



Clinical trial results:

A 12-week, Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel Group, Phase III Study Evaluating the Efficacy and Safety of PT027 Compared to PT008 and PT007 Administered QID in Adults and Children 4 Years of Age or Older with Asthma (DENALI)

Summary

EudraCT number	2018-003674-27
Trial protocol	DE CZ SK
Global end of trial date	20 July 2021

Results information

Result version number	v1 (current)
This version publication date	16 March 2022
First version publication date	16 March 2022

Trial information

Trial identification

Sponsor protocol code	AV004
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03847896
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bond Avillion 2 Development LLP
Sponsor organisation address	Sarnia House, Le Truchot, St Peter Port, Guernsey, GY1 1GR
Public contact	Clinical Operations, Global Project Manager, Avillion LLP, +44 (0)2037649530, avillion@avillionllp.com
Scientific contact	Chief Medical Officer, Avillion LLP, +44 (0)2037649530, 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	20 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 July 2021
Global end of trial reached?	Yes
Global end of trial date	20 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a randomized, double-blind, placebo-controlled, multicenter, parallel group study to compare 2 dose levels of budesonide/albuterol BDA MDI (PT027) to its components budesonide BD MDI (PT008) and albuterol AS MDI (PT007) on improvement in lung function and asthma symptoms after 12 weeks of treatment in adult, adolescent, and child subjects with symptomatic asthma currently being treated with a short/rapid-acting β 2-adrenoreceptor agonist (SABA) as needed alone or with low-dose inhaled corticosteroid (ICS) maintenance therapy plus SABA as needed.

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 investigators/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 Ventolin 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: -

Evidence for comparator: -

Actual start date of recruitment	20 March 2019
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: 522
Country: Number of subjects enrolled	Ukraine: 203
Country: Number of subjects enrolled	Germany: 138
Country: Number of subjects enrolled	Czechia: 71
Country: Number of subjects enrolled	Argentina: 54
Country: Number of subjects enrolled	Serbia: 12
Country: Number of subjects enrolled	Slovakia: 1

Worldwide total number of subjects	1001
EEA total number of subjects	210

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)	10
Adolescents (12-17 years)	25
Adults (18-64 years)	790
From 65 to 84 years	174
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The first subject enrolled on 20 March 2019 and the last subjected completed the study on 20 July 2021. Subjects were enrolled at 126 study centers worldwide (Argentina, Czechia, Germany, Serbia, Slovakia, Ukraine and the United States).

Pre-assignment

Screening details:

A total of 1876 patients were screened for this study, of which 875 patients were not randomized to treatment; 851 were ineligible, 3 were lost to follow up, 1 was excluded due to a protocol deviation, 18 withdrew by subject decision, and 2 withdrew by parent/guardian decision.

Period 1

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

Arms

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

Arm 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, four times a day (QID).

Arm type	Experimental
Investigational medicinal product name	Budesonide/albuterol 160/180 milligrams (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:

4 doses (8 inhalations of BDA MDI 80/90) per day.

Arm title	BDA MDI 80/180
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Arm 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, four times a day (QID).

Arm type	Experimental
Investigational medicinal product name	Budesonide/albuterol 80/180 milligrams (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:

4 doses (8 inhalations of BDA MDI 40/90) per day.

Arm title	BD MDI 160
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Arm description:

Budesonide pressurized metered dose inhaler (BD MDI) 160 micrograms (µg), given as 2 inhalations of BD MDI 80 µg, four times a day (QID).

Arm type	Active comparator
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Investigational medicinal product name	Budesonide 160 milligrams (µg) pressurized metered dose inhaler (MDI)
Investigational medicinal product code	
Other name	PT008
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use
Dosage and administration details: 4 doses (8 inhalations of BD MDI 80) per day.	
Arm title	AS MDI 180
Arm description: Albuterol pressurized metered dose inhaler (AS MDI) 180 micrograms (µg), given as 2 inhalations of AS MDI 90 µg, four times a day (QID)	
Arm type	Active comparator
Investigational medicinal product name	Albuterol 180 milligrams (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: 4 doses (8 inhalations of AS MDI 90) per day.	
Arm title	Placebo MDI
Arm description: Placebo pressurized metered dose inhaler (Placebo MDI), given as 2 inhalations of Placebo MDI four times a day (QID)	
Arm type	Placebo
Investigational medicinal product name	Placebo pressurized metered dose inhaler (MDI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use
Dosage and administration details: 4 doses (8 inhalations) of Placebo MDI per day.	

Number of subjects in period 1^[1]	BDA MDI 160/180	BDA MDI 80/180	BD MDI 160
Started	197	204	199
Completed	190	188	188
Not completed	7	16	11
Consent withdrawn by subject	2	10	6
A severe exacerbation event	-	-	-
Adverse event, non-fatal	2	1	3
Other	3	3	1
Condition under investigation worsened	-	-	-
Lost to follow-up	-	-	-
Protocol deviation	-	2	1

Lack of efficacy	-	-	-
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Number of subjects in period 1 ^[1]	AS MDI 180	Placebo MDI
Started	201	199
Completed	184	178
Not completed	17	21
Consent withdrawn by subject	9	8
A severe exacerbation event	-	3
Adverse event, non-fatal	2	4
Other	2	1
Condition under investigation worsened	1	1
Lost to follow-up	1	-
Protocol deviation	-	2
Lack of efficacy	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: One subject was randomised in error and immediately discontinued without receiving any amount of randomly assigned treatment. This subject was excluded from summaries of baseline characteristics, efficacy, and safety. One subject was randomised and received randomly assigned treatment before being determined to be a duplicate patient. This subject was excluded from summaries of baseline characteristics and efficacy but included in analyses of safety.

Baseline characteristics

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, four times a day (QID).	
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, four times a day (QID).	
Reporting group title	BD MDI 160
Reporting group description:	
Budesonide pressurized metered dose inhaler (BD MDI) 160 micrograms (µg), given as 2 inhalations of BD MDI 80 µg, four times a day (QID).	
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, four times a day (QID)	
Reporting group title	Placebo MDI
Reporting group description:	
Placebo pressurized metered dose inhaler (Placebo MDI), given as 2 inhalations of Placebo MDI four times a day (QID)	

Reporting group values	BDA MDI 160/180	BDA MDI 80/180	BD MDI 160
Number of subjects	197	204	199
Age categorical			
Units: Subjects			
Children (>=4 to <12 years)	0	3	0
Adolescents (>=12 to <18 years)	4	7	5
Adults (>=18 to <65 years)	154	155	161
Elderly (>=65 years)	39	39	33
Age continuous			
Units: years			
arithmetic mean	50.0	48.7	48.3
standard deviation	± 15.80	± 16.79	± 15.80
Gender categorical			
Units: Subjects			
Female	125	128	120
Male	72	76	79
Race			
Units: Subjects			
White	179	185	180
Black or African American	14	15	18
Asian	1	0	0
American Indian or Alaska Native	1	0	0
Other	2	4	1
Ethnicity			
Units: Subjects			
Hispanic or Latino	61	62	50

Not Hispanic or Latino	136	142	149
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Height Units: centimetre arithmetic mean standard deviation	167.8 ± 8.61	166.8 ± 9.71	167.7 ± 9.92
Weight Units: kilogram(s) arithmetic mean standard deviation	80.4 ± 16.43	80.0 ± 16.06	80.0 ± 14.52
Body mass index Units: kilogram(s)/square metre arithmetic mean standard deviation	28.537 ± 5.2488	28.635 ± 4.8491	28.477 ± 4.9140

Reporting group values	AS MDI 180	Placebo MDI	Total
Number of subjects	201	199	1000
Age categorical Units: Subjects			
Children (>=4 to <12 years)	4	3	10
Adolescents (>=12 to <18 years)	5	4	25
Adults (>=18 to <65 years)	159	161	790
Elderly (>=65 years)	33	31	175
Age continuous Units: years arithmetic mean standard deviation	47.0 ± 16.75	48.6 ± 15.82	-
Gender categorical Units: Subjects			
Female	121	127	621
Male	80	72	379
Race Units: Subjects			
White	167	174	885
Black or African American	30	19	96
Asian	0	1	2
American Indian or Alaska Native	1	1	3
Other	3	4	14
Ethnicity Units: Subjects			
Hispanic or Latino	46	63	282
Not Hispanic or Latino	155	136	718
Height Units: centimetre arithmetic mean standard deviation	168.5 ± 9.86	168.0 ± 10.85	-
Weight Units: kilogram(s) arithmetic mean standard deviation	82.3 ± 15.09	81.6 ± 17.79	-

Body mass index			
Units: kilogram(s)/square metre			
arithmetic mean	29.016	28.793	
standard deviation	± 4.8513	± 5.2534	-

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 subjects 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 subjects 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	BD MDI 160 (Full analysis set)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects 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 subjects 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	Placebo MDI (Full analysis set)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects 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 subjects 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.

Reporting group values	BDA MDI 160/180 (Full analysis set)	BDA MDI 80/180 (Full analysis set)	BD MDI 160 (Full analysis set)
Number of subjects	197	204	199
Age categorical			
Units: Subjects			
Children (>=4 to <12 years)	0	3	0
Adolescents (>=12 to <18 years)	4	7	5
Adults (>=18 to <65 years)	154	155	161
Elderly (>=65 years)	39	39	33
Age continuous			
Units: years			
arithmetic mean	50.0	48.7	48.3
standard deviation	± 15.8	± 16.79	± 15.8
Gender categorical			
Units: Subjects			
Female	125	128	120

Male	72	76	79
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Race			
Units: Subjects			
White	179	185	180
Black or African American	14	15	18
Asian	1	0	0
American Indian or Alaska Native	1	0	0
Other	2	4	1
Ethnicity			
Units: Subjects			
Hispanic or Latino	61	62	50
Not Hispanic or Latino	136	142	149
Height			
Units: centimetre			
arithmetic mean	167.8	166.8	167.7
standard deviation	± 8.61	± 9.71	± 9.92
Weight			
Units: kilogram(s)			
arithmetic mean	80.4	80.0	80.0
standard deviation	± 16.43	± 16.06	± 14.52
Body mass index			
Units: kilogram(s)/square metre			
arithmetic mean	28.537	28.635	28.477
standard deviation	± 5.2488	± 4.8491	± 4.9140

Reporting group values	AS MDI 180 (full analysis set)	Placebo MDI (Full analysis set)	Total (Full analysis set)
Number of subjects	200	199	999
Age categorical			
Units: Subjects			
Children (>=4 to <12 years)	4	3	10
Adolescents (>=12 to <18 years)	5	4	25
Adults (>=18 to <65 years)	158	161	789
Elderly (>=65 years)	33	31	175
Age continuous			
Units: years			
arithmetic mean	47.0	48.6	48.5
standard deviation	± 16.79	± 15.82	± 16.21
Gender categorical			
Units: Subjects			
Female	120	127	620
Male	80	72	379
Race			
Units: Subjects			
White	166	174	884
Black or African American	30	19	96
Asian	0	1	2
American Indian or Alaska Native	1	1	3
Other	3	4	14
Ethnicity			

Units: Subjects			
Hispanic or Latino	45	63	281
Not Hispanic or Latino	155	136	718
Height			
Units: centimetre			
arithmetic mean	168.6	168.0	167.8
standard deviation	± 9.86	± 10.85	± 9.81
Weight			
Units: kilogram(s)			
arithmetic mean	82.4	81.6	80.9
standard deviation	± 15.12	± 17.79	± 16.02
Body mass index			
Units: kilogram(s)/square metre			
arithmetic mean	29.011	28.793	28.691
standard deviation	± 4.8629	± 5.2534	± 5.0211

End points

End points 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, four times a day (QID).	
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, four times a day (QID).	
Reporting group title	BD MDI 160
Reporting group description: Budesonide pressurized metered dose inhaler (BD MDI) 160 micrograms (µg), given as 2 inhalations of BD MDI 80 µg, four times a day (QID).	
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, four times a day (QID)	
Reporting group title	Placebo MDI
Reporting group description: Placebo pressurized metered dose inhaler (Placebo MDI), given as 2 inhalations of Placebo MDI four times a day (QID)	
Subject analysis set title	BDA MDI 160/180 (Full analysis set)
Subject analysis set type	Full analysis
Subject analysis set description: All subjects 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 subjects 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	BD MDI 160 (Full analysis set)
Subject analysis set type	Full analysis
Subject analysis set description: All subjects 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 subjects 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	Placebo MDI (Full analysis set)
Subject analysis set type	Full analysis
Subject analysis set description: All subjects 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 subjects 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.	

Primary: Change from baseline FEV1 AUC0-6 hours over 12 weeks

End point title	Change from baseline FEV1 AUC0-6 hours over 12 weeks
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End point description:

FEV1 = Forced expiratory volume in 1 second. AUC0-6hours = Area under the curve from 0 to 6 hours.

The dual-primary endpoint of change from baseline FEV1 AUC0-6 hours is calculated from the changes from baseline in serial spirometry measures following dosing of randomized treatment at each clinical visit. The area under the curve is calculated using the trapezoidal rule and is normalized by dividing through by the time from dosing to the last measurement included in the serial spirometry profile in order to present the result in millilitres. Baseline FEV1 is defined as the average of the 30- and 60-minute pre-dose measures collected on the day of randomization.

End point type	Primary
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End point timeframe:

Estimated over the 12 week period.

End point values	BDA MDI 160/180	BDA MDI 80/180	BD MDI 160	AS MDI 180
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	197	200	199	195
Units: millilitre(s)				
least squares mean (standard error)	258.6 (± 18.87)	242.2 (± 18.80)	178.0 (± 18.79)	157.2 (± 19.08)

End point values	Placebo MDI			
Subject group type	Reporting group			
Number of subjects analysed	196			
Units: millilitre(s)				
least squares mean (standard error)	96.7 (± 19.02)			

Statistical analyses

Statistical analysis title	AS MDI 180 versus Placebo MDI
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Statistical analysis description:

Only includes data from date of first dose up to date of last dose of randomized treatment. A sequential testing strategy is used such that the primary hypothesis tests are listed in ascending order of sequence. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected. Tests are each conducted at the 5% level of significance.

Comparison groups	AS MDI 180 v Placebo MDI
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	60.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	7.7
upper limit	113.4

Statistical analysis title	BDA MDI 160/180 versus Placebo MDI
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Statistical analysis description:

Only includes data from date of first dose up to date of last dose of randomized treatment. A sequential testing strategy is used such that the primary hypothesis tests are listed in ascending order of sequence. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected. Tests are each conducted at the 5% level of significance.

Comparison groups	Placebo MDI v BDA MDI 160/180
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	161.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	109.4
upper limit	214.5

Statistical analysis title	BDA MDI 160/180 versus BD MDI 160
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Statistical analysis description:

Only includes data from date of first dose up to date of last dose of randomized treatment. A sequential testing strategy is used such that the primary hypothesis tests are listed in ascending order of sequence. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected. Tests are each conducted at the 5% level of significance.

Comparison groups	BDA MDI 160/180 v BD MDI 160
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	80.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.4
upper limit	132.9

Primary: Change from baseline in trough FEV1 at Week 12

End point title	Change from baseline in trough FEV1 at Week 12
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End point description:

FEV1 = Forced expiratory volume in 1 second.

Trough FEV1 is calculated at each clinic visit as the average of the 30- and 60-minute pre-dose FEV1 measurements. Baseline FEV1 is defined as the average of the 30- and 60-minute pre-dose measures collected on the day of randomization.

End point type	Primary
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End point timeframe:

At the Week 12 timepoint.

End point values	BDA MDI 160/180	BDA MDI 80/180	BD MDI 160	AS MDI 180
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	197	198	198	192
Units: millilitre(s)				
least squares mean (standard error)	135.5 (± 24.58)	123.5 (± 24.65)	108.9 (± 24.51)	2.7 (± 25.24)

End point values	Placebo MDI			
Subject group type	Reporting group			
Number of subjects analysed	192			
Units: millilitre(s)				
least squares mean (standard error)	35.6 (± 25.12)			

Statistical analyses

Statistical analysis title	BD MDI 160 versus Placebo MDI
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Statistical analysis description:

Only includes data from date of first dose up to date of last dose of randomized treatment. A sequential testing strategy is used such that the primary hypothesis tests are listed in ascending order of sequence. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected. Tests are each conducted at the 5% level of significance.

Comparison groups	BD MDI 160 v Placebo MDI
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	73.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.4
upper limit	142.2

Statistical analysis title	BDA MDI 160/180 versus Placebo MDI
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Statistical analysis description:

Only includes data from date of first dose up to date of last dose of randomized treatment. A sequential testing strategy is used such that the primary hypothesis tests are listed in ascending order of sequence. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected. Tests are each conducted at the 5% level of significance.

Comparison groups	BDA MDI 160/180 v Placebo MDI
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	99.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.9
upper limit	168.8

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

Only includes data from date of first dose up to date of last dose of randomized treatment. A sequential testing strategy is used such that the primary hypothesis tests are listed in ascending order of sequence. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected. Tests are each conducted at the 5% level of significance.

Comparison groups	BDA MDI 160/180 v AS MDI 180
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	132.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	63.6
upper limit	201.9

Statistical analysis title	BDA MDI 80/180 versus Placebo MDI
Statistical analysis description:	
Only includes data from date of first dose up to date of last dose of randomized treatment. A sequential testing strategy is used such that the primary hypothesis tests are listed in ascending order of sequence. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected. Tests are each conducted at the 5% level of significance.	
Comparison groups	BDA MDI 80/180 v Placebo MDI
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	87.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.8
upper limit	156.9

Statistical analysis title	BDA MDI 80/180 versus AS MDI 180
Statistical analysis description:	
Only includes data from date of first dose up to date of last dose of randomized treatment. A sequential testing strategy is used such that the primary hypothesis tests are listed in ascending order of sequence. A null hypothesis can only be rejected if all preceding null hypotheses are also rejected. Tests are each conducted at the 5% level of significance.	
Comparison groups	BDA MDI 80/180 v AS MDI 180
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	120.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	51.5
upper limit	190.1

Secondary: Time to 15% increase in FEV1 over the pre-treatment value on Day 1	
End point title	Time to 15% increase in FEV1 over the pre-treatment value on Day 1

End point description:

FEV1 = Forced expiratory volume in 1 second. CI = Confidence interval.

The time to onset is defined as the time (minutes) from the first inhalation of randomized treatment (Day 1) to the first instance where a percentage change from baseline in FEV1 of at least 15% is observed. Patients were only be included in the analyses if a percent change from baseline of at least

15% is observed within 30 minutes post dose assessment time point. Baseline FEV1 is defined as the average of the 60- and 30-minute pre-dose spirometry measures taken at randomization.

End point type	Secondary
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End point timeframe:

The 30 minute post-treatment spirometry assessment period on Day 1.

End point values	BDA MDI 160/180	BDA MDI 80/180	BD MDI 160	AS MDI 180
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	88	27	84
Units: minute				
median (full range (min-max))	7.5 (3 to 33)	7.0 (3 to 35)	17.0 (4 to 37)	9.5 (4 to 37)

End point values	Placebo MDI			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: minute				
median (full range (min-max))	14.0 (4 to 34)			

Statistical analyses

Statistical analysis title	AS MDI 180 versus Placebo MDI
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Statistical analysis description:

Not Type-I error controlled. The estimated median difference and 95% CIs are calculated using the Hodges-Lehmann method.

Comparison groups	AS MDI 180 v Placebo MDI
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	1

Statistical analysis title	BD MDI 160 versus Placebo MDI
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Statistical analysis description:

Not Type-I error controlled. The estimated median difference and 95% CIs are calculated using the Hodges-Lehmann method.

Comparison groups	BD MDI 160 v Placebo MDI
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Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	9

Statistical analysis title	BDA MDI 80/180 versus Placebo MDI
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Statistical analysis description:

Not Type-I error controlled. The estimated median difference and 95% CIs are calculated using the Hodges-Lehmann method.

Comparison groups	Placebo MDI v BDA MDI 80/180
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	0

Statistical analysis title	BDA MDI 160/180 versus Placebo MDI
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Statistical analysis description:

Not Type-I error controlled. The estimated median difference and 95% CIs are calculated using the Hodges-Lehmann method.

Comparison groups	Placebo MDI v BDA MDI 160/180
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	0

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

Not Type-I error controlled. The estimated median difference and 95% CIs are calculated using the Hodges-Lehmann method.

Comparison groups	BDA MDI 80/180 v AS MDI 180
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	0

Statistical analysis title

BDA MDI 160/180 versus AS MDI 180

Statistical analysis description:

Not Type-I error controlled. The estimated median difference and 95% CIs are calculated using the Hodges-Lehmann method.

Comparison groups	BDA MDI 160/180 v AS MDI 180
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0

Statistical analysis title

BDA MDI 80/180 versus BD MDI 160

Statistical analysis description:

Not Type-I error controlled. The estimated median difference and 95% CIs are calculated using the Hodges-Lehmann method.

Comparison groups	BDA MDI 80/180 v BD MDI 160
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	-2

Statistical analysis title	BDA MDI 160/180 versus BD MDI 160
Statistical analysis description:	
Not Type-I error controlled. The estimated median difference and 95% CIs are calculated using the Hodges-Lehmann method.	
Comparison groups	BD MDI 160 v BDA MDI 160/180
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	-2

Statistical analysis title	BDA MDI 160/180 versus BDA MDI 80/180
Statistical analysis description:	
Not Type-I error controlled. The estimated median difference and 95% CIs are calculated using the Hodges-Lehmann method.	
Comparison groups	BDA MDI 160/180 v BDA MDI 80/180
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1

Secondary: Asthma Control Questionnaire 7-item version (ACQ-7) clinically meaningful difference at Week 12

End point title	Asthma Control Questionnaire 7-item version (ACQ-7) clinically meaningful difference at Week 12
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End point description:

ACQ-7 = Asthma control questionnaire (7-item).

A responder is defined as a patient who achieves a change from baseline in overall ACQ-7 score of at least 0.5. The overall ACQ-7 score is defined as the averaged score across the 7 questions. All patients who discontinue treatment prior to Week 12 are classified as non-responders.

The analysis only includes patients who are uncontrolled at baseline, i.e. baseline ACQ-7 ≥ 1.5 .

End point type	Secondary
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End point timeframe:

At the Week 12 visit.

End point values	BDA MDI 160/180	BDA MDI 80/180	BD MDI 160	AS MDI 180
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	161	165	162	163
Units: Number of patients	107	108	100	77

End point values	Placebo MDI			
Subject group type	Reporting group			
Number of subjects analysed	159			
Units: Number of patients	88			

Statistical analyses

Statistical analysis title	AS MDI 180 versus Placebo MDI
Statistical analysis description:	
Comparisons are not type-I error controlled.	
Comparison groups	AS MDI 180 v Placebo MDI
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.118
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.699
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.445
upper limit	1.096

Statistical analysis title	BD MDI 160 versus Placebo MDI
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BD MDI 160 v Placebo MDI

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.161
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.386
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.878
upper limit	2.187

Statistical analysis title	BDA MDI 80/180 versus Placebo MDI
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 80/180 v Placebo MDI
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.605
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.013
upper limit	2.541

Statistical analysis title	BDA MDI 160/180 versus Placebo MDI
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 160/180 v Placebo MDI
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.626
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.024
upper limit	2.584

Statistical analysis title	BDA MDI 80/180 versus AS MDI 180
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 80/180 v AS MDI 180
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.297
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.456
upper limit	3.626

Statistical analysis title	BDA MDI 160/180 versus AS MDI 180
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 160/180 v AS MDI 180
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.328
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.471
upper limit	3.687

Statistical analysis title	BDA MDI 80/180 versus BD MDI 160
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 80/180 v BD MDI 160

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.532
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.158
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.731
upper limit	1.835

Statistical analysis title	BDA MDI 160/180 versus BD MDI 160
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 160/180 v BD MDI 160
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.499
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.174
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.737
upper limit	1.868

Statistical analysis title	BDA MDI 160/180 versus BDA MDI 80/180
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 160/180 v BDA MDI 80/180
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.955
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.635
upper limit	1.618

Secondary: Change from baseline in trough FEV1 at Week 1

End point title	Change from baseline in trough FEV1 at Week 1
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End point description:

FEV1 = Forced expiratory volume in 1 second.

Trough FEV1 is calculated at each clinic visit as the average of the 30- and 60-minute pre-dose FEV1 measurements. Baseline FEV1 is defined as the average of the 30- and 60-minute pre-dose measures collected on the day of randomization.

End point type	Secondary
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End point timeframe:

Week 1 visit.

End point values	BDA MDI 160/180	BDA MDI 80/180	BD MDI 160	AS MDI 180
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	197	198	198	192
Units: millilitre(s)				
least squares mean (standard error)	107.2 (\pm 21.46)	72.0 (\pm 21.31)	93.4 (\pm 21.35)	-0.8 (\pm 21.69)

End point values	Placebo MDI			
Subject group type	Reporting group			
Number of subjects analysed	192			
Units: millilitre(s)				
least squares mean (standard error)	41.3 (\pm 21.47)			

Statistical analyses

Statistical analysis title	AS MDI 180 versus Placebo MDI
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Statistical analysis description:

Comparison is not type-I error controlled.

Comparison groups	Placebo MDI v AS MDI 180
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Number of subjects included in analysis	384
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.169
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Method	ANCOVA
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Parameter estimate	Mean difference (final values)
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Point estimate	-42.1
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Confidence interval	
level	95 %
sides	2-sided
lower limit	-101.9
upper limit	17.8

Statistical analysis title	BD MDI 160 versus Placebo MDI
Statistical analysis description: Comparison is not type-I error controlled.	
Comparison groups	BD MDI 160 v Placebo MDI
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.086
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	52.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	111.5

Statistical analysis title	BDA MDI 80/180 versus Placebo MDI
Statistical analysis description: Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 80/180 v Placebo MDI
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	30.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.6
upper limit	90.1

Statistical analysis title	BDA MDI 160/180 versus Placebo MDI
Statistical analysis description: Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 160/180 v Placebo MDI

Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	65.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.3
upper limit	125.4

Statistical analysis title	BDA MDI 80/180 versus AS MDI 180
Statistical analysis description:	
Comparisons are not type-I error controlled.	
Comparison groups	BDA MDI 80/180 v AS MDI 180
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	72.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.1
upper limit	132.5

Statistical analysis title	BDA MDI 160/180 versus AS MDI 180
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 160/180 v AS MDI 180
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	107.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	48.1
upper limit	167.8

Statistical analysis title	BDA MDI 80/180 versus BD MDI 160
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 80/180 v BD MDI 160
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-21.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-80.5
upper limit	37.9

Statistical analysis title	BDA MDI 160/180 versus BD MDI 160
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 160/180 v BD MDI 160
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.648
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	13.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.6
upper limit	73.2

Statistical analysis title	BDA MDI 160/180 versus BDA MDI 80/180
Statistical analysis description:	
Comparison is not type-I error controlled.	
Comparison groups	BDA MDI 160/180 v BDA MDI 80/180

Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.246
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	35.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.2
upper limit	94.5

Secondary: Duration of 15% increase in FEV1 over the pre-treatment value on Day 1

End point title	Duration of 15% increase in FEV1 over the pre-treatment value on Day 1
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End point description:

FEV1 = Forced expiratory volume in 1 second.

The duration of onset is defined as the time (minutes) of the continual period in which a percentage change from baseline in FEV1 of at least 15% is observed. Patients will only be included in the analyses if a percent change from baseline of at least 15% is observed within 30 minutes post dose assesment. If a patient has multiple periods of onset, only the first will contribute to the summary. Baseline FEV1 is defined as the average of the 60- and 30-minute pre-dose spirometry taken at randomization.

End point type	Secondary
End point timeframe:	
The 30 minute post-treatment spirometry assessment period on Day 1.	

End point values	BDA MDI 160/180	BDA MDI 80/180	BD MDI 160	AS MDI 180
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	88	27	84
Units: minute				
median (full range (min-max))	185.5 (4 to 363)	174 (10 to 362)	98 (14 to 354)	158.5 (9 to 363)

End point values	Placebo MDI			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: minute				
median (full range (min-max))	229.5 (8 to 356)			

Statistical analyses

No statistical analyses for this end point

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.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	BDA MDI 160/180
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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, four times a day (QID).

Reporting group title	BDA MDI 80/180
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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, four times a day (QID).

Reporting group title	BD MDI 160
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Reporting group description:

Budesonide pressurized metered dose inhaler (BD MDI) 160 micrograms (µg), given as 2 inhalations of BD MDI 80 µg, four times a day (QID).

Reporting group title	AS MDI 180
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Reporting group description:

Albuterol pressurized metered dose inhaler (AS MDI) 180 micrograms (µg), given as 2 inhalations of AS MDI 90 µg, four times a day (QID)

Reporting group title	Placebo MDI
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Reporting group description:

Placebo pressurized metered dose inhaler (Placebo MDI), given as 2 inhalations of Placebo MDI four times a day (QID)

Serious adverse events	BDA MDI 160/180	BDA MDI 80/180	BD MDI 160
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 197 (1.02%)	4 / 204 (1.96%)	3 / 199 (1.51%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Influenza A virus test positive			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	0 / 199 (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
Injury, poisoning and procedural complications			

Subdural haematoma			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 199 (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			
Aortic dissection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 199 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 204 (0.00%)	0 / 199 (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			
Pancreatitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 204 (0.00%)	0 / 199 (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	Additional description: Asthma AE occurring over the randomized treatment period correspond to patients who had a severe exacerbation event.		
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Foot deformity			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metatarsalgia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	1 / 199 (0.50%)
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			
COVID-19			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	1 / 199 (0.50%)
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 pneumonia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 204 (0.49%)	0 / 199 (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
Sepsis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 204 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AS MDI 180	Placebo MDI	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 201 (0.50%)	3 / 199 (1.51%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Influenza A virus test positive			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma			

subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: Asthma AE occurring over the randomized treatment period correspond to patients who had a severe exacerbation event.		
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Foot deformity			
subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metatarsalgia			
subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 201 (0.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	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	BD MDI 160
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 197 (18.78%)	31 / 204 (15.20%)	31 / 199 (15.58%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 197 (2.03%)	2 / 204 (0.98%)	0 / 199 (0.00%)
occurrences (all)	4	2	0
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 197 (5.08%)	10 / 204 (4.90%)	7 / 199 (3.52%)
occurrences (all)	10	10	8

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 197 (1.02%)	2 / 204 (0.98%)	2 / 199 (1.01%)
occurrences (all)	2	2	2
Nausea			
subjects affected / exposed	1 / 197 (0.51%)	2 / 204 (0.98%)	5 / 199 (2.51%)
occurrences (all)	1	2	5
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 197 (1.02%)	2 / 204 (0.98%)	5 / 199 (2.51%)
occurrences (all)	2	2	5
Asthma			
subjects affected / exposed	0 / 197 (0.00%)	2 / 204 (0.98%)	0 / 199 (0.00%)
occurrences (all)	0	2	0
Dysphonia			
subjects affected / exposed	4 / 197 (2.03%)	1 / 204 (0.49%)	2 / 199 (1.01%)
occurrences (all)	5	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 197 (7.61%)	13 / 204 (6.37%)	10 / 199 (5.03%)
occurrences (all)	16	13	10
Upper respiratory tract infection			
subjects affected / exposed	2 / 197 (1.02%)	3 / 204 (1.47%)	4 / 199 (2.01%)
occurrences (all)	2	3	4
COVID-19			
subjects affected / exposed	2 / 197 (1.02%)	1 / 204 (0.49%)	1 / 199 (0.50%)
occurrences (all)	2	1	1

Non-serious adverse events	AS MDI 180	Placebo MDI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 201 (14.43%)	38 / 199 (19.10%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 201 (1.00%)	2 / 199 (1.01%)	
occurrences (all)	2	2	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	11 / 201 (5.47%) 14	14 / 199 (7.04%) 18	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	4 / 201 (1.99%) 4	4 / 199 (2.01%) 4	
Nausea subjects affected / exposed occurrences (all)	0 / 201 (0.00%) 0	5 / 199 (2.51%) 5	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 201 (1.00%) 2	0 / 199 (0.00%) 0	
Asthma subjects affected / exposed occurrences (all)	3 / 201 (1.49%) 3	4 / 199 (2.01%) 4	
Dysphonia subjects affected / exposed occurrences (all)	0 / 201 (0.00%) 0	0 / 199 (0.00%) 0	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 201 (4.48%) 9	11 / 199 (5.53%) 12	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 201 (0.50%) 1	2 / 199 (1.01%) 2	
COVID-19 subjects affected / exposed occurrences (all)	0 / 201 (0.00%) 0	4 / 199 (2.01%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2019	Clarified that sponsor provided IP dose frequency was QID; Confirmed that new IP was to be dispensed and used for in clinic FEV1 measurements at each visit; Clarified instructions regarding proper IP preparation, dispensing, and dosing for postdose assessments at each in clinic dosing visit; Clarified that IP was to be dosed before 10:00am at all in clinic dosing visits; Clarified that pre-dose and post-dose FEV1 measurements for the bronchodilator responsiveness test were in relation to sponsor provided Ventolin; Removed supine as position for measuring blood pressure.
06 July 2020	<p>Updated the number of adult and adolescent subjects randomized from 600 to 1000, the number of subjects within each treatment arm from 120 to 200, and the number of subjects screened from 1000 to 2000, following the protocol specified blinded sample size reassessment that was conducted. Text was added to describe and justify a second blinded sample size re-estimation.</p> <p>Clarified the timepoints for some of the exploratory objectives and endpoints as "at Week 12".</p> <p>Added justification to continue study enrolment and treatment during the COVID-19 pandemic. Added methodology that will be used to evaluate the impact of the COVID-19 pandemic on efficacy and safety variables.</p> <p>Introduced unified language for the country specific protocols, which included age limits in various countries. Minor clarifications to the inclusion and exclusion criteria, and to the study procedures.</p> <p>Added pregnancy testing to Visit 3 and Visit 5.</p> <p>Clarified that primary analysis treatment comparisons will exclude the children (ages 4-11 years) and specified that the analysis will be repeated to include children, but will be considered a supportive analysis of the dual-primary endpoint.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported