



Clinical trial results:

A Phase III, Prospective, Multicenter, Randomized, Controlled Clinical Trial to Demonstrate the Efficacy and Safety of Liposomal Cyclosporine A (LCsA) Inhalation Solution Delivered via the PARI Investigational eFlow® Device plus Standard of Care versus Standard of Care Alone in the Treatment of Chronic Lung Allograft Dysfunction / Bronchiolitis Obliterans Syndrome in Patients post Double Lung Transplantation (BOSTON 2).

Summary

EudraCT number	2018-003205-25
Trial protocol	FR DE AT BE GB ES DK
Global end of trial date	12 March 2024

Results information

Result version number	v1
This version publication date	02 July 2025
First version publication date	02 July 2025

Trial information

Trial identification

Sponsor protocol code	BT-L-CsA-302-DLT
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03656926
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zambon S.p.A.
Sponsor organisation address	Via Lillo del Duca 10, Bresso (Mi), Italy, 20091
Public contact	Sponsor Contact Point, Zambon SpA, Zambon SpA, +39 0266524513, clinicaltrials@zambongroup.com
Scientific contact	Sponsor Contact Point, Zambon SpA, Zambon SpA, +39 0266524513, clinicaltrials@zambongroup.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	12 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2024
Global end of trial reached?	Yes
Global end of trial date	12 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of add-on aerosolized L-CsA to Standard of Care therapy as compared to SoC therapy alone in the treatment of BOS in double lung transplant recipients.

Protection of trial subjects:

The clinical study was performed in accordance with the principles that have their origin in the Declaration of Helsinki, and with local regulations.

The study was carried out in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) notes for guidance on Good Clinical Practice (GCP).

Investigators insured a close follow-up of safety signals, and that everything has been done to reduce the burden of study procedures (e.g. no painful procedures, etc.).

Background therapy:

Standard of Care (SoC). Basic immunosuppression:

Regardless of treatment allocation, all patients received SoC. Eligible patients should have been on a maintenance regimen of immunosuppressive agents including tacrolimus, a second agent such as but not limited to MMF or azathioprine, and a systemic corticosteroid such as prednisone as third agent. The regimen must have been stable within 4 weeks prior to randomization with respect to the therapeutic agents. Patients receiving azithromycin for prophylaxis or treatment of BOS must have been on a stable regimen for at least 4 weeks prior to randomization and continued to receive azithromycin during the trial as deemed appropriate by the study investigator.

Evidence for comparator: -

Actual start date of recruitment	26 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: 61
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 34

Worldwide total number of subjects	169
EEA total number of subjects	97

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)	122
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

There were major recruitment issues in both BOSTON-1 and BOSTON-2 trials, in part due to COVID-19. To obtain an adequately sized safety database for inhaled L-CsA and reach the planned sample size in the 2 trials combined, it was planned to stop randomization into the 2 trials upon achievement of a combined total of around 220 patients.

Pre-assignment

Screening details:

The trial included adults who received a DLT at least 12 months prior to Screening, with clinically defined CLAD-BOS phenotype and screening FEV1 between 51% to 85% of personal best FEV1 value post-transplant or screening FEV1 >85% of personal best post-transplant with either a ≥ 200 mL decrease in FEV1 in the previous 12 months or BOS progression.

Period 1

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

Blinding implementation details:

This was an open-label study hence clinical monitors, physicians, nurses, study coordinators & patients were not blinded to treatment assignment.

However, pulmonary function technicians, respiratory therapists, or physiotherapists who conducted spirometry on-site were blinded to treatment assignment. Patients and other unblinded personnel were asked not to share treatment assignment infos with them. The statistician who made the blinded interim sample size re-assessment was blinded as well.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

L-CsA 10 mg/2.5 mL twice daily for 48 weeks
Plus Standard of Care Therapy

Arm type	Experimental
Investigational medicinal product name	L-CsA
Investigational medicinal product code	
Other name	liposomal cyclosporine A
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

L-CsA 10 mg/2.5 mL twice daily for 48 weeks Plus Standard of Care Therapy. Patients randomized to the L-CsA arm received L-CsA 10 mg twice daily in addition to SoC as prescribed by the treating physician. L-CsA was administered as 10 mg/2.5 mL inhalation via the PARI investigational eFlow device for 48 weeks

Investigational medicinal product name	Standard of care
Investigational medicinal product code	
Other name	SoC
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

SoC had L-CsA as add-on therapy in group A.

Arm title	Group B
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Arm description:

Standard of Care alone (as directed by treating physician)

Arm type	Active comparator
Investigational medicinal product name	Standard of Care
Investigational medicinal product code	
Other name	SoC
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Standard of care as directed by treating physician was administered alone

Number of subjects in period 1	Group A	Group B
Started	84	85
Completed	69	79
Not completed	15	6
Adverse event, serious fatal	5	4
PI decision due to patient condition	1	-
Consent withdrawn by subject	7	2
Screen fail after randomization	1	-
Patient unresponsiveness	1	-

Baseline characteristics

Reporting groups

Reporting group title	Group A
Reporting group description: L-CsA 10 mg/2.5 mL twice daily for 48 weeks Plus Standard of Care Therapy	
Reporting group title	Group B
Reporting group description: Standard of Care alone (as directed by treating physician)	

Reporting group values	Group A	Group B	Total
Number of subjects	84	85	169
Age categorical Units: Subjects			
Adults 18-64	58	64	122
Adults 65-85	26	21	47
Age continuous Units: years			
arithmetic mean	56.5	56.2	
standard deviation	± 12.69	± 10.82	-
Gender categorical Units: Subjects			
Female	34	42	76
Male	50	43	93

Subject analysis sets

Subject analysis set title	Group A - Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The FAS was defined as all randomized patients. Patients were analyzed according to the treatment group to which they were randomized.	
Subject analysis set title	Group A - Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Analysis Set (SAF): The SAF was defined as all randomized patients receiving SoC and/or at least one dose of L-CsA, independently of the treatment allocation at randomization. Independently of the treatment allocation at randomization, patients were analyzed according to the treatment they actually received. All safety and tolerability data were summarized and analyzed using the SAF.	
Subject analysis set title	Group A - Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description: Per Protocol Set (PPS): The PPS was defined as all patients included in the FAS <ul style="list-style-type: none">• who completed randomized treatment as scheduled or who were withdrawn prematurely due to lack of efficacy or lack of tolerability of the clinical trial treatment, and• for whom no major PDs interfering with the assessment of treatment efficacy were observed.	
Subject analysis set title	Group B - Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS): The FAS was defined as all randomized patients. Patients were analyzed according to the treatment group to which they were randomized. All primary, secondary and exploratory endpoints were performed using the FAS, unless otherwise specified.

Subject analysis set title	Group B - Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Analysis Set (SAF): The SAF was defined as all randomized patients receiving SoC and/or at least one dose of L-CsA, independently of the treatment allocation at randomization. Independently of the treatment allocation at randomization, patients were analyzed according to the treatment they actually received. All safety and tolerability data were summarized and analyzed using the SAF.

Subject analysis set title	Group B - Per protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

Per Protocol Set (PPS): The PPS was defined as all patients included in the FAS

- who completed randomized treatment as scheduled or who were withdrawn prematurely due to lack of efficacy or lack of tolerability of the clinical trial treatment, and
- for whom no major PDs interfering with the assessment of treatment efficacy were observed.

Reporting group values	Group A - Full analysis set	Group A - Safety analysis set	Group A - Per protocol set
Number of subjects	84	84	46
Age categorical Units: Subjects			
Adults 18-64	58	58	
Adults 65-85	26	26	
Age continuous Units: years			
arithmetic mean	56.5	56.5	54.7
standard deviation	± 12.69	± 12.69	± 12.68
Gender categorical Units: Subjects			
Female	34	34	18
Male	50	50	28

Reporting group values	Group B - Full analysis set	Group B - Safety analysis set	Group B - Per protocol set
Number of subjects	85	85	70
Age categorical Units: Subjects			
Adults 18-64	64	64	
Adults 65-85	21	21	
Age continuous Units: years			
arithmetic mean	56.2	56.2	56.4
standard deviation	± 10.82	± 10.82	± 10.09
Gender categorical Units: Subjects			
Female	42	42	35
Male	43	43	35

End points

End points reporting groups

Reporting group title	Group A
Reporting group description: L-CsA 10 mg/2.5 mL twice daily for 48 weeks Plus Standard of Care Therapy	
Reporting group title	Group B
Reporting group description: Standard of Care alone (as directed by treating physician)	
Subject analysis set title	Group A - Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The FAS was defined as all randomized patients. Patients were analyzed according to the treatment group to which they were randomized.	
Subject analysis set title	Group A - Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Analysis Set (SAF): The SAF was defined as all randomized patients receiving SoC and/or at least one dose of L-CsA, independently of the treatment allocation at randomization. Independently of the treatment allocation at randomization, patients were analyzed according to the treatment they actually received. All safety and tolerability data were summarized and analyzed using the SAF.	
Subject analysis set title	Group A - Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description: Per Protocol Set (PPS): The PPS was defined as all patients included in the FAS <ul style="list-style-type: none">• who completed randomized treatment as scheduled or who were withdrawn prematurely due to lack of efficacy or lack of tolerability of the clinical trial treatment, and• for whom no major PDs interfering with the assessment of treatment efficacy were observed.	
Subject analysis set title	Group B - Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: Full Analysis Set (FAS): The FAS was defined as all randomized patients. Patients were analyzed according to the treatment group to which they were randomized. All primary, secondary and exploratory endpoints were performed using the FAS, unless otherwise specified.	
Subject analysis set title	Group B - Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Analysis Set (SAF): The SAF was defined as all randomized patients receiving SoC and/or at least one dose of L-CsA, independently of the treatment allocation at randomization. Independently of the treatment allocation at randomization, patients were analyzed according to the treatment they actually received. All safety and tolerability data were summarized and analyzed using the SAF.	
Subject analysis set title	Group B - Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description: Per Protocol Set (PPS): The PPS was defined as all patients included in the FAS <ul style="list-style-type: none">• who completed randomized treatment as scheduled or who were withdrawn prematurely due to lack of efficacy or lack of tolerability of the clinical trial treatment, and• for whom no major PDs interfering with the assessment of treatment efficacy were observed.	

Primary: Mean change in FEV1 (mL) from baseline to Week 48.

End point title	Mean change in FEV1 (mL) from baseline to Week 48.
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End point description:

FEV1 is the Forced Expiratory Volume in One Second.

The FEV1 data collected from the on-site COMPACTTM spirometer were to be considered primary, while data collected with the In2itiveTM home spirometer were to be used for supportive analyses.

End point type	Primary
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End point timeframe:

Week 48

End point values	Group A - Full analysis set	Group B - Full analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	80		
Units: mL				
least squares mean (standard error)	-0.096 (\pm 0.1120)	-0.067 (\pm 0.1147)		

Statistical analyses

Statistical analysis title	Group A vs Group B
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Statistical analysis description:

V9 - week 48

Comparison groups	Group A - Full analysis set v Group B - Full analysis set
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Number of subjects included in analysis	144
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Analysis specification	Pre-specified
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Analysis type	superiority ^[1]
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P-value	= 0.6639 ^[2]
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Method	Mixed models analysis
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Parameter estimate	least square mean difference
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Point estimate	-0.028
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-0.16
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upper limit	0.104
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Notes:

[1] - Estimates are from a Linear Mixed Model on the response variable change from baseline in FEV1 with factors for time splines, treatment, the interactions of time splines by treatment, baseline FEV1, the interactions of time splines with baseline FEV1, region (North America vs all other countries together), age (<55 versus \geq 55 years), use of azithromycin at randomization, and time as random effect.

[2] - This is a 1-side p value.

Secondary: Count of Participants With at Least One Adverse Event (AE)

End point title	Count of Participants With at Least One Adverse Event (AE)
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End point description:

An untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine.

End point type	Secondary
End point timeframe:	
Baseline through study completion (52 weeks)	

End point values	Group A - Safety analysis set	Group B - Safety analysis set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	85		
Units: partecipanti				
with any TEAE	73	77		
with any TEAE Leading to discontinuation of study	12	0		
with any TEAE Leading to study discontinuation	5	3		
with any TEAE Leading to death	2	4		
with any TEAE mild	66	68		
with any TEAE moderate	50	56		
with any TEAE severe	21	18		
with any study treatment-related TEAE	39	0		
with any serious TEAE	46	44		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline throughout the study, till week 52.

Adverse event reporting additional description:

Serious TEAEs by System Organ Class and Preferred Term Reported by at Least 2 Patients Overall while non serious adverse events are reported with a 0% threshold.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Group A - SAF
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Reporting group description:

L-CsA 10 mg/2.5 mL twice daily for 48 weeks

Plus Standard of Care Therapy

Reporting group title	Group B - SAF
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Reporting group description:

Standard of Care alone (as directed by treating physician)

Serious adverse events	Group A - SAF	Group B - SAF	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 84 (54.76%)	44 / 85 (51.76%)	
number of deaths (all causes)	2	4	
number of deaths resulting from adverse events	2	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bowen's disease			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Multiple organ dysfunction syndrome			

subjects affected / exposed	2 / 84 (2.38%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Transplant rejection			
subjects affected / exposed	2 / 84 (2.38%)	2 / 85 (2.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 84 (2.38%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 84 (2.38%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 84 (2.38%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	2 / 84 (2.38%)	3 / 85 (3.53%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	1 / 1	0 / 1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 84 (5.95%)	2 / 85 (2.35%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	23 / 84 (27.38%)	21 / 85 (24.71%)	
occurrences causally related to treatment / all	2 / 23	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	5 / 84 (5.95%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 84 (3.57%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 84 (3.57%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prainfluenzae virus infection			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 84 (3.57%)	3 / 85 (3.53%)	
occurrences causally related to treatment / all	1 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	

Urinary tract infection			
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Group A - SAF	Group B - SAF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 84 (86.90%)	77 / 85 (90.59%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences (all)	1	1	
Bowen's disease			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences (all)	1	4	
Colon adenoma			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Haemangioma of skin			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Malignant melanoma			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Melanocytic naevus			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Metastases to salivary gland			

subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Prostate cancer			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Seborrhoeic keratosis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Skin cancer			
subjects affected / exposed	1 / 84 (1.19%)	2 / 85 (2.35%)	
occurrences (all)	1	2	
Skin papilloma			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences (all)	1	1	
Skin squamous cell carcinoma recurrent			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	2	0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 84 (0.00%)	3 / 85 (3.53%)	
occurrences (all)	0	3	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 84 (2.38%)	1 / 85 (1.18%)	
occurrences (all)	2	1	
Transitional cell carcinoma			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Vascular disorders			
Flushing			

subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	2 / 84 (2.38%)	4 / 85 (4.71%)	
occurrences (all)	2	4	
Hypotension			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences (all)	1	1	
Orthostatic hypotension			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Thrombophlebitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Disease progression			
subjects affected / exposed	16 / 84 (19.05%)	15 / 85 (17.65%)	
occurrences (all)	18	20	
Early satiety			

subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	5 / 84 (5.95%)	2 / 85 (2.35%)	
occurrences (all)	5	2	
Impaired healing			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences (all)	1	1	
Medical device site pain			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 84 (2.38%)	0 / 85 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	7 / 84 (8.33%)	7 / 85 (8.24%)	
occurrences (all)	8	7	
Peripheral swelling			
subjects affected / exposed	2 / 84 (2.38%)	0 / 85 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	4 / 84 (4.76%)	0 / 85 (0.00%)	
occurrences (all)	7	0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences (all)	1	1	

Transplant rejection subjects affected / exposed occurrences (all)	2 / 84 (2.38%) 2	3 / 85 (3.53%) 3	
Reproductive system and breast disorders			
Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Erectile dysfunction subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Prostatomegaly subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Respiratory, thoracic and mediastinal disorders			
Increased bronchial secretion subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Acute respiratory failure subjects affected / exposed occurrences (all)	2 / 84 (2.38%) 3	1 / 85 (1.18%) 1	
Aspiration subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Bronchospasm subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Bronchostenosis subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Cough subjects affected / exposed occurrences (all)	19 / 84 (22.62%) 20	7 / 85 (8.24%) 8	
Dry throat			

subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Dyspnoea		
subjects affected / exposed	9 / 84 (10.71%)	5 / 85 (5.88%)
occurrences (all)	11	6
Dyspnoea exertional		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Epistaxis		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Hypoxia		
subjects affected / exposed	2 / 84 (2.38%)	1 / 85 (1.18%)
occurrences (all)	2	1
Larynx irritation		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Nasal disorders		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Oropharyngeal pain		
subjects affected / exposed	2 / 84 (2.38%)	1 / 85 (1.18%)
occurrences (all)	2	1
Pleural effusion		
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	3
Pneumonia aspiration		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Pneumothorax		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Productive cough		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Pulmonary congestion		

subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Pulmonary embolism		
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	2
Pulmonary mass		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Pulmonary oedema		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Respiratory failure		
subjects affected / exposed	2 / 84 (2.38%)	3 / 85 (3.53%)
occurrences (all)	2	4
Respiratory tract congestion		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Respiratory tract irritation		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Rhinitis allergic		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Rhinorrhoea		
subjects affected / exposed	3 / 84 (3.57%)	4 / 85 (4.71%)
occurrences (all)	3	4
Sinus congestion		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Sleep apnoea syndrome		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Sneezing		
subjects affected / exposed	1 / 84 (1.19%)	2 / 85 (2.35%)
occurrences (all)	1	2
Sputum discoloured		

subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences (all)	1	1	
Throat clearing			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Throat irritation			
subjects affected / exposed	9 / 84 (10.71%)	0 / 85 (0.00%)	
occurrences (all)	9	0	
Upper respiratory tract irritation			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	3 / 84 (3.57%)	1 / 85 (1.18%)	
occurrences (all)	3	1	
Oropharyngeal discomfort			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)	
occurrences (all)	0	2	
Depressed mood			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 84 (1.19%)	2 / 85 (2.35%)	
occurrences (all)	1	2	
Panic attack			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Suicidal ideation			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	

Investigations			
Actinomyces test positive			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Blood bilirubin increased			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Blood phosphorus decreased			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Blood potassium decreased			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Breath sounds abnormal			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Bronchoscopy			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences (all)	1	1	
Cardiac murmur			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Drug level increased			

subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Eosinophil count decreased		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Forced expiratory volume abnormal		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Forced expiratory volume decreased		
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	2
Fungal test positive		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Gamma-glutamyltransferase increased		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Haematocrit decreased		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Haemoglobin decreased		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Haptoglobin increased		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	2	0
Hepatic enzyme increased		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Liver function test increased		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Lymphocyte count decreased		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0

Monocyte count increased subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 2	0 / 85 (0.00%) 0	
Neutrophil count increased subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 2	0 / 85 (0.00%) 0	
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
SARS-CoV-2 test positive subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Transaminases increased subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	2 / 85 (2.35%) 2	
Troponin increased subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Vitamin D increased subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Weight decreased subjects affected / exposed occurrences (all)	3 / 84 (3.57%) 3	2 / 85 (2.35%) 2	
White blood cell count increased subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 2	0 / 85 (0.00%) 0	
Injury, poisoning and procedural complications			
Ankle fracture subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Breast injury subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Contusion			

subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Fall		
subjects affected / exposed	2 / 84 (2.38%)	1 / 85 (1.18%)
occurrences (all)	2	1
Femur fracture		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Gastrointestinal procedural complication		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Heat exhaustion		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Humerus fracture		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Injury		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Ligament sprain		
subjects affected / exposed	1 / 84 (1.19%)	2 / 85 (2.35%)
occurrences (all)	1	2
Limb injury		
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	2
Muscle injury		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Pelvic fracture		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Periorbital haematoma		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1

Post procedural diarrhoea		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Post procedural haematoma		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Post procedural haemorrhage		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Post-traumatic pain		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Procedural pain		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	2	0
Seroma		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Skin abrasion		
subjects affected / exposed	2 / 84 (2.38%)	0 / 85 (0.00%)
occurrences (all)	2	0
Skin laceration		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Spinal compression fracture		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Toxicity to various agents		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Traumatic haematoma		
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	2
Ulna fracture		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1

Upper limb fracture subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Wound subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Wrist fracture subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Muscle strain subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	1 / 85 (1.18%) 1	
Post procedural complications subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Congenital, familial and genetic disorders Alpha-1 antitrypsin deficiency subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Cardiac disorders Acute myocardial infarction subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Angina pectoris subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	2 / 85 (2.35%) 2	
Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	2 / 85 (2.35%) 2	
Atrial flutter subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Cardiac arrest subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Cardiac failure			

subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	2	0	
Cardiac failure congestive			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Extrasystoles			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Myocarditis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Pericarditis constrictive			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)	
occurrences (all)	0	2	
Tricuspid valve incompetence			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	3 / 84 (3.57%)	0 / 85 (0.00%)	
occurrences (all)	4	0	
Headache			
subjects affected / exposed	8 / 84 (9.52%)	0 / 85 (0.00%)	
occurrences (all)	8	0	

Hypoaesthesia		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Hyposmia		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Lethargy		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Loss of consciousness		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Neuropathy perypheral		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Orthostatic intolerance		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	2
Paraesthesia		
subjects affected / exposed	2 / 84 (2.38%)	0 / 85 (0.00%)
occurrences (all)	2	0
Sciatica		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Seizure		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Sensory loss		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Tremor		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Trigeminal neuralgia		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1

Visual field defect subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	2 / 85 (2.35%) 3	
Anaemia macrocytic subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Hypochromic anaemia subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	3 / 85 (3.53%) 3	
Iron deficiency anaemia subjects affected / exposed occurrences (all)	2 / 84 (2.38%) 2	1 / 85 (1.18%) 1	
Leukocytosis subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Leukopenia subjects affected / exposed occurrences (all)	2 / 84 (2.38%) 2	1 / 85 (1.18%) 1	
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Lymphopenia subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	1 / 85 (1.18%) 1	
Microangiopathic haemolytic anaemia subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Neutropenia subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Neutrophilia			

subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	2 / 85 (2.35%) 2	
Thrombotic microangiopathy subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Eye disorders Cataract subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 2	
Dry eye subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Ocular hyperaemia subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Vision blurred subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Visual impairment subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Abdominal distension subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	2 / 85 (2.35%) 2	
Abdominal pain			

subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Abdominal pain upper		
subjects affected / exposed	1 / 84 (1.19%)	2 / 85 (2.35%)
occurrences (all)	1	2
Abdominal strangulated hernia		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Barret's oesophagus		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Colitis		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Constipation		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Diarrhoea		
subjects affected / exposed	8 / 84 (9.52%)	6 / 85 (7.06%)
occurrences (all)	11	6
Diverticular perforation		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Dyspepsia		
subjects affected / exposed	2 / 84 (2.38%)	1 / 85 (1.18%)
occurrences (all)	2	1
Gastritis		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Gastroesophageal reflux disease		
subjects affected / exposed	1 / 84 (1.19%)	4 / 85 (4.71%)
occurrences (all)	1	4
Haematochezia		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Hiatus hernia		

subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Leukoplakia oral			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	3 / 84 (3.57%)	3 / 85 (3.53%)	
occurrences (all)	3	3	
Pancreatitis acute			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Retching			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Tongue discomfort			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	3 / 84 (3.57%)	1 / 85 (1.18%)	
occurrences (all)	3	1	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 84 (1.19%)	2 / 85 (2.35%)	
occurrences (all)	1	5	
Decubitus ulcer			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Erythema			

subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences (all)	1	1	
Hand dermatitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Onychoclasia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Pain of skin			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Precancerous skin lesion			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	2 / 84 (2.38%)	0 / 85 (0.00%)	
occurrences (all)	2	0	
Scab			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Skin lesion			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 84 (7.14%)	4 / 85 (4.71%)	
occurrences (all)	6	4	
Azotaemia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Chronic kidney disease			
subjects affected / exposed	3 / 84 (3.57%)	0 / 85 (0.00%)	
occurrences (all)	3	0	

Hypertonic bladder subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Proteinuria subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Renal disorder subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Renal failure subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	3 / 85 (3.53%) 4	
Renal impairment subjects affected / exposed occurrences (all)	4 / 84 (4.76%) 4	1 / 85 (1.18%) 1	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Back pain subjects affected / exposed occurrences (all)	3 / 84 (3.57%) 3	4 / 85 (4.71%) 5	
Foot deformity subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Intervertebral disc protusion subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Joint swelling subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Muscle contracture subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0	1 / 85 (1.18%) 1	
Muscle spasms			

subjects affected / exposed	2 / 84 (2.38%)	1 / 85 (1.18%)	
occurrences (all)	2	1	
Muscular weakness			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Osteoporotic fracture			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	3 / 84 (3.57%)	0 / 85 (0.00%)	
occurrences (all)	3	0	
Rhabdomyolysis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Rheumatoid arthritis			
subjects affected / exposed	2 / 84 (2.38%)	0 / 85 (0.00%)	
occurrences (all)	2	0	
Tendonitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Bacterial disease carrier			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Bacteriuria			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	

Bordetella infection		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	2
Bronchitis		
subjects affected / exposed	8 / 84 (9.52%)	5 / 85 (5.88%)
occurrences (all)	9	6
Bronchitis bacterial		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	2
COVID-19		
subjects affected / exposed	23 / 84 (27.38%)	21 / 85 (24.71%)
occurrences (all)	23	23
COVID-19 pneumonia		
subjects affected / exposed	5 / 84 (5.95%)	1 / 85 (1.18%)
occurrences (all)	5	1
Candida infection		
subjects affected / exposed	1 / 84 (1.19%)	2 / 85 (2.35%)
occurrences (all)	1	2
Cellulitis		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Chronic sinusitis		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Clostridium colitis		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Clostridium difficile infection		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Cystitis		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Cytomegalovirus infection		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1

Diverticulitis		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Enterovirus infection		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Fungal infection		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Gastroenteritis		
subjects affected / exposed	5 / 84 (5.95%)	1 / 85 (1.18%)
occurrences (all)	5	1
Gastroenteritis infection		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Gastroenteritis norovirus		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Gastroenteritis viral		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Gastroenteritis viral infection		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Genital herpes		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
H1N1 influenza		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Hepatitis E		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Herpes zoster		
subjects affected / exposed	3 / 84 (3.57%)	4 / 85 (4.71%)
occurrences (all)	3	4

Herpes simplex		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Influenza		
subjects affected / exposed	3 / 84 (3.57%)	1 / 85 (1.18%)
occurrences (all)	3	1
Large intestine infection		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Localised infection		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Lower respiratory tract infection		
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	2
Lower respiratory tract infection fungal		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Metapneumovirus infection		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Nasopharyngitis		
subjects affected / exposed	6 / 84 (7.14%)	8 / 85 (9.41%)
occurrences (all)	7	9
Oral candidiasis		
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	2
Oral herpes		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Parainfluenzae virus infection		
subjects affected / exposed	1 / 84 (1.19%)	3 / 85 (3.53%)
occurrences (all)	1	4
Pharyngitis		

subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	2
Pneumonia		
subjects affected / exposed	4 / 84 (4.76%)	4 / 85 (4.71%)
occurrences (all)	4	7
Pneumonia bacterial		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Pneumonia pseudomonal		
subjects affected / exposed	2 / 84 (2.38%)	0 / 85 (0.00%)
occurrences (all)	2	0
Pseudomonas bronchitis		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Pseudomonas infection		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Pustule		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	2	0
Respiratory syncytial virus infection		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Respiratory tract infection		
subjects affected / exposed	2 / 84 (2.38%)	3 / 85 (3.53%)
occurrences (all)	2	3
Respiratory tract infection bacterial		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Respiratory tract infection viral		
subjects affected / exposed	2 / 84 (2.38%)	1 / 85 (1.18%)
occurrences (all)	2	1
Rhinitis		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Rhinovirus infection		

subjects affected / exposed	1 / 84 (1.19%)	4 / 85 (4.71%)
occurrences (all)	1	5
Septic shock		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Sinusitis		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Superinfection bacterial		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Tinea pedis		
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)
occurrences (all)	1	0
Tooth infection		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Upper respiratory tract infection		
subjects affected / exposed	4 / 84 (4.76%)	5 / 85 (5.88%)
occurrences (all)	6	5
Urinary tract infection		
subjects affected / exposed	4 / 84 (4.76%)	4 / 85 (4.71%)
occurrences (all)	4	5
Urinary tract infection bacterial		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Viral infection		
subjects affected / exposed	2 / 84 (2.38%)	0 / 85 (0.00%)
occurrences (all)	2	0
Viral upper respiratory tract infection		
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)
occurrences (all)	1	1
Clostridium difficile colitis		
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Cytomegalovirus colitis		

subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1	0 / 85 (0.00%) 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 84 (2.38%)	1 / 85 (1.18%)	
occurrences (all)	2	1	
Dehydration			
subjects affected / exposed	2 / 84 (2.38%)	2 / 85 (2.35%)	
occurrences (all)	2	2	
Diabetes mellitus			
subjects affected / exposed	0 / 84 (0.00%)	2 / 85 (2.35%)	
occurrences (all)	0	2	
Dyslipidaemia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Electrolyte imbalance			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Fluid overload			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Gout			
subjects affected / exposed	1 / 84 (1.19%)	2 / 85 (2.35%)	
occurrences (all)	1	2	
Hypercholesterolaemia			
subjects affected / exposed	2 / 84 (2.38%)	2 / 85 (2.35%)	
occurrences (all)	2	2	
Hyperglycaemia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	4 / 84 (4.76%)	1 / 85 (1.18%)	
occurrences (all)	4	2	
Hypoproteinaemia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	

Hyperuricaemia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Hypervoleamia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	4 / 84 (4.76%)	2 / 85 (2.35%)	
occurrences (all)	5	2	
Hypomagnesaemia			
subjects affected / exposed	1 / 84 (1.19%)	2 / 85 (2.35%)	
occurrences (all)	1	2	
Iron deficiency			
subjects affected / exposed	0 / 84 (0.00%)	3 / 85 (3.53%)	
occurrences (all)	0	4	
Steroid diabetes			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 84 (1.19%)	1 / 85 (1.18%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2019	Amendment 1 has been issued to review the Eligibility Criteria, Treatment of Patients, Assessment of Efficacy and Safety, Visits Schedule and Statistical considerations. This amendment had considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.
09 June 2020	Amendment 2 has been issued to add the COVID-19 related measures in order to ensure patient safety and efficacy data collection in case a given on-site visits cannot take place due to COVID-19 outbreak, including the possibility to perform remote visits, to carry out spirometry examination at patient home and the IMP re-supply at patient home. Furthermore the Eligibility Criteria have been reviewed. The amendment had considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union
19 January 2021	Amendment 3 has been issued to include the Sponsorship change and to revise the Eligibility Criteria to ensure that the study population is aligned with the most recent criteria for CLAD-BOS (Chronic Lung Allograft Dysfunction - Bronchiolitis Obliterans Syndrome) stages. Furthermore Statistical sections have been modified according to the FDA Written Response Only discussions (type C meeting) and the EMA guidelines on clinical trial conducted during the COVID-19 contingency was added. This amendment had considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.
28 October 2022	Amendment 4 has been issued to accomplish with FDA recommendations received during last interactions (WRO) to continue BOSTON-1 and BOSTON-2 enrolment to achieve the originally planned total number of 220 patients for both clinical trials combined, to ensure the adequacy of the safety database and to implement the efforts to minimize missing data in both studies. This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. The main changes are related to the Sample Size re-estimation to accomplish with the FDA recommendation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

No limitations or caveats are applicable to this summary of results.

Notes: