Clinical trial results:
A Phase IIa Multi-Center, Randomized, Single-Blind Safety Study of Liposomal Cyclosporine A to Treat Bronchiolitis Obliterans Syndrome Following Allogeneic Hematopoietic Stem Cell Transplantation.

Summary

EudraCT number	2019-000718-13
Trial protocol	DE ES FR
Global end of trial date	16 June 2022

Results information

Result version number	v1 (current)
This version publication date	05 July 2023
First version publication date	05 July 2023
Summary attachment (see zip file)	Boston 4 - Termination Letter (Boston 4 - Termination Letter_Final.pdf)

Trial information

Trial identification

Sponsor protocol code	BT–L-CsA–201–SCT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04107675
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zambon S.p.A.
Sponsor organisation address	Via Lillo del Duca, 10 , Bresso, Milan, Italy, 20091
Public contact	Sponsor Contact Point, Zambon SpA, Zambon S.p.A., +39 02 66524513, clinicaltrials@zambongroup.com
Scientific contact	Sponsor Contact Point, Zambon SpA, Zambon S.p.A., +39 02 66524513, 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	15 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 June 2022
Global end of trial reached?	Yes
Global end of trial date	16 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the tolerability and safety, of two dose levels of aerosolized L-CsA vs placebo in addition to SoC therapy for the treatment of BOS in adult allo-HSCT recipients.
The secondary objectives of this study are to assess PK and exploratory efficacy and quality of life of two dose levels of aerosolized L-CsA vs placebo in addition to SoC therapy for BOS in adult allo-HSCT recipients.

Protection of trial subjects:

This study was conducted in compliance with the protocol and amendments approved by the appropriate EC and health authorities, according to International Committee for Harmonisation and applicable good clinical practice standards, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

Background therapy:

Standard of care (SoC). SoC included prophylaxis against common opportunistic infections, immunosuppression, and any other chronic medication.

Evidence for comparator: -

Actual start date of recruitment	11 February 2020
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	Spain: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	6
EEA total number of subjects	6

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

At the time of the premature termination of this study, a total of 11 patients were screened for the study, of whom 5 patients did not fulfil the inclusion criteria and 6 patients were randomized into 3 treatment groups (L-CsA 10 mg + SoC, L-CsA 5 mg + SoC, or placebo + SoC).

Pre-assignment

Screening details:

With low patient recruitment, the BOSTON-4 safety and tolerability study was terminated early by the sponsor on 18 March 2022. This decision was made after a careful and due diligent analysis performed by Zambon of the study status and considering the impact of coronavirus disease 2019 (COVID-19) pandemic on sites activities.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

This was a single-blind trial. Due to the different appearance of the 3 tested strengths of IMP, a full blinding of the study was not possible. Only the randomized study patients were blinded to study treatment assignment. The members of the DMC were unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	L-CsA 10 mg + SoC

Arm description:

Liposomal Cyclosporine A 10 mg (10 mg/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.

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

Dosage and administration details:

Liposomal Cyclosporine A is administered at 10 mg bid with a new technology of nebulizing liquid drugs, creating an aerosol with a low ballistic momentum and a high percentage of droplets in a respirable size range of 3-5 µm. The inhalations were scheduled to be taken approximately 12 hours (but not less than 6 hours) apart, eg, at 08:00 and 20:00 each day. Nebulization time per inhalation dose was approximately 8 to 13 minutes for the 0- and 10-mg doses.

Arm title	L-CsA 5 mg + SoC

Arm description:

Liposomal Cyclosporine A 10 mg (10 mg/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.

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

Dosage and administration details:

Liposomal Cyclosporine A is administered at 5 mg bid with a new technology of nebulizing liquid drugs, creating an aerosol with a low ballistic momentum and a high percentage of droplets in a respirable size range of 3-5 µm. The inhalations were scheduled to be taken approximately 12 hours (but not less than 6 hours) apart, eg, at 08:00 and 20:00 each day. Nebulization time per inhalation dose was approximately 8 to 13 minutes for the 0- and 10-mg doses.

Arm title	Liposomal Placebo + SoC

Arm description:

Liposomal Placebo 2.5 mg (0 mg L-CsA/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Liposomal placebo
Investigational medicinal product code	placebo
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Liposomal placebo is administered with the same new technology of nebulizing liquid drugs used for L-CsA, creating an aerosol with a low ballistic momentum and a high percentage of droplets in a respirable size range of 3-5 µm. The inhalations were scheduled to be taken approximately 12 hours (but not less than 6 hours) apart, eg, at 08:00 and 20:00 each day. Nebulization time per inhalation dose was approximately 8 to 13 minutes for the 0- and 10-mg doses.

Number of subjects in period 1	L-CsA 10 mg + SoC	L-CsA 5 mg + SoC	Liposomal Placebo + SoC
Started	2	2	2
Completed	2	2	2

Baseline characteristics

Reporting groups	
Reporting group title	L-CsA 10 mg + SoC
Reporting group description:	
Liposomal Cyclosporine A 10 mg (10 mg/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.	

Reporting group title	L-CsA 5 mg + SoC
Reporting group description:	
Liposomal Cyclosporine A 10 mg (10 mg/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.	
Reporting group title	Liposomal Placebo + SoC
Reporting group description:	
Liposomal Placebo 2.5 mg (0 mg L-CsA/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.	

Reporting group values	L-CsA 10 mg + SoC	L-CsA 5 mg + SoC	Liposomal Placebo + SoC
Number of subjects	2	2	2
Age categorical Units: Subjects			
Adults (18-64 years)	2	2	2
Age continuous Units: years			
arithmetic mean	55.5	63.0	46
standard deviation	± 0.71	± 0.00	± 12.73
Gender categorical Units: Subjects			
Female	0	2	1
Male	2	0	1

Reporting group values	Total		
Number of subjects	6		
Age categorical Units: Subjects			
Adults (18-64 years)	6		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	3		
Male	3		

End points

End points reporting groups

Reporting group title	L-CsA 10 mg + SoC
Reporting group description:	
Liposomal Cyclosporine A 10 mg (10 mg/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.	

Reporting group title	L-CsA 5 mg + SoC
Reporting group description:	
Liposomal Cyclosporine A 10 mg (10 mg/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.	
Reporting group title	Liposomal Placebo + SoC
Reporting group description:	
Liposomal Placebo 2.5 mg (0 mg L-CsA/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.	

Primary: Number of Local Tolerability Events of Interest From Baseline to Visit 3 (week 4)

End point title	Number of Local Tolerability Events of Interest From Baseline to Visit 3 (week 4)[1]
End point description:	
The local tolerability events of interest taken into consideration were: Cough, Wheezing, Bronchospasm, Throat irritation and Change from baseline in FEV1 to Visit 3.	
End point type	Primary
End point timeframe:	
at Week 4 (visit 3)	

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 are possible with only 2 subjects per arm.

End point values	L-CsA 10 mg + SoC	L-CsA 5 mg + SoC	Liposomal Placebo + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	2	
Units: Number of Local Tolerability Events				
Any Local Tolerability Event	1	5	4	
Cough	0	1	1	
Wheezing	0	0	0	
Bronchospasm	0	0	0	
Throat irritation	1	3	2	
Change in FEV1	0	1	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With AE and sAE of Different Level of Severity During the First 4 Weeks of Treatment

End point title	Number of Participants With AE and sAE of Different Level of Severity During the First 4 Weeks of Treatment[2]

End point description:

An adverse event (AE) is any untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
A serious adverse event is an adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect.

End point type	Primary

End point timeframe:

During the first 4 weeks of treatment

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 are possible with only 2 subjects per arm.

End point values	L-CsA 10 mg + SoC	L-CsA 5 mg + SoC	Liposomal Placebo + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	2	
Units: Number of participants with AE and sAE				
Any TEAEs	1	1	1	
Mild TEAEs	1	1	1	
Moderate TEAEs	0	0	0	
Severe TEAEs	0	0	0	
Serious TEAEs	0	0	0	
Related TEAEs	1	1	1	
COVID-19 related TEAEs	0	0	0	
Patients discontinued study due to TEAEs	0	0	0	
Patients discontinued treatment due to TEAEs	0	0	0	
TEAEs Leading to Death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Local Tolerability Events of Interest from baseline to week 12

End point title	Number of Local Tolerability Events of Interest from baseline to week 12

End point description:

The local tolerability events of interest taken into consideration were: Cough, Wheezing, Bronchospasm, Throat irritation and Change from baseline in FEV1 to Visit 3.

End point type	Secondary

End point timeframe:

at Week 12

End point values	L-CsA 10 mg + SoC	L-CsA 5 mg + SoC	Liposomal Placebo + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	2	
Units: Number of Local Tolerability Events				
Any Local Tolerability Event	1	7	6	
Cough	0	2	2	
Wheezing	0	0	0	
Bronchospasm	0	0	0	
Throat irritation	1	4	3	
Change in FEV1	0	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With AE and sAE of Different Level of Severity During the First 12 Weeks of Treatment

End point title	Number of Participants With AE and sAE of Different Level of Severity During the First 12 Weeks of Treatment

End point description:

An adverse event (AE) is any untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
A serious adverse event is an adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect.

End point type	Secondary

End point timeframe:

During the first 12 weeks of treatment

End point values	L-CsA 10 mg + SoC	L-CsA 5 mg + SoC	Liposomal Placebo + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	2	
Units: number of participants				
Any TEAEs	2	1	1	
Mild TEAEs	2	1	1	
Moderate TEAEs	1	0	0	
Severe TEAEs	0	0	0	
Serious TEAEs	1	0	0	

Related TEAEs	1	1	1	
COVID-19 related TEAEs	0	0	0	
Patients discontinued study due to TEAEs	0	0	0	
Patients discontinued treatment due to TEAEs	1	0	0	
TEAEs Leading to Death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: CsA Whole Blood Concentrations and CsA Whole Blood Trough Levels

End point title	CsA Whole Blood Concentrations and CsA Whole Blood Trough Levels

End point description:

Whole Blood concentrations (Week 0) are at pre-dose, directly after end of inhalation, 15, 30, and 45 minutes, and 1, 1.5, 2, and 4 hours after end of inhalation, and whole blood trough levels (CsA concentration) at Weeks 2, 4, 8, and 12 were calculated.

End point type	Secondary

End point timeframe:

Weeks 0 (pre-dose, directly after end of inhalation, 15, 30, 45, 60 min, 1.5 h, 2h, 4h), 2, 4, 8, and 12

End point values	L-CsA 10 mg + SoC	L-CsA 5 mg + SoC	Liposomal Placebo + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	2	
Units: ng/ml				
arithmetic mean (standard deviation)				
Week 0 - predose	12.2115 (± 17.26967)	0.0000 (± 0.0000)	11.7750 (± 16.65236)	
Directly after end of inhalation	84.6510 (± 69.82821)	19.3420 (± 15.91980)	12.1760 (± 17.21946)	
15 min	73.5110 (± 59.82123)	30.0500 (± 24.34003)	11.2440 (± 15.90142)	
30 min	68.3640 (± 60.56228)	26.9400 (± 22.19184)	13.1780 (± 18.63651)	
45 min	70.1555 (± 64.88483)	23.2780 (± 18.52761)	13.3145 (± 18.82955)	
1 hour	117.8030 (± 00000)	19.4395 (± 18.15638)	14.0835 (± 19.91708)	
1.5 hour	115.4350 (± 00000)	16.0300 (± 13.34876)	13.0425 (± 18.44488)	
2 hours	67.0700 (± 71.46587)	13.4045 (± 10.80530)	10.9615 (± 15.50190)	
4 hours	33.3425 (± 35.73506)	8.3950 (± 8.09920)	7.6615 (± 10.83500)	
Whole Blood Trough Levels - Week 2	48.6725 (± 64.65148)	4.6365 (± 3.62534)	6.0500 (± 8.55599)	
Whole Blood Trough Levels - Week 4	16.2465 (± 17.33048)	16.8475 (± 21.28745)	6.3000 (± 8.90955)	

Whole Blood Trough Levels - Week 8	18.7280 (± 26.48539)	9.0405 (± 3.16855)	4.9500 (± 7.00036)	
Whole Blood Trough Levels - Week 12	23.0195 (± 32.55449)	0.0000 (± 00000)	4.9500 (± 7.00036)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the complete clinical trial period, i.e. up to week 14 (visit 6 / EoS).	
Adverse event reporting additional description:	
Please note that if a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	L-CsA 10 mg + SoC
Reporting group description:	
Liposomal Cyclosporine A 10 mg (10 mg/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.	
Reporting group title	L-CsA 5 mg + SoC
Reporting group description:	
Liposomal Cyclosporine A 10 mg (10 mg/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.	
Reporting group title	Liposomal Placebo + SoC
Reporting group description:	
Liposomal Placebo 2.5 mg (0 mg L-CsA/2.5 mL) bid, once in the morning and once in the evening, for up to 12 weeks.	

Serious adverse events	L-CsA 10 mg + SoC	L-CsA 5 mg + SoC	Liposomal Placebo + SoC
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
moderate acute respiratory failure			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	L-CsA 10 mg + SoC	L-CsA 5 mg + SoC	Liposomal Placebo + SoC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	1 / 2 (50.00%)	1 / 2 (50.00%)
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	1 / 2 (50.00%)	1 / 2 (50.00%)	1 / 2 (50.00%)
occurrences (all)	1	1	1
Cough			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	1 / 2 (50.00%)
occurrences (all)	0	1	1
Productive cough			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2020	COVID-19 specific considerations were implemented following the sponsor risk-benefit assessment, and the request from French CA, asking to amend the protocol to include actions in response to COVID-19 emergency. The below details were added and clarified, including but not limited to: o Screening and Visits 1, 2 and 5 were mandatory on-site visits while remote visits were possible for other visits due to COVID-19 restrictions. In case the planned on-site visit could not be performed due to COVID-19 restrictions, a remote visit via telephone would be performed to assess any potential AEs and to confirm the patient's status and well-being. o Full amount of assigned IMP would be dispensed during Visit 1 to cover the entire treatment period of 12 weeks to guarantee IMP supply for the patient, in case a site visit could not be performed due to COVID-19 restrictions. IMP availability check was added to be performed at Visit 2 through Visit 5. o Drug accountability check would be performed at Visit 5 only instead of at Visit 2 though Visit 5. o The CGI was specified to be assessed on-site only, as CGI required evaluation of a physician. o COVID-19 related AEs would be reported as SAEs. o Schedule of assessments table was modified accordingly to clarify remove visit activities. • As this was a safety study, an additional investigator's tolerability assessment was added at Visit 5. • Other administrative changes and minor edits were made
30 April 2021	Study title was amended and certain wording in the protocol was changed or added to add clarification and ensure consistency throughout the protocol. • Five inclusion criteria were modified to allow suitable patients to be identified and enrolled in a reasonable period of time. • One exclusion criterion was added to ensure exclusion of other confounding pulmonary diseases. • Two exclusion criteria were deleted as 1 was mentioned elsewhere and 1 was no longer applicable. • "Changes in the dose of corticosteroids and immunosuppressive therapy administered throughout trial duration" was added as an exploratory endpoint. • Wording was added to justify single-blind study scheme. • The concomitant medication section was updated to clarify that patients who had received the vaccination against SARS-CoV-2 were still eligible to participate and those already randomized could continue with clinical study program, and to add further clarification on concurrent treatments included. • Wording was added and changed for clarification as it was decided to evaluate the L-CsA PK measurements centrally only. • Other administrative changes and minor edits were made.

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.

From the beginning of the trial, in December 2019, only 6 pts were enrolled.
Due to the low number of pts recruited and the slow enrollment pace of pts, on 18 March 2022, the sponsor decided to terminate this safety/tolerability trial early.

Notes: