			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Irritable bowel syndrome			
subjects affected / exposed	1 / 585 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal polyp			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bile duct stone			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Nephrolithiasis				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Thyroid mass				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Intervertebral disc protrusion				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal osteoarthritis				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal disorder				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gouty arthritis				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Bursitis				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arthritis				
subjects affected / exposed	0 / 585 (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	2 / 585 (0.34%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 585 (0.68%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Upper respiratory tract infection				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic inflammatory disease				

subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection bacterial				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia mycoplasmal				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic sinusitis				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia pneumococcal				
subjects affected / exposed	1 / 585 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	0 / 585 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 585 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	BGF MDI 320/14.4/9.6 µg BID	Symbicort pMDI 320/9 µg BID	BFF MDI 320/9.6 µg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	122 / 384 (31.77%)	162 / 594 (27.27%)	169 / 604 (27.98%)
Infections and infestations			
COVID-19			
subjects affected / exposed	29 / 384 (7.55%)	38 / 594 (6.40%)	38 / 604 (6.29%)
occurrences (all)	29	38	39
Upper respiratory tract infection			
subjects affected / exposed	58 / 384 (15.10%)	83 / 594 (13.97%)	93 / 604 (15.40%)
occurrences (all)	79	121	131
Nasopharyngitis			
subjects affected / exposed	46 / 384 (11.98%)	61 / 594 (10.27%)	51 / 604 (8.44%)
occurrences (all)	53	82	66

Non-serious adverse events	BGF MDI 320/28.8/9.6 µg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	157 / 585 (26.84%)		
Infections and infestations			
COVID-19			
subjects affected / exposed	43 / 585 (7.35%)		
occurrences (all)	43		
Upper respiratory tract infection			
subjects affected / exposed	74 / 585 (12.65%)		
occurrences (all)	97		
Nasopharyngitis			

subjects affected / exposed occurrences (all)	62 / 585 (10.60%) 87		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2020	Clarity was required for the Type 1 Error Control for each region, an equivalence table was added for oral corticosteroids in the treatment of asthma exacerbations, and contraceptive language was updated to address Europe's (EU) recommendation for contraception and pregnancy testing in clinical trials.
07 January 2022	An amendment was required due to recruitment challenges, and to make 1) updates to the inclusion and exclusion criteria, 2) adjustment to the multiple testing procedures, 3) a reduction in sample size, and 4) an update to the primary estimand for the US approach to address FDA recommendations.
21 February 2023	An amendment was required due to recruitment challenges, to make 1) an update to stop recruitment to the BGF MDI 320/14.4/9.6 µg treatment arm, 2) an update to the Type I error control procedure and power estimates, and 3) updates to statistical methodology, including changes to estimands, covariates in the analysis models, and populations for analyses.
19 November 2024	An amendment was required to update the statistical methodological approaches to handling intercurrent events and the Type I error control procedure for US, EU, China, and Japan health authorities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Protocol amendments were instituted during the SARS-CoV-2 pandemic to facilitate recruitment, including removal of the history of exacerbation criteria and terminating recruitment to the BGF 320/14.4/9.6 µg treatment group.

Notes: