Clinical trial results:
A Randomized, Open-Label, Active-Controlled, Parallel-Group, Multicenter, Long-Term Safety Trial of Treatment With Nebulized SUN-101 in Patients With COPD: GOLDEN-5 (Glycopyrrolate for Obstructive Lung Disease Via Electronic Nebulizer)

Summary

EudraCT number	2013-002696-18
Trial protocol	CZ HU
Global end of trial date	29 February 2016

Results information

Result version number	v1 (current)
This version publication date	10 August 2017
First version publication date	10 August 2017

Trial information

Trial identification

Sponsor protocol code	SUN101-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02276222
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sunovion Respiratory Development Inc.
Sponsor organisation address	84 Waterford Drive, Marlboro, United States, 01752
Public contact	Respiratory Medical Director, Sunovion Respiratory Development Inc., 1+ 866-503-6351 , ClinicalTrialDisclosure@sunovion.com
Scientific contact	Respiratory Medical Director, Sunovion Respiratory Development Inc., 1+ 866-503-6351 , ClinicalTrialDisclosure@sunovion.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	29 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 February 2016
Global end of trial reached?	Yes
Global end of trial date	29 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety and tolerability of SUN-101 given as 50 mcg twice daily (BID) over 48 weeks of treatment

Protection of trial subjects:

The study was conducted according to the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), ICH guidelines, and the ethical principles that have their origin in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Hungary: 54
Country: Number of subjects enrolled	United States: 977
Worldwide total number of subjects	1086
EEA total number of subjects	63

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	586
From 65 to 84 years	500

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects will undergo Screening (Visit 1), including Holter monitoring and assessments to determine study eligibility. Subjects will be provided an electronic diary (eDiary) to record rescue medication use, COPD symptoms, and to complete the EXAcerbations of Chronic Pulmonary Disease Tool (EXACT).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	SUN-101 50 mcg BID eFlow (CS) nebulizer

Arm description:

SUN-101 (Glycopyrrolate) 50 mcg twice daily (BID) via eFlow Closed System (CS) nebulizer

SUN-101 50 mcg BID eFlow (CS) nebulizer: SUN-101 (Glycopyrrolate) 50 mcg twice daily (BID) via eFlow Closed System (CS) nebulizer

Arm type	Experimental
Investigational medicinal product name	Glycopyrrolate
Investigational medicinal product code	
Other name	SUN101
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

SUN-101 (Glycopyrrolate) 50 mcg twice daily (BID) via eFlow Closed System (CS) nebulizer

Arm title	Spiriva 18 mcg QD Handihaler

Arm description:

Spiriva (tiotropium) 18 mcg once daily (QD) via Handihaler

Spiriva® 18 mcg QD Handihaler: Spiriva (tiotropium) 18 mcg once daily (QD) via Handihaler

Arm type	Active comparator
Investigational medicinal product name	(tiotropium)
Investigational medicinal product code	
Other name	Spiriva
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Spiriva (tiotropium) 18 mcg once daily (QD) via Handihaler

Number of subjects in period 1	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler
Started	620	466
Completed	436	402
Not completed	184	64
Adverse event, serious fatal	3	4
sponsor decision	-	3
Consent withdrawn by subject	79	33
Physician decision	2	1
Adverse event, non-fatal	62	11
non compliance with study medication	6	2
Lost to follow-up	15	5
sheduling conflict	1	-
Lack of efficacy	13	3
Protocol deviation	3	2

Baseline characteristics

Reporting groups	
Reporting group title	SUN-101 50 mcg BID eFlow (CS) nebulizer
Reporting group description:	
SUN-101 (Glycopyrrolate) 50 mcg twice daily (BID) via eFlow Closed System (CS) nebulizer SUN-101 50 mcg BID eFlow (CS) nebulizer: SUN-101 (Glycopyrrolate) 50 mcg twice daily (BID) via eFlow Closed System (CS) nebulizer	
Reporting group title	Spiriva 18 mcg QD Handihaler
Reporting group description:	
Spiriva (tiotropium) 18 mcg once daily (QD) via Handihaler Spiriva® 18 mcg QD Handihaler: Spiriva (tiotropium) 18 mcg once daily (QD) via Handihaler	

Reporting group values	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler	Total
Number of subjects	620	466	1086
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	330	256	586
>=65 years	290	210	500
Age Continuous Units: years			
arithmetic mean	63.3	63.3	
standard deviation	± 8.46	± 8.97	-
Gender categorical Units: Subjects			
Female	270	206	476
Male	350	260	610
Sex: Female, Male Units: Subjects			
Female	270	206	476
Male	350	260	610
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9	9	18
Not Hispanic or Latino	611	457	1068
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	2	4
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	35	27	62
White	582	436	1018
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Region of Enrollment Units: Subjects			
Russian Federation	25	21	46
Czech Republic	5	4	9
Hungary	34	20	54
United States	556	421	977
cardiovascular risk (low/high) Units: Subjects			
low cardiovascular risk	219	169	388
high cardiovascular risk	401	297	698
background long-acting beta (2) agonist (LABA) use Units: Subjects			
background LABA use -yes	267	192	459
background LABA use -no	353	274	627
Forced expiratory volume in one second (FEV1) Units: liters			
arithmetic mean	1.3399	1.3257	
standard deviation	± 0.49604	± 0.50186	-

End points

End points reporting groups

Reporting group title	SUN-101 50 mcg BID eFlow (CS) nebulizer

Reporting group description:

SUN-101 (Glycopyrrolate) 50 mcg twice daily (BID) via eFlow Closed System (CS) nebulizer

SUN-101 50 mcg BID eFlow (CS) nebulizer: SUN-101 (Glycopyrrolate) 50 mcg twice daily (BID) via eFlow Closed System (CS) nebulizer

Reporting group title	Spiriva 18 mcg QD Handihaler

Reporting group description:

Spiriva (tiotropium) 18 mcg once daily (QD) via Handihaler

Spiriva® 18 mcg QD Handihaler: Spiriva (tiotropium) 18 mcg once daily (QD) via Handihaler

Primary: Number of subjects with treatment-emergent adverse events (TEAE)

End point title	Number of subjects with treatment-emergent adverse events (TEAE)[1]

End point description:

A TEAE is any adverse event (AE) that occurred on or after the first dose of study medication, any AE with a missing start date and a stop date on or after the first dose of study medication, or any AE with both a missing start and stop date.

End point type	Primary

End point timeframe:

Up to Week 48

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were performed on this endpoint

End point values	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	620	466		
Units: participants				
number (not applicable)	430	312		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with treatment-emergent adverse events

End point title	Percentage of subjects with treatment-emergent adverse events[2]

End point description:

A TEAE is any adverse event (AE) that occurred on or after the first dose of study medication, any AE with a missing start date and a stop date on or after the first dose of study medication, or any AE with both a missing start and stop date.

End point type	Primary

End point timeframe:

Up to Week 48

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were performed on this endpoint

End point values	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	620	466		
Units: percentage of participants				
number (not applicable)	69.4	67		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with treatment-emergent serious adverse events (SAE)

End point title	Number of subjects with treatment-emergent serious adverse events (SAE)[3]

End point description:

A treatment emergent serious adverse event (SAE) is any SAE that occurred on or after the first dose of study medication, any SAE with a missing start date and a stop date on or after the first dose of study medication, or any SAE with both a missing start and stop date.

End point type	Primary

End point timeframe:

Up to Week 48

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were performed on this endpoint

End point values	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	620	466		
Units: participants				
number (not applicable)	76	49		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with treatment-emergent serious adverse

End point title	Percentage of subjects with treatment-emergent serious adverse[4]

End point description:

A treatment emergent serious adverse event (SAE) is any SAE that occurred on or after the first dose of study medication, any SAE with a missing start date and a stop date on or after the first dose of study medication, or any SAE with both a missing start and stop date.

End point type	Primary

End point timeframe:

Up to Week 48

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were performed on this endpoint

End point values	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	620	466		
Units: percentage of participants				
number (not applicable)	12.3	10.5		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects who discontinue the study due to TEAE

End point title	Number of subjects who discontinue the study due to TEAE[5]

End point description:

A TEAE is any adverse event (AE) that occurred on or after the first dose of study medication, any AE with a missing start date and a stop date on or after the first dose of study medication, or any AE with both a missing start and stop date.

End point type	Primary

End point timeframe:

Up to Week 48

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were performed on this endpoint

End point values	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	620	466		
Units: participants				
number (not applicable)	62	13		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects who discontinue the study due to TEAE

End point title	Percentage of subjects who discontinue the study due to

End point description:

A TEAE is any adverse event (AE) that occurred on or after the first dose of study medication, any AE with a missing start date and a stop date on or after the first dose of study medication, or any AE with both a missing start and stop date.

End point type	Primary

End point timeframe:

Up to 48 Weeks

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were performed on this endpoint

End point values	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	620	466		
Units: percentage of participants				
number (not applicable)	10	2.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with major adverse cardiac events (MACE), including cardiovascular death, ischemia/infarction, and stroke

End point title	Number of subjects with major adverse cardiac events (MACE), including cardiovascular death, ischemia/infarction, and stroke

End point description:

All deaths and any other findings suggestive of a potential MACE (including clinically relevant information and SAEs, and all PTs form the SMQs “myocardial infarction”, “other ischemic heart disease”, “central nervous system hemorrhages and cerebrovascular conditions”) were sent to an adjudication committee for review and categorized as CV death, nonfatal MI, and nonfatal stroke. The MACE score was defined as the total number of subjects with CV deaths, nonfatal MIs, and nonfatal strokes. These events were collected from the first date of study medication until the date of last contact.

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	620	466		
Units: participants				
number (not applicable)				
MACE score	3	8		

cardiovascular death	1	2		
non-fatal myocardial infarction	2	5		
non-fatal stroke	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with major adverse cardiac events (MACE), including cardiovascular death, ischemia/infarction, and stroke

End point title	Percentage of subjects with major adverse cardiac events (MACE), including cardiovascular death, ischemia/infarction, and stroke

End point description:

All deaths and any other findings suggestive of a potential MACE (including clinically relevant information and SAEs, and all PTs form the SMQs "myocardial infarction", "other ischemic heart disease", "central nervous system hemorrhages and cerebrovascular conditions") were sent to an adjudication committee for review and categorized as CV death, nonfatal MI, and nonfatal stroke. The MACE score was defined as the total number of subjects with CV deaths, nonfatal MIs, and nonfatal strokes. These events were collected from the first date of study medication until the date of last contact.

End point type	Secondary

End point timeframe:

Up to 48 Weeks

End point values	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	620	466		
Units: percentage of participants				
number (not applicable)				
MACE score	0.5	1.7		
cardiovascular death	0.2	0.4		
non-fatal myocardial infarction	0.3	1.1		
non-fatal stroke	0	0.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate per 1000 person years of subjects with major adverse cardiac events (MACE), including cardiovascular death, ischemia/infarction, and stroke

End point title	Incidence rate per 1000 person years of subjects with major adverse cardiac events (MACE), including cardiovascular death, ischemia/infarction, and stroke

End point description:

All deaths and any other findings suggestive of a potential MACE (including clinically relevant information and SAEs, and all PTs form the SMQs "myocardial infarction", "other ischemic heart disease", "central nervous system hemorrhages and cerebrovascular conditions") were sent to an adjudication committee for review and categorized as CV death, nonfatal MI, and nonfatal stroke. The MACE score was defined as the total number of subjects with CV deaths, nonfatal MIs, and nonfatal strokes. These events were collected from the first date of study medication until the date of last contact.

End point type	Secondary

End point timeframe:

up to week 48

End point values	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	620	466		
Units: incidence rate per 1000 person years				
number (not applicable)				
MACE score	6.4	20.3		
cardiovascular death	2.1	5.1		
non-fatal myocardial infarction	4.3	12.7		
non-fatal stroke	0	2.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline over 48 weeks in trough FEV1 for all subjects

End point title	Mean change from baseline over 48 weeks in trough FEV1 for all subjects

End point description:

Spirometry was performed according to internationally accepted standards.
Trough FEV1 was defined as the average of the FEV1 values collected at the end of the dosing interval at each clinic visit. The mean change from baseline in trough FEV1 over the 48 week treatment period is calculated by averaging the trough FEV1 changes from baseline across all study visits while subjects are taking randomized treatment.
Values affected by other medication use were to be set to missing.

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	620	466		
Units: liters				
least squares mean (standard error)	0.1016 (± 0.00698)	0.0931 (± 0.00779)		

Statistical analyses

Statistical analysis title	STATISTICAL_ANALYSIS_TITLE
Comparison groups	SUN-101 50 mcg BID eFlow (CS) nebulizer v Spiriva 18 mcg QD Handihaler
Number of subjects included in analysis	1086
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4041
Method	Least squares mean (SE)
Parameter estimate	Least Squares Mean (SE)
Point estimate	0.0084
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0114
upper limit	0.0283
Variability estimate	Standard error of the mean
Dispersion value	0.01012

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to week 48	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	SUN-101 50 mcg BID eFlow (CS) nebulizer
Reporting group description: SUN-101 (Glycopyrrolate) 50 mcg twice daily (BID) via eFlow Closed System (CS) nebulizer SUN-101 50 mcg BID eFlow (CS) nebulizer: SUN-101 (Glycopyrrolate) 50 mcg twice daily (BID) via eFlow Closed System (CS) nebulizer	
Reporting group title	Spiriva 18 mcg QD Handihaler
Reporting group description: Spiriva (tiotropium) 18 mcg once daily (QD) via Handihaler Spiriva® 18 mcg QD Handihaler: Spiriva (tiotropium) 18 mcg once daily (QD) via Handihaler	

Serious adverse events	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler	
Total subjects affected by serious adverse events			
subjects affected / exposed	76 / 620 (12.26%)	49 / 466 (10.52%)	
number of deaths (all causes)	3	4	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
benign lung neoplasm			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bladder cancer			
subjects affected / exposed	1 / 620 (0.16%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast cancer			

subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
carcinoid tumor of the apendix			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colon cancer			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
endometrial cancer			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung adenocarcinoma			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
meningioma			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastatic renal cell carcinoma			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
non-hodgkins lymphoma			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancreatic carcinoma			

subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
prostate cancer			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal cancer			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
small cell lung cancer stage unspecified			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
aortic aneurysm			
subjects affected / exposed	2 / 620 (0.32%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertension			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
chest pain			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

generalized oedema			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
non-cardiac chest pain			
subjects affected / exposed	1 / 620 (0.16%)	2 / 466 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
acute respiratory distress syndrome			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute respiratory failure			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
chronic obstructive pulmonary disease			
subjects affected / exposed	17 / 620 (2.74%)	14 / 466 (3.00%)	
occurrences causally related to treatment / all	0 / 18	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
dyspnoea			
subjects affected / exposed	2 / 620 (0.32%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

hypoxia			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleurisy			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia aspiration			
subjects affected / exposed	2 / 620 (0.32%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax			
subjects affected / exposed	3 / 620 (0.48%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
subjects affected / exposed	1 / 620 (0.16%)	2 / 466 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory failure			
subjects affected / exposed	1 / 620 (0.16%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pluritic pain			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COPD exacerbation			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			

anxiety			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (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			
accidental overdose			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ankle fracture			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hip fracture			
subjects affected / exposed	3 / 620 (0.48%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
impacted fracture			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
joint injury			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pubis fracture			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
road traffic accident			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

subdural haematoma			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vascular pseudoaneurysm			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
acute myocardial infarction			
subjects affected / exposed	1 / 620 (0.16%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
angina pectoris			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial fibrillation			
subjects affected / exposed	2 / 620 (0.32%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
arterial flutter			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac failure congestive			
subjects affected / exposed	1 / 620 (0.16%)	2 / 466 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardio respiratory arrest			
subjects affected / exposed	3 / 620 (0.48%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
coronary artery disease			

subjects affected / exposed	3 / 620 (0.48%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infraction			
subjects affected / exposed	1 / 620 (0.16%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
verntricular arrhythmia			
subjects affected / exposed	1 / 620 (0.16%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
hashimoto's encephalopathy			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lumbar radiculopathy			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
multile sclerosis relapse			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
serotonin syndrome			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
transient ischaemic attack			

subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
suicidal ideation			
subjects affected / exposed	2 / 620 (0.32%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
diplopia			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (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	1 / 620 (0.16%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
constipation			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
duodenal ulcer, obstructive			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric ulcer haemorrhage			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric ulcer perforation			

subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal perforation			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrooesophageal reflux disease			
subjects affected / exposed	2 / 620 (0.32%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematochezia			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
large intestinal obstruction			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancreatitis			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal haemorrhage			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestinal obstruction			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
cholecystitis			

subjects affected / exposed	2 / 620 (0.32%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholecystitis acute			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholelithiasis			
subjects affected / exposed	2 / 620 (0.32%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
angioedema			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
renal failure			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal mass			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary retention			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
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			
back pain			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

joint effsion			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteoarthritis			
subjects affected / exposed	1 / 620 (0.16%)	2 / 466 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
abdominal infection			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
appendicitis			
subjects affected / exposed	1 / 620 (0.16%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchitis			
subjects affected / exposed	2 / 620 (0.32%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastronenteritis viral			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteomyelitis			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pheumonia			

subjects affected / exposed	8 / 620 (1.29%)	3 / 466 (0.64%)	
occurrences causally related to treatment / all	2 / 8	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
sepsis			
subjects affected / exposed	0 / 620 (0.00%)	3 / 466 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
septic shock			
subjects affected / exposed	0 / 620 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
systemic candida			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection			
subjects affected / exposed	2 / 620 (0.32%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
urosepsis			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
dehydration			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
malnutrition			

subjects affected / exposed	1 / 620 (0.16%)	0 / 466 (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: 5 %

Non-serious adverse events	SUN-101 50 mcg BID eFlow (CS) nebulizer	Spiriva 18 mcg QD Handihaler	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	195 / 620 (31.45%)	133 / 466 (28.54%)	
Respiratory, thoracic and mediastinal disorders			
chronic obstructive pulmonary disease			
subjects affected / exposed	91 / 620 (14.68%)	82 / 466 (17.60%)	
occurrences (all)	119	107	
cough			
subjects affected / exposed	73 / 620 (11.77%)	26 / 466 (5.58%)	
occurrences (all)	78	28	
Infections and infestations			
nasopharyngitis			
subjects affected / exposed	25 / 620 (4.03%)	28 / 466 (6.01%)	
occurrences (all)	31	32	
upper respiratory tract infection			
subjects affected / exposed	38 / 620 (6.13%)	25 / 466 (5.36%)	
occurrences (all)	42	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None

Notes: