

**Clinical trial results:****A Randomized, Double-Blind, Parallel Group, Multi-Center 24-Week Study Comparing the Efficacy and Safety of Three Doses of PT001 to Placebo and Open-label Spiriva® Respimat® in Subjects With Persistent Asthma****Summary**

EudraCT number	2020-000532-22
Trial protocol	Outside EU/EEA
Global end of trial date	12 September 2019

Results information

Result version number	v1 (current)
This version publication date	29 March 2020
First version publication date	29 March 2020

Trial information**Trial identification**

Sponsor protocol code	PT001102
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03358147
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pearl Therapeutics, Inc.
Sponsor organisation address	200 Cardinal Way, Redwood City, California, United States, 94063
Public contact	Colin Reisner, Pearl Therapeutics Inc., 1 1-877-240-9479, information.center@astrazeneca.com
Scientific contact	Pearl Therapeutics, Inc., Pearl Therapeutics, Inc., 1 18772409479, information.center@astrazeneca.com
Sponsor organisation name	Pearl Therapeutics, Inc.
Sponsor organisation address	200 Cardinal Way, 2nd Floor, Redwood City, California, United States, 94063
Public contact	Colin Reisner, Pearl Therapeutics, Inc., 1 1-877-240-9479, information.center@astrazeneca.com
Scientific contact	Colin Reisner, Pearl Therapeutics, Inc., 1 1-877-240-9479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002017-PIP03-48
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2019
Global end of trial reached?	Yes
Global end of trial date	12 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Efficacy and Safety

Protection of trial subjects:

Subjects were enrolled who were already taking background ICS/LABA therapy (with or without tiotropium) and continued background therapy of ICS/LABA therapy throughout the study. If a subject was taking ICS/LABA plus tiotropium, tiotropium was discontinued and these subjects were provided Ipratropium Bromide during the screening period. Sponsor-provided Albuterol sulfate was also dispensed to subjects as rescue medication during the study. Subjects were to be discontinued from study drug if had an asthma exacerbation requiring inpatient hospitalization or more than 2 severe asthma exacerbations requiring oral corticosteroid treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 December 2017
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: 1071
Worldwide total number of subjects	1071
EEA total number of subjects	0

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	35
Adults (18-64 years)	867
From 65 to 84 years	169
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study randomized subjects at 194 sites in the United States from December 2017 to September 2019. The entire study period was scheduled to take up to approximately 26 weeks for each individual subject from the time of screening through the follow up period.

Pre-assignment

Screening details:

Subjects were randomized in a 2:2:2:2:1 Scheme to follow 1 of the 5 treatment groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GP MDI 28.8 µg

Arm description:

Glycopyrronium Metered Dose Inhalation 28.8 µg

Arm type	Experimental
Investigational medicinal product name	Glycopyrronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

GP MDI 14.4 µg per actuation Taken as 2 inhalations BID

Arm title	GP MDI 14.4 µg
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Arm description:

Glycopyrronium Metered Dose Inhalation 14.4 µg

Arm type	Experimental
Investigational medicinal product name	Glycopyrronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

GP MDI 7.2 µg per actuation Taken as 2 inhalations BID

Arm title	GP MDI 7.2 µg
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Arm description:

Glycopyrronium Metered Dose Inhalation 7.2µg

Arm type	Experimental
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Investigational medicinal product name	Glycopyrronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details: GP MDI 3.6 µg per actuation Taken as 2 inhalations BID	
Arm title	Placebo MDI
Arm description: Placebo Metered Dose Inhalation	
Arm type	Placebo
Investigational medicinal product name	Placebo MDI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details: Placebo MDI (no active ingredient) Taken as 2 inhalations BID	
Arm title	Spiriva Respimat
Arm description: Spiriva Respimat	
Arm type	Active comparator
Investigational medicinal product name	Spiriva® Respimat® 2.5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details: tiotropium bromide 1.25 µg per actuation Taken as 2 inhalations QD	

Number of subjects in period 1	GP MDI 28.8 µg	GP MDI 14.4 µg	GP MDI 7.2 µg
Started	235	240	240
Completed	201	201	206
Not completed	34	39	34
Consent withdrawn by subject	13	19	16
Physician decision	1	-	1
Major Protocol Deviation	11	3	2
Adverse event, non-fatal	3	9	7
Protocol specified criteria	2	3	-
Administrative reasons	-	1	-
Lost to follow-up	4	3	7
Lack of efficacy	-	1	1

Number of subjects in period 1	Placebo MDI	Spiriva Respimat
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Started	237	119
Completed	201	105
Not completed	36	14
Consent withdrawn by subject	10	5
Physician decision	6	1
Major Protocol Deviation	3	1
Adverse event, non-fatal	5	2
Protocol specified criteria	3	1
Administrative reasons	3	-
Lost to follow-up	6	4
Lack of efficacy	-	-

Baseline characteristics

Reporting groups

Reporting group title	GP MDI 28.8 µg
Reporting group description: Glycopyrronium Metered Dose Inhalation 28.8 µg	
Reporting group title	GP MDI 14.4 µg
Reporting group description: Glycopyrronium Metered Dose Inhalation 14.4 µg	
Reporting group title	GP MDI 7.2 µg
Reporting group description: Glycopyrronium Metered Dose Inhalation 7.2µg	
Reporting group title	Placebo MDI
Reporting group description: Placebo Metered Dose Inhalation	
Reporting group title	Spiriva Respimat
Reporting group description: Spiriva Respimat	

Reporting group values	GP MDI 28.8 µg	GP MDI 14.4 µg	GP MDI 7.2 µg
Number of subjects	235	240	240
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	5	12	7
Adults (18-64 years)	196	185	198
From 65-84 years	34	43	35
85 years and over	0	0	0
Age Continuous Units: Number			
arithmetic mean	48.4	47.7	46.7
standard deviation	± 15.1	± 16.8	± 15.5
Sex: Female, Male Units: Participants			
Female	146	153	151
Male	89	87	89
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	3
Asian	6	1	6
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	62	68	52
White	165	168	177

More than one race	0	0	0
Unknown or Not Reported	1	2	2
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	36	61	52
Not Hispanic or Latino	198	179	186
Unknown or Not Reported	1	0	2

Reporting group values	Placebo MDI	Spiriva Respimat	Total
Number of subjects	237	119	1071
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	9	2	35
Adults (18-64 years)	193	95	867
From 65-84 years	35	22	169
85 years and over	0	0	0
Age Continuous			
Units: Number			
arithmetic mean	47.1	49.8	
standard deviation	± 16.2	± 15.3	-
Sex: Female, Male			
Units: Participants			
Female	134	76	660
Male	103	43	411
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	1	5
Asian	2	0	15
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	52	25	259
White	179	93	782
More than one race	0	0	0
Unknown or Not Reported	4	0	9
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	51	21	221
Not Hispanic or Latino	186	98	847
Unknown or Not Reported	0	0	3

End points

End points reporting groups

Reporting group title	GP MDI 28.8 µg
Reporting group description:	Glycopyrronium Metered Dose Inhalation 28.8 µg
Reporting group title	GP MDI 14.4 µg
Reporting group description:	Glycopyrronium Metered Dose Inhalation 14.4 µg
Reporting group title	GP MDI 7.2 µg
Reporting group description:	Glycopyrronium Metered Dose Inhalation 7.2µg
Reporting group title	Placebo MDI
Reporting group description:	Placebo Metered Dose Inhalation
Reporting group title	Spiriva Respimat
Reporting group description:	Spiriva Respimat

Primary: Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve from 0 to 4 hours (AUC0-4)

End point title	Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve from 0 to 4 hours (AUC0-4)
End point description:	Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve from 0 to 4 hours (AUC0-4)AUC was normalized for length of follow up (e.g. typically 4 hours).
End point type	Primary
End point timeframe:	Week 24

End point values	GP MDI 28.8 µg	GP MDI 14.4 µg	GP MDI 7.2 µg	Placebo MDI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	195	199	205	196
Units: Liter				
least squares mean (confidence interval 95%)	0.294 (0.248 to 0.341)	0.284 (0.238 to 0.331)	0.308 (0.263 to 0.354)	0.240 (0.194 to 0.287)

End point values	Spiriva Respimat			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: Liter				
least squares mean (confidence interval 95%)	0.347 (0.282 to 0.412)			

Statistical analyses

Statistical analysis title	Change from baseline in FEV1 AUC0-4
Statistical analysis description: Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve from 0 to 4 hours (AUC0-4)	
Comparison groups	GP MDI 28.8 µg v Placebo MDI
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.105
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.054
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	-0.011
upper limit	0.119

Statistical analysis title	Change from baseline in FEV1 AUC0-4
Statistical analysis description: Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve from 0 to 4 hours (AUC0-4)	
Comparison groups	GP MDI 14.4 µg v Placebo MDI
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1825
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.044
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	-0.021
upper limit	0.109

Statistical analysis title	Change from baseline in FEV1 AUC0-4
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Statistical analysis description:

Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve from 0 to 4

hours (AUC0-4)

Comparison groups	GP MDI 7.2 µg v Placebo MDI
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0392
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.068
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	0.003
upper limit	0.133

Statistical analysis title

Change from baseline in FEV1 AUC0-4

Statistical analysis description:

Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve from 0 to 4 hours (AUC0-4)

Comparison groups	Spiriva Respimat v Placebo MDI
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0084
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.107
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	0.027
upper limit	0.186

Secondary: Change from baseline in morning pre-dose trough FEV1

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

End point type	Secondary
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End point timeframe:

Week 24

End point values	GP MDI 28.8 µg	GP MDI 14.4 µg	GP MDI 7.2 µg	Placebo MDI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	196	199	205	198
Units: Liter				
least squares mean (confidence interval 95%)	0.142 (0.097 to 0.188)	0.108 (0.063 to 0.153)	0.142 (0.098 to 0.187)	0.129 (0.084 to 0.174)

End point values	Spiriva Respimat			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: Liter				
least squares mean (confidence interval 95%)	0.150 (0.087 to 0.213)			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of moderate to severe Asthma exacerbations

End point title	Rate of moderate to severe Asthma exacerbations
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End point description:

Rate of moderate to severe Asthma exacerbations (A deterioration of asthma requiring a new or increased dose of ICS for at least 3 days) or severe Asthma exacerbation (Use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days OR a hospitalization or ER visit because of asthma)

End point type	Secondary
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End point timeframe:

over 24 Weeks (timepoints of 4, 12 & 20 weeks)

End point values	GP MDI 28.8 µg	GP MDI 14.4 µg	GP MDI 7.2 µg	Placebo MDI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	231	240	240	237
Units: Participants per year				
arithmetic mean (standard error)	0.43 (± 0.078)	0.44 (± 0.080)	0.41 (± 0.076)	0.55 (± 0.092)

End point values	Spiriva Respimat			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Participants per year				
arithmetic mean (standard error)	0.50 (± 0.123)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in ACQ-7 (Asthma Control Questionnaire)

End point title Change from baseline in ACQ-7 (Asthma Control Questionnaire)

End point description:

ACQ-7:ACQ questions 1 through 7, which is the ACQ-6 plus 1 item that scores lung function (FEV1 percent predicted)

End point type Secondary

End point timeframe:

Week 24

End point values	GP MDI 28.8 µg	GP MDI 14.4 µg	GP MDI 7.2 µg	Placebo MDI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	189	189	194	187
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-0.78 (-0.89 to -0.66)	-0.73 (-0.84 to -0.62)	-0.90 (-1.01 to -0.79)	-0.80 (-0.91 to -0.69)

End point values	Spiriva Respimat			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-0.90 (-1.06 to -0.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in ACQ-5 (Asthma Control Questionnaire)

End point title Change from baseline in ACQ-5 (Asthma Control Questionnaire)

End point description:

ACQ-5:ACQ questions 1 through 5, which measure the frequency, intensity or limitations from asthma symptoms using 1-week recall

End point type Secondary

End point timeframe:

Week 24

End point values	GP MDI 28.8 µg	GP MDI 14.4 µg	GP MDI 7.2 µg	Placebo MDI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	195	198	196	196
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-0.87 (-1.00 to -0.73)	-0.80 (-0.93 to -0.67)	-1.02 (-1.15 to -0.89)	-0.93 (-1.06 to -0.80)

End point values	Spiriva Respimat			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-1.03 (-1.22 to -0.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Asthma Quality of Life Questionnaire for 12 years and older (AQLQ +12)

End point title	Change from baseline in Asthma Quality of Life Questionnaire for 12 years and older (AQLQ +12)
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End point description:

AQLQ +12 - Asthma Quality of Life Questionnaire for 12 years and older

End point type	Secondary
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End point timeframe:

Week 24

End point values	GP MDI 28.8 µg	GP MDI 14.4 µg	GP MDI 7.2 µg	Placebo MDI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	191	191	191	188
Units: Scores on a scale				
least squares mean (confidence interval 95%)	0.89 (0.74 to 1.04)	0.90 (0.75 to 1.04)	1.02 (0.87 to 1.16)	0.96 (0.82 to 1.11)

End point values	Spiriva Respimat			
Subject group type	Reporting group			
Number of subjects analysed	94			
Units: Scores on a scale				
least squares mean (confidence interval 95%)	1.04 (0.84 to 1.25)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse events were collected from the time subject signed Informed Consent to the time of the final follow-up telephone call. Adverse Events were collected from the time subject was randomized.

Adverse event reporting additional description:

The safety analysis set was defined as data from all subjects who were randomized to treatment and received any amount of the study treatment

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	GP MDI 28.8 µg
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Reporting group description:

Glycopyrronium Metered Dose Inhalation 28.8 µg

Reporting group title	GP MDI 14.4 µg
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Reporting group description:

Glycopyrronium Metered Dose Inhalation 14.4 µg

Reporting group title	GP MDI 7.2 µg
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Reporting group description:

Glycopyrronium Metered Dose Inhalation 7.2µg

Reporting group title	Placebo MDI
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Reporting group description:

Placebo Metered Dose Inhalation

Reporting group title	Spiriva Respimat
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Reporting group description:

Spiriva Respimat

Serious adverse events	GP MDI 28.8 µg	GP MDI 14.4 µg	GP MDI 7.2 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 235 (3.83%)	7 / 240 (2.92%)	6 / 240 (2.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 235 (0.00%)	0 / 240 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non cardiac chest pain			

subjects affected / exposed	0 / 235 (0.00%)	1 / 240 (0.42%)	0 / 240 (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
Social circumstances			
Miscarriage of partner			
subjects affected / exposed	1 / 235 (0.43%)	0 / 240 (0.00%)	0 / 240 (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
Reproductive system and breast disorders			
Adnexal torsion			
subjects affected / exposed	0 / 235 (0.00%)	0 / 240 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 235 (0.43%)	0 / 240 (0.00%)	2 / 240 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 235 (0.00%)	1 / 240 (0.42%)	0 / 240 (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
Respiratory failure			
subjects affected / exposed	1 / 235 (0.43%)	0 / 240 (0.00%)	0 / 240 (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
Acute respiratory failure			
subjects affected / exposed	0 / 235 (0.00%)	0 / 240 (0.00%)	0 / 240 (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
Psychiatric disorders			
Suicidal ideation			

subjects affected / exposed	0 / 235 (0.00%)	0 / 240 (0.00%)	0 / 240 (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			
Concussion			
subjects affected / exposed	0 / 235 (0.00%)	1 / 240 (0.42%)	0 / 240 (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
Post traumatic pain			
subjects affected / exposed	0 / 235 (0.00%)	1 / 240 (0.42%)	0 / 240 (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			
Cerebrovascular accident			
subjects affected / exposed	0 / 235 (0.00%)	0 / 240 (0.00%)	0 / 240 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 235 (0.43%)	0 / 240 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 240 (0.00%)	0 / 240 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 235 (0.43%)	0 / 240 (0.00%)	0 / 240 (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
Nephrolithiasis			

subjects affected / exposed	0 / 235 (0.00%)	0 / 240 (0.00%)	0 / 240 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 235 (0.43%)	0 / 240 (0.00%)	0 / 240 (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
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 235 (0.00%)	1 / 240 (0.42%)	0 / 240 (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
Influenza			
subjects affected / exposed	0 / 235 (0.00%)	0 / 240 (0.00%)	0 / 240 (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
Cellulitis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 240 (0.42%)	0 / 240 (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	2 / 235 (0.85%)	0 / 240 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 235 (0.00%)	0 / 240 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kindey infection			
subjects affected / exposed	0 / 235 (0.00%)	1 / 240 (0.42%)	0 / 240 (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

Klebsiella bacteraemia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 240 (0.00%)	0 / 240 (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
Metapneumovirus infection			
subjects affected / exposed	0 / 235 (0.00%)	0 / 240 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 235 (0.00%)	1 / 240 (0.42%)	0 / 240 (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	1 / 235 (0.43%)	0 / 240 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 235 (0.00%)	1 / 240 (0.42%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo MDI	Spiriva Respimat	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 237 (2.95%)	2 / 119 (1.68%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non cardiac chest pain			

subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Miscarriage of partner			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexal torsion			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (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			
subjects affected / exposed	1 / 237 (0.42%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			

subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post traumatic pain			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (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			
Urinary tract infection			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 237 (0.42%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kindeg infection			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Klebsiella bacteraemia			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (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	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 237 (0.00%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	GP MDI 28.8 µg	GP MDI 14.4 µg	GP MDI 7.2 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	100 / 235 (42.55%)	106 / 240 (44.17%)	104 / 240 (43.33%)
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	14 / 235 (5.96%)	14 / 240 (5.83%)	14 / 240 (5.83%)
occurrences (all)	15	14	14
Nasopharyngitis			
subjects affected / exposed	11 / 235 (4.68%)	15 / 240 (6.25%)	17 / 240 (7.08%)
occurrences (all)	12	19	19
Sinusitis			

subjects affected / exposed	10 / 235 (4.26%)	7 / 240 (2.92%)	4 / 240 (1.67%)
occurrences (all)	10	8	4

Non-serious adverse events	Placebo MDI	Spiriva Respimat	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 237 (46.41%)	44 / 119 (36.97%)	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	19 / 237 (8.02%)	6 / 119 (5.04%)	
occurrences (all)	20	7	
Nasopharyngitis			
subjects affected / exposed	8 / 237 (3.38%)	2 / 119 (1.68%)	
occurrences (all)	10	2	
Sinusitis			
subjects affected / exposed	3 / 237 (1.27%)	7 / 119 (5.88%)	
occurrences (all)	3	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2018	Increased the upper limit of the pre-bronchodilator FEV1 for study inclusion, Clarified that FEV1 inclusion criterion, Revised the Schedule of Events, Changed the Fridericia-corrected QT (QTcF) interval limits for study drug discontinuation, Added the Schwartz formula for age-appropriate calculation of creatinine clearance for subjects 12 to <19 years of age,
07 June 2018	Increased the upper limit of the pre-bronchodilator FEV1 for study inclusion to <85% instead of <80% of predicted normal value for subjects 18 to 80 years of age, Decreased the minimum time on inhaled corticosteroid (ICS)/long-acting 2-agonist (LABA) from, Text regarding follow-up phone call necessity clarified, Added text to describe the analysis of the Holter Monitoring data
22 August 2018	Decreased the number of subjects required to have 24-hour Holter monitoring, Removed Visit 5 (Week 4) post-dose spirometry measurements, Added the word "heterosexual" to those females of childbearing potential and sexually active who require use of birth control, Increased number of subjects to be screened from 1875 to approximately 2250, number of sites from 175 to 225 to approximately 250 and removed Canada from the countries participating in the study
08 March 2019	Removed Visit 5 (Week 4) post-dose vital sign measurements, Reduced the time gaps around Visits 1, 2, and 3 by 2 days, Added height requirement at Visits 4, 5, and 7 for subjects 12 to 18 years of age, Age range for creatinine clearance equations corrected, Added wording that any clarification to the definition and analysis of consecutive asthma exacerbations will be detailed in the statistical analysis plan Added wording that any clarification to the definition and analysis of consecutive asthma exacerbations will be detailed in the statistical analysis plan Added wording that any clarification to the definition and analysis of consecutive asthma exacerbations will be detailed in the statistical analysis plan Added wording that any clarification to the definition and analysis of consecutive asthma exacerbations will be detailed in the statistical analysis plan

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported