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 (KALOS)

Summary

EudraCT number	2020-001520-34
Trial protocol	DK NL BG BE PL HU IT RO
Global end of trial date	21 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	D5982C00007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04609878
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
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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	12 June 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2025
Global end of trial reached?	Yes
Global end of trial date	21 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	15 December 2020
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	India: 140
Country: Number of subjects enrolled	Japan: 52
Country: Number of subjects enrolled	Philippines: 111
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	Taiwan: 34

Country: Number of subjects enrolled	Thailand: 50
Country: Number of subjects enrolled	Viet Nam: 75
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 298
Country: Number of subjects enrolled	Hungary: 130
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Poland: 199
Country: Number of subjects enrolled	Romania: 71
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	Argentina: 361
Country: Number of subjects enrolled	Chile: 84
Country: Number of subjects enrolled	Peru: 164
Country: Number of subjects enrolled	Canada: 53
Country: Number of subjects enrolled	United States: 224
Worldwide total number of subjects	2144
EEA total number of subjects	754

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)	70
Adults (18-64 years)	1566
From 65 to 84 years	508
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 2274 subjects were randomised at 378 study centers in 20 countries from 15 December 2020. The last subject completed their last study visit on 21 March 2025. Of the 2274 randomised subjects, all populations excluded 125 subjects due to GCP violations and 5 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 treatment groups: BGF MDI 320/14.4/9.6 µg, BGF MDI 320/28.8/9.6 µg, BFF MDI, or Symbicort. Those who were eligible 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	342	594	606
Completed	316	541	560
Not completed	26	53	46
Consent withdrawn by subject	12	30	29
Physician decision	3	3	8
Adverse event, non-fatal	4	2	2
Death	1	1	1
Not specified	2	6	1
Failure to meet randomisation criteria	1	-	1
Non-compliance with study drug	-	2	-
Lost to follow-up	2	5	2
Withdrawal by parent/guardian	-	2	1
Development of study-specific withdrawal criteria	-	1	-
Lack of efficacy	1	1	1

Number of subjects in period 1	Symbicort® pMDI 320/9 µg BID
Started	602

Completed	551
Not completed	51
Consent withdrawn by subject	28
Physician decision	4
Adverse event, non-fatal	3
Death	2
Not specified	3
Failure to meet randomisation criteria	1
Non-compliance with study drug	-
Lost to follow-up	6
Withdrawal by parent/guardian	1
Development of study-specific withdrawal criteria	-
Lack of efficacy	3

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	342	594	606
Age Categorical Units: Participants			
Adolescents (12-17 years)	10	16	22
Adults (18-64 years)	247	437	450
From 65-84 years	85	141	134
Age Continuous Units: years			
arithmetic mean	51.6	52.7	51.9
standard deviation	± 16.0	± 14.8	± 15.3
Gender Categorical Units: Participants			
Female	228	384	376
Male	114	210	230
Race Units: Subjects			
White	216	384	397
Asian	72	147	142
Black or African American	9	12	15
American Indian or Alaska Native	4	2	5
Native Hawaiian or Other Pacific Islander	0	0	0
Other	41	49	47
Ethnicity Units: Subjects			
Hispanic or Latino	112	184	178
Not Hispanic or Latino	230	410	428
Prior Inhaled Corticosteroid (ICS) Dose			
Classification of the prior inhaled corticosteroid (ICS) total daily dose (defined as a stable dose for at least 4 weeks prior to Visit 1).			
Units: Subjects			

Low	9	4	3
Medium	176	351	341
High	156	239	261
Missing	1	0	1
Baseline Severe Asthma Exacerbation History Within the Prior Year Units: Subjects			
0 exacerbations	74	204	216
1 exacerbation	186	275	261
≥2 exacerbations	82	115	129
Baseline Pre-bronchodilator Percent Predicted FEV1 (%) Units: Percentage			
arithmetic mean	58.6	58.3	59.2
standard deviation	± 12.5	± 12.1	± 12.0
Baseline Reversibility (%)			
Reversibility (%) was calculated as (Post-Albuterol FEV1 - Pre-Albuterol FEV1)/Pre-Albuterol FEV1 x100			
Units: Percentage			
arithmetic mean	24.5	23.6	22.5
standard deviation	± 19.8	± 19.9	± 17.4

Reporting group values	Symbicort® pMDI 320/9 µg BID	Total	
Number of subjects	602	2144	
Age Categorical Units: Participants			
Adolescents (12-17 years)	22	70	
Adults (18-64 years)	432	1566	
From 65-84 years	148	508	
Age Continuous Units: years			
arithmetic mean	53.1		
standard deviation	± 14.7	-	
Gender Categorical Units: Participants			
Female	403	1391	
Male	199	753	
Race Units: Subjects			
White	378	1375	
Asian	157	518	
Black or African American	9	45	
American Indian or Alaska Native	4	15	
Native Hawaiian or Other Pacific Islander	0	0	
Other	54	191	
Ethnicity Units: Subjects			
Hispanic or Latino	190	664	
Not Hispanic or Latino	412	1480	
Prior Inhaled Corticosteroid (ICS) Dose			
Classification of the prior inhaled corticosteroid (ICS) total daily dose (defined as a stable dose for at least 4 weeks prior to Visit 1).			

Units: Subjects			
Low	3	19	
Medium	344	1212	
High	255	911	
Missing	0	2	
Baseline Severe Asthma Exacerbation History Within the Prior Year Units: Subjects			
0 exacerbations	204	698	
1 exacerbation	272	994	
≥2 exacerbations	126	452	
Baseline Pre-bronchodilator Percent Predicted FEV1 (%) Units: Percentage			
arithmetic mean	58.4		
standard deviation	± 12.4	-	
Baseline Reversibility (%)			
Reversibility (%) was calculated as (Post-Albuterol FEV1 - Pre-Albuterol FEV1)/Pre-Albuterol FEV1 x100			
Units: Percentage			
arithmetic mean	22.0		
standard deviation	± 16.9	-	

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 from protocol D5982C00007 (2020-001520-34). In the EU regional multiple testing approach, BGF MDI was compared to these combined treatment groups (with a total of 1208 subjects in the Efficacy Set; 606 in the BFF treatment group and 602 in the Symbicort treatment group).	
Subject analysis set title	Pooled (KALOS/LOGOS) 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 D5982C00007 (2020-001520-34) and protocol D5982C00008 (2020-001521-31) who received BGF MDI 320/14.4/9.6 µg study intervention. A total of 725 subjects were included in this pooled analysis Efficacy Set comprising 342 subjects from D5982C00007 (KALOS) and 383 subjects from D5982C00008 (LOGOS).	
Subject analysis set title	Pooled (KALOS/LOGOS) 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 D5982C00007 (2020-001520-34) and protocol D5982C00008 (2020-001521-31) who received BGF MDI 320/28.8/9.6 µg study intervention. A total of 1179 subjects were included in this pooled analysis Efficacy Set comprising 594 subjects from D5982C00007 (KALOS) and 585 subjects from D5982C00008 (LOGOS).	
Subject analysis set title	Pooled (KALOS/LOGOS) 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 D5982C00007 (2020-001520-34) and protocol D5982C00008 (2020-001521-31) 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 pMDI. A total of 2400 subjects were included in this pooled analysis Efficacy Set comprising 1208 subjects from D5982C00007 (KALOS) and 1192 subjects from D5982C00008 (LOGOS).	

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	339	593	1204	
Units: Litres				
least squares mean (standard error)				
Estimate (SE)	0.124 (± 0.014)	0.155 (± 0.011)	0.099 (± 0.008)	

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 320/14.4/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1543
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.126
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.056
Variability estimate	Standard error of the mean
Dispersion value	0.016

Notes:

[2] - An increase in estimate for comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.

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	1797
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.031
upper limit	0.082
Variability estimate	Standard error of the mean
Dispersion value	0.013

Notes:

[3] - An increase in estimate for comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.
[4] - Statistically significant per the Type I error control procedure.

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

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

End point description:

Rate of severe asthma exacerbations was assessed in a pre-specified pooled analysis across replicate studies D5982C00007 and D5982C00008 (2020-001521-31). 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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (KALOS/LOGOS) 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[5]	
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:

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

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 (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3579
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.012 [7]
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:

[6] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

[7] - 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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3125
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.017 [9]
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:

[8] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.
[9] - 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[10]

End point description:

Change from baseline in FEV1 AUC0-3 (L) 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:

[10] - 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	341	593	1205	
Units: Litres				
least squares mean (standard error)				
Estimate (SE)	0.284 (± 0.014)	0.308 (± 0.010)	0.239 (± 0.007)	

Statistical analyses

Statistical analysis title	Change from 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	1546
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.003 [12]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.045

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.076
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[11] - An increase in estimate for comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.
[12] - Nominally significant due to placement in Type I error control for EU submission.

Statistical analysis title	Change from 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	1798
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.001 [14]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.044
upper limit	0.094
Variability estimate	Standard error of the mean
Dispersion value	0.013

Notes:

[13] - An increase in estimate for comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.
[14] - Statistically significant per the Type I error control procedure.

Secondary: Rate of severe asthma exacerbations

End point title	Rate of severe asthma exacerbations[15]

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:

[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	342	594	1208	
Units: Exacerbations/Subject years				
number (not applicable)				
Number of subjects with exacerbations	143	218	528	
Percentage of subjects with exacerbations	41.8	36.7	43.7	
Number of exacerbations	242	353	877	
Total time at risk (subject-years)	336.6	540.5	1097.5	
Adjusted exacerbation rate per year	0.64	0.62	0.77	

Statistical analyses

Statistical analysis title	Rate of Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression (applying a bootstrap approach for multiple imputation). 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	1802
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.007 [17]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.804
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.685
upper limit	0.943

Notes:

[16] - A rate ratio below 1 favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates were included in the analysis.
[17] - Nominally significant due to placement in Type I error control for EU submission.

Statistical analysis title	Rate of Severe Asthma Exacerbations

Statistical analysis description:

The analysis for rate ratio used a negative binomial regression (applying a bootstrap approach for

multiple imputation). 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	1550
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.041 [19]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.821
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.679
upper limit	0.992

Notes:

[18] - A rate ratio below 1 favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates were included in the analysis.
[19] - Nominally significant due to placement in Type I error control for EU submission.

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	329	561	579	573
Units: Litres				
number (standard deviation)				
Mean change from baseline (SD)	0.129	0.161	0.143	0.122

Statistical analyses

Statistical analysis title	Absolute Change in FEV1 (L) 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	BGF MDI 320/28.8/9.6 µg BID v BFF MDI 320/9.6 µg BID v Symbicort® pMDI 320/9 µg BID
Number of subjects included in analysis	1713
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	< 0.001 [21]
Method	t-test, 1-sided
Parameter estimate	Within BGF MDI group T-test estimate
Point estimate	0.161
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.145
upper limit	0.177

Notes:

[20] - Analysis was within the BGF MDI 320/28.8/9.6 µg group. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing value at the visit were included in the analysis.
[21] - Statistically significant per the Type I error control procedure.

Statistical analysis title	Absolute Change in FEV1 (L) 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	BGF MDI 320/14.4/9.6 µg BID v BFF MDI 320/9.6 µg BID v Symbicort® pMDI 320/9 µg BID
Number of subjects included in analysis	1481
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.003 [23]
Method	t-test, 1-sided
Parameter estimate	Within BGF MDI group T-test estimate
Point estimate	0.129
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.108
upper limit	0.15

Notes:

[22] - Analysis was within the BGF MDI 320/14.4/9.6 µg group. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing value at the visit were included in the analysis.
[23] - Nominally significant due to placement in Type I error control for EU submission.

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[24]

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:

[24] - 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	339	592	1203	
Units: Responders				
number (not applicable)				
Number of responders	222	418	799	
Percentage (%)	65.5	70.6	66.4	

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 320/28.8/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID
Number of subjects included in analysis	1795
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.099
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.49

Notes:

[25] - An odds ratio >1 for the comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model 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 320/14.4/9.6 µg BID v BFF MDI 320/9.6 µg BID or Symbicort pMDI 320/9 µg BID

Number of subjects included in analysis	1542
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.862
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.27

Notes:

[26] - An odds ratio >1 for the comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.

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

End point title	Percentage of responders in ACQ-5 (≥0.5 decrease equals response) over 24 weeks[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	340	592	1203	
Units: Responders				
number (not applicable)				
Number of responders	237	428	840	
Percentage (%)	69.7	72.3	69.8	

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	1795
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.33
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.4

Notes:

[28] - An odds ratio >1 for the comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model 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	1543
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.877
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.33

Notes:

[29] - An odds ratio >1 for the comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model 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	323	566	1153	
Units: Responders				
number (not applicable)				
Number of responders	187	333	645	
Percentage (%)	57.9	58.8	55.9	

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	1719
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.439
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.35

Notes:

[31] - An odds ratio >1 for the comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model 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	1476
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.948
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.29

Notes:

[32] - An odds ratio >1 for the comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model 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) (≥4.0 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	331	581	1158	
Units: Responders				
number (not applicable)				
Number of responders	215	426	771	
Percentage (%)	65.0	73.3	66.6	

Statistical analyses

Statistical analysis title	Percentage of Responders in SGRQ

Statistical analysis description:

The logistic regression 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	1739
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.021 [35]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.64

Notes:

[34] - An odds ratio >1 for the comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.

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

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	1489
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.593
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.21

Notes:

[36] - An odds ratio greater than 1 for the comparison favors study drug. The number of subjects analysed is based on the Efficacy Set. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.

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

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

End point description:

Rate of severe asthma exacerbations for subjects with percent predicted FEV1 ≤55% at baseline was assessed in a pre-specified pooled analysis across replicate studies D5982C00007 and D5982C00008

(2020-001521-31). 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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (KALOS/LOGOS) 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[37]	
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:

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

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 (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	1231
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.058
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:

[38] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 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), region, and study.

Comparison groups	Pooled (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (KALOS/LOGOS) 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
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 in D5982C00008 who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

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

End point title	Pooled (KALOS/LOGOS): 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 subjects with ≥1 severe exacerbation in the 12 months prior to Visit 1 was assessed in a pre-specified pooled analysis across replicate studies D5982C00007 and D5982C00008 (2020-001521-31). 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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (KALOS/LOGOS) 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[40]	
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:

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

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 (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	2032
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.055
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:

[41] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 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), region, and study.

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

Number of subjects included in analysis	1848
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.417
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:

[42] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

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

End point title	Pooled (KALOS/LOGOS): 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 D5982C00007 and D5982C00008 (2020-001521-31). 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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (KALOS/LOGOS) 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[43]	
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:

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

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 (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3567
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.005 [45]
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:

[44] - A hazard ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.
[45] - 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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3115
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.03 [47]
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:

[46] - A hazard ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.
[47] - Endpoint not included in the Type I error control procedure.

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

End point title	Pooled (KALOS/LOGOS): 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 D5982C00007 and D5982C00008 (2020-001521-31). An asthma exacerbation

was severe if it resulted in at least 1 of the following: 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. A moderate asthma exacerbation was defined as worsening of asthma 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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (KALOS/LOGOS) 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[48]	
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:

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

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 (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3579
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.008 [50]
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:

[49] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 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.

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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3125
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.011 [52]
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:

[51] - A rate ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

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

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

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

End point description:

Time to first severe asthma exacerbation was assessed in a pre-specified pooled analysis across replicate studies D5982C00007 and D5982C00008 (2020-001521-31). 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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (KALOS/LOGOS) 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[53]	
Units: Weeks				

number (not applicable)				
Number of subjects with exacerbations	259	406	933	
Percentage of subjects with exacerbations	35.8	34.6	39.0	
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:

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

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 (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3567
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.004 [55]
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:

[54] - A hazard ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 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.

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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3115
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	= 0.017 [57]
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:

[56] - A hazard ratio below 1 favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.

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

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

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

End point description:

Percentage responders in ACQ-7 (≥0.5 decrease equals response) over 24 weeks was assessed in a pre-specified pooled analysis across replicate studies D5982C00007 and D5982C00008 (2020-001521-31). 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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (KALOS/LOGOS) 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[58]	
Units: Responders				
number (not applicable)				
Number of responders	486	821	1556	
Percentage (%)	67.4	70.0	65.3	

Notes:

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

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 (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3556
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	= 0.003 [60]
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:

[59] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 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.

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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3104
Analysis specification	Pre-specified
Analysis type	superiority[61]
P-value	= 0.217 [62]
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:

[61] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.
[62] - Endpoint not included in the Type I error control procedure.

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

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

End point description:

Percentage responders in ACQ-5 (≥0.5 decrease equals response) over 24 weeks was assessed in a pre-specified pooled analysis across replicate studies D5982C00007 and D5982C00008 (2020-001521-31). 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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (KALOS/LOGOS) 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[63]	
Units: Responders				
number (not applicable)				
Number of responders	520	853	1666	
Percentage (%)	72.0	72.7	69.9	

Notes:

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

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 (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3556
Analysis specification	Pre-specified
Analysis type	superiority[64]
P-value	= 0.057 [65]
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:

[64] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 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.

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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	3105
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	= 0.173 [67]
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:

[66] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 who were randomised multiple times. Only subjects with nonmissing covariates used in the analysis model were included in the analysis.
[67] - Endpoint not included in the Type I error control procedure.

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

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

End point description:

Percentage 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 D5982C00007 and D5982C00008 (2020-001521-31). 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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID	Pooled (KALOS/LOGOS) BGF MDI 320/28.8/9.6 µg BID	Pooled (KALOS/LOGOS) 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[68]	
Units: Responders				
number (not applicable)				
Number of responders	415	654	1293	
Percentage (%)	59.7	58.2	56.5	

Notes:

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

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

Number of subjects included in analysis	3414
Analysis specification	Pre-specified
Analysis type	superiority[69]
P-value	= 0.215 [70]
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:

[69] - An odds ratio greater than 1 for the comparison favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 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.

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 (KALOS/LOGOS) BGF MDI 320/14.4/9.6 µg BID v Pooled (KALOS/LOGOS) BFF MDI or Symbicort pMDI BID
Number of subjects included in analysis	2985
Analysis specification	Pre-specified
Analysis type	superiority[71]
P-value	= 0.275 [72]
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:

[71] - An odds ratio >1 for the comparison favors study drug. Number of subjects analysed is based on the Efficacy Set, which excluded 7 subjects in D5982C00008 who were randomised multiple times. Only subjects with nonmissing covariates were included in the analysis.
[72] - 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 meet 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

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	18 / 342 (5.26%)	32 / 602 (5.32%)	34 / 606 (5.61%)
number of deaths (all causes)	1	2	1
number of deaths resulting from adverse events	1	2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Pancreatic carcinoma			

subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Ovarian cancer			
subjects affected / exposed	1 / 342 (0.29%)	0 / 602 (0.00%)	0 / 606 (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
Nasopharyngeal cancer			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Mucinous breast carcinoma			
subjects affected / exposed	1 / 342 (0.29%)	0 / 602 (0.00%)	0 / 606 (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
Breast cancer stage II			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Rectal cancer			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Renal neoplasm			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Vascular disorders			
Varicose vein			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Hypertensive crisis			

subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 342 (0.29%)	1 / 602 (0.17%)	0 / 606 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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			
Acquired hydrocele			
subjects affected / exposed	1 / 342 (0.29%)	0 / 602 (0.00%)	0 / 606 (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
Adenomyosis			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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			
Asthma			
subjects affected / exposed	3 / 342 (0.88%)	8 / 602 (1.33%)	11 / 606 (1.82%)
occurrences causally related to treatment / all	0 / 3	0 / 8	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Paranasal sinus inflammation			

subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Nasal polyps			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Interstitial lung disease			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Haemoptysis			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Tonsillar hypertrophy			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Injury, poisoning and procedural complications			
Craniofacial fracture			
subjects affected / exposed	1 / 342 (0.29%)	0 / 602 (0.00%)	0 / 606 (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
Head injury			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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

Hip fracture			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Incisional hernia			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Joint injury			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Lip injury			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 342 (0.29%)	0 / 602 (0.00%)	0 / 606 (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
Wrist fracture			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Coronary artery disease			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	3 / 606 (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
Pericarditis			

subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	2 / 606 (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
Myocardial infarction			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Coronary artery occlusion			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Atrial flutter			
subjects affected / exposed	1 / 342 (0.29%)	0 / 602 (0.00%)	0 / 606 (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			
Dizziness			
subjects affected / exposed	1 / 342 (0.29%)	0 / 602 (0.00%)	0 / 606 (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
Cerebral infarction			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Cervicogenic vertigo			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Ischaemic stroke			

subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Migraine			
subjects affected / exposed	1 / 342 (0.29%)	0 / 602 (0.00%)	0 / 606 (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
Seizure			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	2 / 342 (0.58%)	0 / 602 (0.00%)	0 / 606 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Middle ear inflammation			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Gastritis			

subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Inguinal hernia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Cholecystitis acute			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Cholecystitis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Biliary obstruction			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Bile duct stone			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Endocrine disorders			

Adrenal insufficiency			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Goitre			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Joint instability			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Pneumonia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	4 / 606 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	1 / 606 (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
Lung abscess			
subjects affected / exposed	1 / 342 (0.29%)	1 / 602 (0.17%)	0 / 606 (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

Carbuncle			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Pneumonia bacterial			
subjects affected / exposed	1 / 342 (0.29%)	1 / 602 (0.17%)	2 / 606 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Influenza			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Infective exacerbation of asthma			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Eye abscess			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Dengue haemorrhagic fever			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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 respiratory tract infection			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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
Otitis media chronic			

subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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 viral			
subjects affected / exposed	1 / 342 (0.29%)	0 / 602 (0.00%)	0 / 606 (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
Pyelonephritis acute			
subjects affected / exposed	1 / 342 (0.29%)	0 / 602 (0.00%)	0 / 606 (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
Septic shock			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	0 / 606 (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
Viral pericarditis			
subjects affected / exposed	0 / 342 (0.00%)	0 / 602 (0.00%)	1 / 606 (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
Tubo-ovarian abscess			
subjects affected / exposed	1 / 342 (0.29%)	0 / 602 (0.00%)	0 / 606 (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
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 602 (0.17%)	0 / 606 (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	32 / 594 (5.39%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 594 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian cancer			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasopharyngeal cancer			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mucinous breast carcinoma			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer stage II			
subjects affected / exposed	1 / 594 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal cancer			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal neoplasm			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Varicose vein			
subjects affected / exposed	1 / 594 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	0 / 594 (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 death			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 594 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Acquired hydrocele			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenomyosis			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	11 / 594 (1.85%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			

subjects affected / exposed	1 / 594 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paranasal sinus inflammation				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasal polyps				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tonsillar hypertrophy				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Panic attack				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Craniofacial fracture				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Head injury				
subjects affected / exposed	1 / 594 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 594 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Incisional hernia				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint injury				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lip injury				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	2 / 594 (0.34%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				

subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery occlusion				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	1 / 594 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atrial flutter				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	1 / 594 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 594 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervicogenic vertigo				

subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 594 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Middle ear inflammation			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 594 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			

subjects affected / exposed	1 / 594 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 594 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	1 / 594 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 594 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Biliary obstruction			
subjects affected / exposed	1 / 594 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bile duct stone			
subjects affected / exposed	1 / 594 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Nephrolithiasis				
subjects affected / exposed	1 / 594 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Adrenal insufficiency				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Goitre				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint instability				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 594 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 594 (0.67%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
COVID-19 pneumonia				

subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung abscess				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carbuncle				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dengue fever				
subjects affected / exposed	1 / 594 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 594 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of asthma				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye abscess				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dengue haemorrhagic fever				

subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Otitis media chronic				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 594 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral pericarditis				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tubo-ovarian abscess				
subjects affected / exposed	0 / 594 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypoglycaemia				

subjects affected / exposed	0 / 594 (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	81 / 342 (23.68%)	119 / 602 (19.77%)	123 / 606 (20.30%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	37 / 342 (10.82%)	52 / 602 (8.64%)	51 / 606 (8.42%)
occurrences (all)	40	60	57
COVID-19			
subjects affected / exposed	28 / 342 (8.19%)	33 / 602 (5.48%)	30 / 606 (4.95%)
occurrences (all)	28	34	30
Upper respiratory tract infection			
subjects affected / exposed	21 / 342 (6.14%)	39 / 602 (6.48%)	52 / 606 (8.58%)
occurrences (all)	36	56	73

Non-serious adverse events	BGF MDI 320/28.8/9.6 µg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 594 (18.35%)		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	49 / 594 (8.25%)		
occurrences (all)	55		
COVID-19			
subjects affected / exposed	30 / 594 (5.05%)		
occurrences (all)	31		
Upper respiratory tract infection			
subjects affected / exposed	43 / 594 (7.24%)		
occurrences (all)	65		

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 criterion and terminating recruitment to the BGF 320/14.4/9.6 µg treatment group.

Notes: