Clinical trial results:
A Long-term, Randomized, Double-blind, Multicenter, Parallel-group, Phase III Study Evaluating the Efficacy and Safety of PT027 Compared to PT007 Administered as Needed in Response to Symptoms in Symptomatic Adults and Children 4 Years of Age or Older with Asthma (MANDALA).

Summary

EudraCT number	2018-003673-10
Trial protocol	DE CZ GB SK ES IT
Global end of trial date	07 February 2022

Results information

Result version number	v1 (current)
This version publication date	28 July 2022
First version publication date	28 July 2022

Trial information

Trial identification

Sponsor protocol code	AV003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03769090
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bond Avillion 2 Development LP
Sponsor organisation address	Sarnia House, Le Truchot, St Peter Port, Guernsey, GY1 1GR
Public contact	Clinical Operations, Global Project Manager, Avillion LLP, +44 (0)203 764 9530, avillion@avillionllp.com
Scientific contact	Chief Medical Officer, Avillion LLP, +44 (0)203 764 9530, avillion@avillionllp.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 August 2021
Global end of trial reached?	Yes
Global end of trial date	07 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of budesonide/albuterol sulfate (salbutamol) metered-dose inhaler 80/180 µg and 160/180 µg administered prn in response to symptoms compared to albuterol sulfate (salbutamol) metered-dose inhaler 180 µg.

Protection of trial subjects:

The final protocol, informed consent form (ICF) and other written materials provided to patients were submitted to and approved by an Ethics Committee (EC). The investigator at each study centre ensured that the distribution of these documents to the applicable EC and to the study site staff. An Independent data monitoring committee (IDMC) was established to assess the ongoing safety of the study. The IDMC reviewed blinded data (open session) and unblinded safety data (closed session) quarterly to assess any safety related reasons why the study should continue, be modified, or stopped. The IDMC chair and all committee members were independent specialists separate from the study team or contract research organization. Electronic diary alerted patients, investigator site and the Sponsor’s medical monitoring team when the patient’s symptoms and/or study medication prn use had increased and/or PEF decreased over 2 days in order to initiate contact between the patient and the investigator site to determine the well-being of the patient. Patients were advised to contact the investigator if their symptoms necessitated more than 8 puffs in a day.

Background therapy:

Patients enrolled onto the trial were allowed to continue to take their background asthma maintenance therapy following randomization to investigational product. Per eligibility criteria, acceptable background maintenance therapies included:

Medium-to-high-dose inhaled corticosteroids (ICS) with or without 1 additional controller (leukotriene receptor agonist (LTRA), long-acting muscarinic antagonist (LAMA), or theophylline); Or

Low-to-high-dose ICS in combination with long-acting ß2-agonist (LABA), with or without 1 additional controller (LTRA, LAMA, or theophylline).

Evidence for comparator: -	
Actual start date of recruitment	13 December 2018
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	United States: 842
Country: Number of subjects enrolled	Argentina: 564
Country: Number of subjects enrolled	Ukraine: 434
Country: Number of subjects enrolled	South Africa: 341
Country: Number of subjects enrolled	Germany: 330

Country: Number of subjects enrolled	Czechia: 211
Country: Number of subjects enrolled	Serbia: 176
Country: Number of subjects enrolled	Slovakia: 83
Country: Number of subjects enrolled	Spain: 75
Country: Number of subjects enrolled	Canada: 42
Country: Number of subjects enrolled	United Kingdom: 34
Worldwide total number of subjects	3132
EEA total number of subjects	699

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)	83
Adolescents (12-17 years)	100
Adults (18-64 years)	2383
From 65 to 84 years	566
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject enrolled on 13DEC2018 and the last subject completed the study on 07FEB2022. Subjects were enrolled at 347 study centers worldwide (ARG, CAN, CZE, DEU, ESP, GBR, SRB, SVK, UKR, USA, ZAF).

Pre-assignment

Screening details:

A total of 5620 patients were screened for this study, of which 2488 patients were not randomized to treatment; 2456 were ineligible for participation in the trial, the next most frequent reason was withdrawal by patient, of which 18 patients met this criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BDA MDI 160/180

Arm description:

Combination product: Budesonide/albuterol sulfate (salbutamol) pressurized metered dose inhaler (BDA MDI) 160/180 micrograms (µg), given as 2 inhalations of BDA MDI 80/90 µg for as needed use (prn).

Arm type	Experimental
Investigational medicinal product name	Budesonide/albuterol 160/180 micrograms (µg) pressurized metered dose inhaler (MDI)
Investigational medicinal product code	
Other name	PT027 high dose
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

Taken as needed (prn) in response to asthma symptoms.

Arm title	BDA MDI 80/180

Arm description:

Combination product: Budesonide/albuterol sulfate (salbutamol) pressurized metered dose inhaler (BDA MDI) 80/180 micrograms (µg), given as 2 inhalations of BDA MDI 40/90 µg, for as needed use (prn).

Arm type	Experimental
Investigational medicinal product name	Budesonide/albuterol 80/180 micrograms (µg) pressurized metered dose inhaler (MDI)
Investigational medicinal product code	
Other name	PT027 low dose
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

Taken as needed (prn) in response to asthma symptoms.

Arm title	AS MDI 180

Arm description:

Albuterol sulfate (salbutamol) pressurized metered dose inhaler (AS MDI) 180 micrograms (µg), given as 2 inhalations of AS MDI 90 µg, for as needed use (prn)

Arm type	Active comparator

Investigational medicinal product name	Albuterol 180 micrograms (µg) pressurized metered dose inhaler (MDI)
Investigational medicinal product code	
Other name	PT007
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

Taken as needed (prn) in response to asthma symptoms.

Number of subjects in period 1[1]	BDA MDI 160/180	BDA MDI 80/180	AS MDI 180
Started	1015	1055	1057
Completed	909	919	898
Not completed	106	136	159
Adverse event, serious fatal	4	2	1
On-going at the primary database lock	6	14	18
Condition under investigation worsened	2	-	1
>=3 severe exacerbations within a 3-month period	1	4	4
Consent withdrawn by subject	52	62	74
>=5 total severe exacerbation events	-	1	1
Adverse event, non-fatal	7	7	8
Other	8	12	16
Pregnancy	1	-	3
A single severe exacerbation lasting >20 days	-	1	2
Lost to follow-up	19	25	21
Protocol deviation	5	6	8
Lack of efficacy	1	2	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Four patients were randomized in error and immediately discontinued without receiving any amount of randomly assigned treatment. One patient was randomized but never exposed to randomized study drug. These subjects are excluded from summaries of baseline characteristics, efficacy, and safety. A further four randomized subjects were excluded from the summaries of baseline characteristics and efficacy in the full analysis set due to being determined to be duplicate patients.

Baseline characteristics

Reporting groups	
Reporting group title	BDA MDI 160/180
Reporting group description:	
Combination product: Budesonide/albuterol sulfate (salbutamol) pressurized metered dose inhaler (BDA MDI) 160/180 micrograms (µg), given as 2 inhalations of BDA MDI 80/90 µg for as needed use (prn).	
Reporting group title	BDA MDI 80/180
Reporting group description:	
Combination product: Budesonide/albuterol sulfate (salbutamol) pressurized metered dose inhaler (BDA MDI) 80/180 micrograms (µg), given as 2 inhalations of BDA MDI 40/90 µg, for as needed use (prn).	
Reporting group title	AS MDI 180
Reporting group description:	
Albuterol sulfate (salbutamol) pressurized metered dose inhaler (AS MDI) 180 micrograms (µg), given as 2 inhalations of AS MDI 90 µg, for as needed use (prn)	

Reporting group values	BDA MDI 160/180	BDA MDI 80/180	AS MDI 180
Number of subjects	1015	1055	1057
Age categorical Units: Subjects			
Children (>=4 to <12 years)	0	41	42
Adolescents (>=12 to <18 years)	34	32	34
Adults (>=18 to <65 years)	789	805	784
Elderly (>=65 years)	192	177	197
Age continuous Units: years			
arithmetic mean	50.6	48.5	49.1
standard deviation	± 15.05	± 16.71	± 17.22
Gender categorical Units: Subjects			
Female	647	686	695
Male	368	369	362
Race Units: Subjects			
White	820	848	869
Black or African American	139	141	137
Asian	29	33	23
American Indian or Alaska Native	1	1	0
Other	26	32	28
Ethnicity Units: Subjects			
Hispanic or Latino	235	261	316
Not Hispanic or Latino	780	794	741
Height Units: centimetre			
arithmetic mean	166.8	165.1	164.4
standard deviation	± 9.92	± 11.45	± 11.67
Weight Units: kilogram(s)			
arithmetic mean	80.5	78.2	78.8

standard deviation	± 16.88	± 18.93	± 18.47
Body mass index			
Units: kilogram(s)/square metre			
arithmetic mean	28.887	28.496	28.948
standard deviation	± 5.4002	± 5.5886	± 5.6271

Reporting group values	Total		
Number of subjects	3127		
Age categorical			
Units: Subjects			
Children (>=4 to <12 years)	83		
Adolescents (>=12 to <18 years)	100		
Adults (>=18 to <65 years)	2378		
Elderly (>=65 years)	566		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	2028		
Male	1099		
Race			
Units: Subjects			
White	2537		
Black or African American	417		
Asian	85		
American Indian or Alaska Native	2		
Other	86		
Ethnicity			
Units: Subjects			
Hispanic or Latino	812		
Not Hispanic or Latino	2315		
Height			
Units: centimetre			
arithmetic mean			
standard deviation	-		
Weight			
Units: kilogram(s)			
arithmetic mean			
standard deviation	-		
Body mass index			
Units: kilogram(s)/square metre			
arithmetic mean			
standard deviation	-		

Subject analysis sets	
Subject analysis set title	BDA MDI 160/180 (Full analysis set)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who are randomized, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.

Subject analysis set title	BDA MDI 80/180 (Full analysis set)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who are randomized, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.

Subject analysis set title	AS MDI 180 (Full analysis set)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who are randomized, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.

Subject analysis set title	Total (Full analysis set)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who are randomized, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.

Subject analysis set title	BDA MDI 160/180 (Full analysis set; >=12 years)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients aged >=12 years at randomization, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.

Subject analysis set title	BDA MDI 80/180 (Full analysis set; >=12 years)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients aged >=12 years at randomization, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.

Subject analysis set title	AS MDI 180 (full analysis set; >=12 years)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients aged >=12 years at randomization, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.

Subject analysis set title	Total (Full analysis set; >= 12 years)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients aged >=12 years at randomization, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.

Reporting group values	BDA MDI 160/180 (Full analysis set)	BDA MDI 80/180 (Full analysis set)	AS MDI 180 (Full analysis set)
Number of subjects	1013	1054	1056
Age categorical Units: Subjects			
Children (>=4 to <12 years)	0	41	42
Adolescents (>=12 to <18 years)	34	32	34
Adults (>=18 to <65 years)	787	804	783
Elderly (>=65 years)	192	177	197
Age continuous Units: years			
arithmetic mean	50.6	48.5	49.1
standard deviation	± 15.06	± 16.71	± 17.23
Gender categorical Units: Subjects			
Female	645	685	694

Male	368	369	362

Race Units: Subjects			
White	818	847	868
Black or African American	139	141	137
Asian	29	33	23
American Indian or Alaska Native	1	1	0
Other	26	32	28
Ethnicity Units: Subjects			
Hispanic or Latino	233	260	315
Not Hispanic or Latino	780	794	741
Height Units: centimetre			
arithmetic mean	166.8	165.1	164.4
standard deviation	± 9.93	± 11.46	± 11.67
Weight Units: kilogram(s)			
arithmetic mean	80.4	78.2	78.8
standard deviation	± 16.86	± 18.92	± 18.48
Body mass index Units: kilogram(s)/square metre			
arithmetic mean	28.869	28.487	28.950
standard deviation	± 5.3903	± 5.5832	± 5.6296

Reporting group values	Total (Full analysis set)	BDA MDI 160/180 (Full analysis set; >=12 years)	BDA MDI 80/180 (Full analysis set; >=12 years)
Number of subjects	3123	1013	1013
Age categorical Units: Subjects			
Children (>=4 to <12 years)	83	0	0
Adolescents (>=12 to <18 years)	100	34	32
Adults (>=18 to <65 years)	2374	787	804
Elderly (>=65 years)	566	192	177
Age continuous Units: years			
arithmetic mean	49.4	50.6	50.1
standard deviation	± 16.40	± 15.06	± 15.02
Gender categorical Units: Subjects			
Female	2024	645	671
Male	1099	368	342
Race Units: Subjects			
White	2533	818	819
Black or African American	417	139	131
Asian	85	29	32
American Indian or Alaska Native	2	1	1
Other	86	26	30

Ethnicity Units: Subjects			
Hispanic or Latino	808	233	241
Not Hispanic or Latino	2315	780	772
Height Units: centimetre			
arithmetic mean	165.4	166.8	166.2
standard deviation	± 11.10	± 9.93	± 9.99
Weight Units: kilogram(s)			
arithmetic mean	79.1	80.4	79.8
standard deviation	± 18.14	± 16.86	± 17.4
Body mass index Units: kilogram(s)/square metre			
arithmetic mean	28.767	28.869	28.817
standard deviation	± 5.5392	± 5.3903	± 5.3706

Reporting group values	AS MDI 180 (full analysis set; >=12 years)	Total (Full analysis set; >= 12 years)	
Number of subjects	1014	3040	
Age categorical Units: Subjects			
Children (>=4 to <12 years)	0	0	
Adolescents (>=12 to <18 years)	34	100	
Adults (>=18 to <65 years)	783	2374	
Elderly (>=65 years)	197	566	
Age continuous Units: years			
arithmetic mean	50.7	50.5	
standard deviation	± 15.49	± 15.19	
Gender categorical Units: Subjects			
Female	681	1997	
Male	333	1043	
Race Units: Subjects			
White	843	2480	
Black or African American	125	395	
Asian	21	82	
American Indian or Alaska Native	0	2	
Other	25	81	
Ethnicity Units: Subjects			
Hispanic or Latino	293	767	
Not Hispanic or Latino	721	2273	
Height Units: centimetre			
arithmetic mean	165.6	166.2	
standard deviation	± 10.02	± 9.99	
Weight Units: kilogram(s)			

arithmetic mean	80.5	80.2	
standard deviation	± 16.61	± 16.96	
Body mass index Units: kilogram(s)/square metre			
arithmetic mean	29.328	29.005	
standard deviation	± 5.3341	± 5.3682	

End points

End points reporting groups

Reporting group title	BDA MDI 160/180
Reporting group description:	
Combination product: Budesonide/albuterol sulfate (salbutamol) pressurized metered dose inhaler (BDA MDI) 160/180 micrograms (µg), given as 2 inhalations of BDA MDI 80/90 µg for as needed use (prn).	
Reporting group title	BDA MDI 80/180
Reporting group description:	
Combination product: Budesonide/albuterol sulfate (salbutamol) pressurized metered dose inhaler (BDA MDI) 80/180 micrograms (µg), given as 2 inhalations of BDA MDI 40/90 µg, for as needed use (prn).	
Reporting group title	AS MDI 180
Reporting group description:	
Albuterol sulfate (salbutamol) pressurized metered dose inhaler (AS MDI) 180 micrograms (µg), given as 2 inhalations of AS MDI 90 µg, for as needed use (prn)	
Subject analysis set title	BDA MDI 160/180 (Full analysis set)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who are randomized, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.	
Subject analysis set title	BDA MDI 80/180 (Full analysis set)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who are randomized, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.	
Subject analysis set title	AS MDI 180 (Full analysis set)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who are randomized, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.	
Subject analysis set title	Total (Full analysis set)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who are randomized, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.	
Subject analysis set title	BDA MDI 160/180 (Full analysis set; >=12 years)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients aged >=12 years at randomization, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.	
Subject analysis set title	BDA MDI 80/180 (Full analysis set; >=12 years)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients aged >=12 years at randomization, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.	
Subject analysis set title	AS MDI 180 (full analysis set; >=12 years)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients aged >=12 years at randomization, take at least 1 puff of randomized treatment and have at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.	
Subject analysis set title	Total (Full analysis set; >= 12 years)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients aged >=12 years at randomization, take at least 1 puff of randomized treatment and have	

at least one efficacy assessment, excluding patients who have been identified as confirmed duplicates.

Primary: Time to first severe exacerbation

End point title	Time to first severe exacerbation

End point description:

The descriptive summary shows the number of patients with a severe exacerbaton event, occurring between the date of randomization up to the date of randomized treatment discontinuation or a change in maintenance therapy.

End point type	Primary

End point timeframe:

From randomization up to discontinuation of randomized treatment or a change in maintenance therapy.

End point values	BDA MDI 80/180 (Full analysis set)	AS MDI 180 (Full analysis set)	BDA MDI 160/180 (Full analysis set; >=12 years)	AS MDI 180 (full analysis set; >=12 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1054	1056	1013	1014
Units: Number of patients				
Patients with a severe exacerbation event	241	276	207	266

Statistical analyses

Statistical analysis title	BDA MDI 160/180 versus AS MDI 180

Statistical analysis description:

H0 = Null hypothesis.

Hazard ratios, 95% CIs for hazard ratios and p-values are estimated using a Cox regression model with treatment group, age group, region and number of severe exacerbations in the last 12 months prior to randomization as factors. A hazard ratio less than 1 favours BDA MDI treatment.

Comparison groups	BDA MDI 160/180 (Full analysis set; >=12 years) v AS MDI 180 (full analysis set; >=12 years)
Number of subjects included in analysis	2027
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.733
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.611
upper limit	0.879

Statistical analysis title	BDA MDI 80/180 versus AS MDI 180

Statistical analysis description:

H0 = Null hypothesis.

Hazard ratios, 95% CIs for hazard ratios and p-values are estimated using a Cox regression model with treatment group, age group, region and number of severe exacerbations in the last 12 months prior to randomization as factors. A hazard ratio less than 1 favours BDA MDI treatment.

Comparison groups	BDA MDI 80/180 (Full analysis set) v AS MDI 180 (Full analysis set)
Number of subjects included in analysis	2110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.835
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.702
upper limit	0.992

Secondary: Annualized severe exacerbation rate.

End point title	Annualized severe exacerbation rate.

End point description:

The annualized severe exacerbation rate (severe exacerbation per year) is estmated from a negative binomial model with treatment, age group, region, and number of severe exacerbations in the last 12 months prior to randomization as categorical covariates. The logarithm of the time at risk is included as an offset variable.

End point type	Secondary

End point timeframe:

From randomization up to discontinuation of randomized treatment or a change in maintenance therapy.

End point values	BDA MDI 80/180 (Full analysis set)	AS MDI 180 (Full analysis set)	BDA MDI 160/180 (Full analysis set; >=12 years)	AS MDI 180 (full analysis set; >=12 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1054	1056	1013	1014
Units: Severe exacerbations per year				
least squares mean (confidence interval 95%)	0.49 (0.37 to 0.64)	0.61 (0.46 to 0.80)	0.45 (0.34 to 0.60)	0.59 (0.44 to 0.78)

Statistical analyses

Statistical analysis title	BDA MDI 160/180 versus AS MDI 180

Statistical analysis description:

Estimated from a negative binomial model with treatment, age group, region, and number of severe exacerbations in the last 12 months prior to randomization as categorical covariates. The logarithm of the time at risk is included as an offset variable. A sequential testing strategy is used for secondary endpoints. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected.

Comparison groups	BDA MDI 160/180 (Full analysis set; >=12 years) v AS MDI 180 (full analysis set; >=12 years)
Number of subjects included in analysis	2027
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.93

Statistical analysis title	BDA MDI 80/180 versus AS MDI 180

Statistical analysis description:

Estimated from a negative binomial model with treatment, age group, region, and number of severe exacerbations in the last 12 months prior to randomization as categorical covariates. The logarithm of the time at risk is included as an offset variable. A sequential testing strategy is used for secondary endpoints. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected.

Comparison groups	BDA MDI 80/180 (Full analysis set) v AS MDI 180 (Full analysis set)
Number of subjects included in analysis	2110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.98

Secondary: Total annualized dose of systemic corticosteroid

End point title	Total annualized dose of systemic corticosteroid

End point description:

This endpoint includes all systemic corticosteroids (SCS) taken in response to a severe exacerbation event from randomization up to randomized treatment discontinuation or a change in maintenance therapy. All SCS are standardized to equipotent doses of prednisone before deriving the total dose. The total annualized dose is calculated as the total dose of SCS divided by the duration of the randomized treatment period.

End point type	Secondary

End point timeframe:

From randomization up to discontinuation of randomized treatment or a change in maintenance therapy.

End point values	BDA MDI 80/180 (Full analysis set)	AS MDI 180 (Full analysis set)	BDA MDI 160/180 (Full analysis set; >=12 years)	AS MDI 180 (full analysis set; >=12 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1052	1052	1012	1011
Units: milligram(s)				
arithmetic mean (full range (min-max))	95.5 (0 to 4974)	127.1 (0 to 18941)	86.2 (0 to 3678)	129.3 (0 to 18941)

Statistical analyses

Statistical analysis title	BDA MDI 160/180 versus AS MDI 180

Statistical analysis description:

P-values are calculated via a Wilcoxon rank sum test. A sequential testing strategy is used for secondary endpoints. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected.

Comparison groups	BDA MDI 160/180 (Full analysis set; >=12 years) v AS MDI 180 (full analysis set; >=12 years)
Number of subjects included in analysis	2023
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Wilcoxon rank sum test

Statistical analysis title	BDA MDI 80/180 versus AS MDI 180

Statistical analysis description:

P-values are calculated via a Wilcoxon rank sum test. A sequential testing strategy is used for secondary endpoints. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected.

Comparison groups	BDA MDI 80/180 (Full analysis set) v AS MDI 180 (Full analysis set)
Number of subjects included in analysis	2104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Wilcoxon rank sum test

Secondary: Asthma Control Questionnaire 5-item version (ACQ-5) minimal important difference at Week 24

End point title	Asthma Control Questionnaire 5-item version (ACQ-5) minimal important difference at Week 24

End point description:

A responder is defined as a patient with a change from baseline to Week 24 overall ACQ-5 score of -0.5 or less.

ACQ-5 is not validated for children less than 6 years old, data for subjects who are 4 or 5 years of age were excluded from the analyses of ACQ-5.

End point type	Secondary

End point timeframe:

From randomization up to discontinuation of randomized treatment or a change in maintenance therapy.

End point values	BDA MDI 80/180 (Full analysis set)	AS MDI 180 (Full analysis set)	BDA MDI 160/180 (Full analysis set; >=12 years)	AS MDI 180 (full analysis set; >=12 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1052	1055	1013	1014
Units: Number of patients	681	650	677	630

Statistical analyses

Statistical analysis title	BDA MDI 160/180 versus AS MDI 180

Statistical analysis description:

Logistic regression model with baseline ACQ-5 as a continuous covariate and age group, region and number of severe exacerbations in the past 12 months prior to randomization (Visit 2) as categorical covariates. A sequential testing strategy is used for secondary endpoints. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected.

Comparison groups	BDA MDI 160/180 (Full analysis set; >=12 years) v AS MDI 180 (full analysis set; >=12 years)
Number of subjects included in analysis	2027
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.221
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.016
upper limit	1.467

Notes:

[1] - Nominal p-value following type-I error control on secondary endpoints.

Statistical analysis title	BDA MDI 80/180 versus AS MDI 180

Statistical analysis description:

Logistic regression model with baseline ACQ-5 as a continuous covariate and age group, region and number of severe exacerbations in the past 12 months prior to randomization (Visit 2) as categorical covariates. A sequential testing strategy is used for secondary endpoints. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected.

Comparison groups	BDA MDI 80/180 (Full analysis set) v AS MDI 180 (Full analysis

	set)
Number of subjects included in analysis	2107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.132
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.946
upper limit	1.353

Secondary: Asthma Quality of Life Questionnaire for patients aged 12 years and older (AQLQ+12) minimal important difference at Week 24

End point title	Asthma Quality of Life Questionnaire for patients aged 12 years and older (AQLQ+12) minimal important difference at Week 24

End point description:

A responder is defined as a patient with an increase from baseline to week 24 AQLQ+12 score of at least 0.5.

End point type	Secondary

End point timeframe:

From randomization up to discontinuation of randomized treatment or a change in maintenance therapy.

End point values	BDA MDI 160/180 (Full analysis set; >=12 years)	BDA MDI 80/180 (Full analysis set; >=12 years)	AS MDI 180 (full analysis set; >=12 years)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	994	987	993	
Units: Number of patients	508	489	461	

Statistical analyses

Statistical analysis title	BDA MDI 160/180 versus AS MDI 180

Statistical analysis description:

Logistic regression model with baseline AQLQ+12 as a continuous covariate and age group, region and number of severe exacerbations in the past 12 months prior to randomization (Visit 2) as categorical covariates. A sequential testing strategy is used for secondary endpoints. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected.

Comparison groups	BDA MDI 160/180 (Full analysis set; >=12 years) v AS MDI 180 (full analysis set; >=12 years)

Number of subjects included in analysis	1987
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.228
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.022
upper limit	1.475

Notes:

[2] - Nominal p-value following type-I error control on secondary endpoints.

Statistical analysis title	BDA MDI 80/180 versus AS MDI 180

Statistical analysis description:

Logistic regression model with baseline AQLQ+12 as a continuous covariate and age group, region and number of severe exacerbations in the past 12 months prior to randomization (Visit 2) as categorical covariates. A sequential testing strategy is used for secondary endpoints. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected.

Comparison groups	BDA MDI 80/180 (Full analysis set; >=12 years) v AS MDI 180 (full analysis set; >=12 years)
Number of subjects included in analysis	1980
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.925
upper limit	1.335

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the time of signed informed consent/assent and up to the safety follow up period. Reported AEs are those that occurred from the date of first dose of randomized treatment up to date of treatment discontinuation.

Adverse event reporting additional description:

Adverse events reported include the AEs accrued between the primary database lock and up to the final database lock, treatment completion and safety follow-up for the patients who were still on-going at the time of the primary database lock.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	BDA MDI 160/180

Reporting group description:

Combination product: Budesonide/albuterol pressurized metered dose inhaler (BDA MDI) 160/180 micrograms (µg), given as 2 inhalations of BDA MDI 80/90 µg for as needed use (prn).

Reporting group title	BDA MDI 80/180

Reporting group description:

Combination product: Budesonide/albuterol pressurized metered dose inhaler (BDA MDI) 80/180 micrograms (µg), given as 2 inhalations of BDA MDI 40/90 µg, for as needed use (prn).

Reporting group title	AS MDI 180

Reporting group description:

Albuterol pressurized metered dose inhaler (AS MDI) 180 micrograms (µg), given as 2 inhalations of AS MDI 90 µg, for as needed use (prn)

Serious adverse events	BDA MDI 160/180	BDA MDI 80/180	AS MDI 180
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 1015 (5.22%)	40 / 1055 (3.79%)	48 / 1057 (4.54%)
number of deaths (all causes)	4	2	2
number of deaths resulting from adverse events	4	2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute promyelocytic leukaemia			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Adenocarcinoma of colon			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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

Cholesteatoma			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Haemangioma			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Lung neoplasm malignant			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Metastases to lung			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Neoplasm skin			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenoma			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Deep vein thrombosis			

subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Haematoma			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Hypertensive crisis			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Pyrexia			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Anaphylactic shock			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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

Drug hypersensitivity			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food allergy			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Colpocele			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Vaginal haemorrhage			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	7 / 1015 (0.69%)	8 / 1055 (0.76%)	20 / 1057 (1.89%)
occurrences causally related to treatment / all	0 / 7	0 / 9	0 / 20
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Pneumothorax			

subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Mixed anxiety and depressive disorder			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Post-traumatic stress disorder			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Troponin I increased			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Animal bite			

subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Concussion			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Femur fracture			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Joint dislocation			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Limb injury			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Radius fracture			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Tendon rupture			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention postoperative			

subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Atrial fibrillation			
subjects affected / exposed	0 / 1015 (0.00%)	2 / 1055 (0.19%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Supraventricular tachycardia			

subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Tachycardia			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicobrachial syndrome			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intensive care unit acquired weakness			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Migraine			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Transient ischaemic attack			

subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Intestinal obstruction			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Nausea			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Umbilical hernia			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Cholecystitis acute			
subjects affected / exposed	3 / 1015 (0.30%)	0 / 1055 (0.00%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cirrhosis alcoholic			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			

subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 1015 (0.10%)	1 / 1055 (0.09%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	11 / 1015 (1.08%)	5 / 1055 (0.47%)	8 / 1057 (0.76%)
occurrences causally related to treatment / all	0 / 12	0 / 5	0 / 8
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1

COVID-19 pneumonia			
subjects affected / exposed	3 / 1015 (0.30%)	4 / 1055 (0.38%)	5 / 1057 (0.47%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (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
Infection			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 1015 (0.00%)	3 / 1055 (0.28%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 1015 (0.00%)	1 / 1055 (0.09%)	0 / 1057 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 1015 (0.49%)	4 / 1055 (0.38%)	2 / 1057 (0.19%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia viral			

subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Sepsis			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suspected COVID-19			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	3 / 1057 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 1015 (0.10%)	0 / 1055 (0.00%)	0 / 1057 (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
Vitamin D deficiency			
subjects affected / exposed	0 / 1015 (0.00%)	0 / 1055 (0.00%)	1 / 1057 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	BDA MDI 160/180	BDA MDI 80/180	AS MDI 180
Total subjects affected by non-serious adverse events			
subjects affected / exposed	244 / 1015 (24.04%)	253 / 1055 (23.98%)	243 / 1057 (22.99%)
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 1015 (2.17%)	27 / 1055 (2.56%)	26 / 1057 (2.46%)
occurrences (all)	23	27	27

Nervous system disorders			
Headache			
subjects affected / exposed	44 / 1015 (4.33%)	50 / 1055 (4.74%)	49 / 1057 (4.64%)
occurrences (all)	71	77	76
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	27 / 1015 (2.66%)	23 / 1055 (2.18%)	20 / 1057 (1.89%)
occurrences (all)	29	23	20
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	76 / 1015 (7.49%)	61 / 1055 (5.78%)	54 / 1057 (5.11%)
occurrences (all)	95	68	67
COVID-19			
subjects affected / exposed	33 / 1015 (3.25%)	47 / 1055 (4.45%)	38 / 1057 (3.60%)
occurrences (all)	33	47	38
Upper respiratory tract infection			
subjects affected / exposed	26 / 1015 (2.56%)	31 / 1055 (2.94%)	26 / 1057 (2.46%)
occurrences (all)	31	35	28
Bronchitis			
subjects affected / exposed	25 / 1015 (2.46%)	27 / 1055 (2.56%)	28 / 1057 (2.65%)
occurrences (all)	30	30	32
Sinusitis			
subjects affected / exposed	15 / 1015 (1.48%)	17 / 1055 (1.61%)	25 / 1057 (2.37%)
occurrences (all)	16	17	28
Influenza			
subjects affected / exposed	21 / 1015 (2.07%)	20 / 1055 (1.90%)	14 / 1057 (1.32%)
occurrences (all)	23	22	16

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2019	Incorporated country-specific changes. Added the de facto estimand as a treatment policy strategy defined in the draft International Conference on Harmonization E9 addendum. Updated the current versions of the AQLQ+12, PAQLQ, and ACQ-5 and ACQ-7.
21 July 2020	Incorporated country-specific changes. Updated a secondary endpoint to "systemic corticosteroids". Added additional exploratory endpoints. Provided clarifications for statistical analyses. Adjusted inclusion criterion for subjects aged < 18 years. Incorporated temporary measures to protect subjects and site staff safety during the COVID 19 pandemic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported