Health Technology Briefing
October 2023

Liposomal cyclosporine A for treating bronchiolitis obliterans syndrome after lung transplant

Company/Developer	Zambon Company SpA

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 6420	NICE TSID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Liposomal cyclosporine A (L-CsA) is currently in clinical development for the treatment of bronchiolitis obliterans syndrome (BOS) following a single or double lung transplant. BOS is a form of rejection in which the immune system causes the airways inside the lungs to become inflamed, which blocks the flow of oxygen through the lungs. BOS typically occurs in the first year after a lung transplant but could occur up to a decade later. Symptoms of BOS include a dry cough, shortness of breath and wheezing. BOS is a debilitating and life-threatening disease, and there remains a need for effective treatments with better tolerability and method of administration.

Liposomal cyclosporine A (L-CsA) is a medicine that is used to suppress the immune system after a transplant. L-CsA works by blocking the activity of proteins known as cyclophilins to trigger an antiviral immune response and prevent infection. L-CsA inhalation offers an improved ease of administration (inhaled into the lungs as a mist) through its eFlow nebuliser system and has been shown to potentially reduce rejections and improve function following a lung transplant. If licensed, L-CsA will offer an effective treatment option for patients with BOS following lung transplantation.

Proposed Indication

Treatment of adults with bronchiolitis obliterans syndrome (BOS) following a single or double lung transplant.[1,2]

Technology

Description

Liposomal cyclosporine A (L-CsA) is an immunophilin inhibitor that is used to prevent graft-versus-host disease after organ transplant. L-CsA works by blocking the peptidyl-prolyl *cis-trans* isomerase activity of cyclophilins mediating diverse cellular processes. L-CsA triggers a potent antiviral immune response by inducing IFN (interferon) regulatory factor 1–dependent IFN-lambda (type III IFN) release, resulting in IFN-stimulated gene–dependent antiviral reprogramming of the lung epithelium and preservation of barrier function.[3]

L-CsA is currently in clinical development for the treatment of BOS following a single or double lung transplant. In the phase III clinical trials (BOSTON-1, NCT03657342; BOSTON-2, NCT03656926), patients are administered, via an eFLow nebuliser, L-CsA 5 mg twice daily plus standard of care for 48 weeks following single lung transplant or 10 mg twice daily plus standard of care for 48 weeks following double lung transplant.[1,2]

Key Innovation

L-CsA inhalation has been shown to potentially reduce rejections and improve function following a lung transplant. The current method of administering cyclosporine A (using a propylene glycol vehicle) is poorly tolerated and requires bronchodilation as well as local anaesthetic drug pre-medication. L-CsA inhalation offers an improved ease of administration through an eFlow nebuliser system. This mode of administration provides excellent tolerability without pre-medication while maintaining high peripheral deposition within short inhalation times.[4] If licensed, L-CsA will offer an alternative treatment option for patients with BOS following lung transplantation.

Regulatory & Development Status

Cyclosporin A does not currently have Marketing Authorisation in the EU/UK for any indication.

L-CsA received an orphan drug designation in the EU in 2017 for the treatment of BOS.[5,6]

L-CsA is not in clinical development for any other indications.

Patient Group

Disease Area and Clinical Need

BOS is a form of rejection in which the immune system causes the airways inside the lungs to become inflamed, which blocks the flow of oxygen through the lungs. When a new organ is transplanted, the body's immune system treats it as a threat and produces antibodies against it, which can stop it from working properly. BOS typically occurs in the first year after a lung transplant but could occur up to a decade later. Symptoms of BOS include a dry cough, shortness of breath and wheezing.[7] Some risk factors for BOS

include noncompliance with medications, primary graft dysfunction, older donor age, Epstein-Barr virus reactivation, and recurrent infection.[8]

The development of BOS is rare within the first year after lung transplant, but the cumulative incidence ranges from 43 to 80% within the first five years of transplantation.[8] In 2021-22, there were 97 lung transplants carried out in England.[9] Based on the cumulative incidence range (43 to 80%), it can be estimated that 42 to 78 patients could develop BOS within the first five years of receiving a lung transplant. As of 2017, BOS affected less than 1 in 10,000 people in the EU.[6] In England, 2022-23, there were 732 finished consultant episodes (FCE) and 500 admissions for other specified chronic obstructive pulmonary disease (ICD-10 code J448) which resulted in 2,231 FCE bed days and 136 day cases.[10]

Recommended Treatment Options
There are currently no NICE recommendations for the treatment of BOS in adults.

Clinical Trial Information	
Trial	**BOSTON 1; NCT03657342; EudraCT 2018-003204-39;** A Phase III Clinical Trial to Demonstrate Efficacy / Safety of Liposomal Cyclosporine A + Standard of Care (SoC) vs SoC Alone in Treating Chronic Lung Allograft Dysfunction / Bronchiolitis Obliterans in Patients Post Single Lung Transplant **Phase III-** Recruiting **Location(s):** 4 EU countries, UK, USA and Israel **Primary completion date:** June 2024
Trial Design	Randomised, parallel assignment
Population	N(estimated)=110; adults aged 18 years or older who received a single lung transplant at least 12 months prior to screening; patients with bronchiolitis obliterans diagnosis
Intervention(s)	L-CsA 5 mg twice daily for 48 weeks (via eFlow device) plus standard of care therapy
Comparator(s)	Standard of care therapy
Outcome(s)	Primary outcome measure: Mean change in FEV1 (mL) from baseline to Week 48 [Time frame: Baseline to Week 48] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**BOSTON-2; NCT03656926; EudraCT 2018-003205-25;** A Phase III Clinical Trial to Demonstrate Efficacy / Safety of Liposomal Cyclosporine A + Standard of Care

	(SoC) vs SoC Alone in Treating Chronic Lung Allograft Dysfunction / Bronchiolitis Obliterans in Patients Post Double Lung Transplant **Phase III**- Recruiting **Location(s):** 5 EU countries, UK, USA and Israel **Primary completion date:** August 2023
Trial Design	Randomised, parallel assignment
Population	N(estimated)=152; adults aged 18 years or older who received a double lung transplant at least 12 months prior to screening; patients with bronchiolitis obliterans diagnosis
Intervention(s)	L-CsA 10 mg twice daily for 48 weeks (via eFlow device) plus standard of care therapy
Comparator(s)	Standard of care therapy
Outcome(s)	Primary outcome measure: Mean change in FEV1 (mL) from baseline to Week 48) [Time frame: Baseline to Week 48] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**BOSTON-3; NCT04039347; EudraCT 2019-002987-29;** A Phase III, Extension Clinical Trial to Demonstrate Efficacy and Safety of Liposomal Cyclosprine A Via the PARI Investigational eFlow Device and SoC in Treating Bronchiolitis Obliterans in Patients Post Single or Double Lung Transplant **Phase III**- Enrolling by invitation **Location(s):** 4 EU countries, USA and Israel **Primary completion date:** September 2024
Trial Design	Non-randomised, parallel assignment, open label
Population	N(estimated)=262; adults aged 18 years or older; patients who have completed all visits through the End of Treatment Visit in either BOSTON-1 or BOSTON-2
Intervention(s)	• L-CsA 5 mg twice daily (via eFlow device) plus standard of care for up to 144 weeks for patients post single lung transplant • L-CsA 10 mg twice daily (via eFlow device) plus standard of care for up to 144 weeks for patients post double lung transplant
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: Mean change in FEV1 from Baseline to Week 24 [Time frame: Baseline to Week 24]

	See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of L-CsA is not yet known.

Relevant Guidance

NICE Guidance

No relevant NICE guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant NHS England guidance identified.

Other Guidance

- International Society for Heart and Lung Transplantation, American Thoracic Society, and European Respiratory Society. Clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. 2014.[11]

Additional Information

Zambon Company SpA did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 Clinicaltrials.gov. *A Phase III Clinical Trial to Demonstrate Efficacy / Safety of Liposomal Cyclosporine A + Standard of Care (SoC) vs SoC Alone in Treating Chronic Lung Allograft Dysfunction / Bronchiolitis Obliterans in Patients Post Single Lung Transplant (BOSTON-1)*. 2018. Available from: https://classic.clinicaltrials.gov/ct2/show/record/NCT03657342 [Accessed 4 September 2023].

2 Clinicaltrials.gov. *A Phase III Clinical Trial to Demonstrate Efficacy / Safety of Liposomal Cyclosporine A + Standard of Care (SoC) vs SoC Alone in Treating Chronic Lung Allograft Dysfunction / Bronchiolitis Obliterans in Patients Post Double Lung Transplant (BOSTON-2)*. 2018. Available from: https://classic.clinicaltrials.gov/ct2/show/record/NCT03656926 [Accessed 4 September 2023].

3 Sauerhering L, Kuznetsova I, Kupke A, Meier L, Halwe S, Rohde C, et al. Cyclosporin A Reveals Potent Antiviral Effects in Preclinical Models of SARS-CoV-2 Infection. *Am J Respir Crit Care Med*. 2022;205(8):964-8. Available from: https://doi.org/10.1164/rccm.202108-1830LE.

4 Neurohr C, Kneidinger N, Ghiani A, Monforte V, Knoop C, Jaksch P, et al. A randomized controlled trial of liposomal cyclosporine A for inhalation in the prevention of bronchiolitis obliterans syndrome following lung transplantation. *American Journal of Transplantation*. 2022;22(1):222-9. Available from: https://doi.org/10.1111/ajt.16858.

5 Zambon. *Zambon Completes Enrollment in Phase 3 Clinical Development Program Evaluating Liposomal Cyclosporine A for Inhalation (L-CsA-i) in Patients with Bronchiolitis Obliterans Syndrome (BOS)*. 2023. Available from: https://www.zambon.com/en/media/press/2023-05-02-zambon-completes-enrollment-phase-3-clinical-development-program-evaluating [Accessed 5 September 2023].

6 European Medicines Agency (EMA). *Public summary of opinion on orphan designation: Ciclosporin for the treatment of bronchiolitis obliterans syndrome*. 2018. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/04/210-public-summary-positive-opinion-orphan-designation-ciclosporin-treatment-bronchiolitis_en.pdf [Accessed 26 September 2023].

7 National Health Service (NHS). *Lung transplant risks: BOS*. 2022. Available from: https://www.nhs.uk/conditions/lung-transplant/risks/ [Accessed 11 September 2023].

8 Hayes D. A review of bronchiolitis obliterans syndrome and therapeutic strategies. *Journal of Cardiothoracic Surgery*. 2011;6(1):92. Available from: https://doi.org/10.1186/1749-8090-6-92.

9 Statista. *Number of Lung Transplants in the United Kingdom in the Year to March 2022*. 2022. Available from: https://www.statista.com/statistics/518774/number-of-lung-transplants-united-kingdom-uk/ [Accessed 16 Ocotber 2023].

10 NHS Digital. *NHS Digital. Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23 [Accessed 17 October 2023].

11 Meyer KC, Raghu G, Verleden GM, Corris PA, Aurora P, Wilson KC, et al. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J*. 2014;44(6):1479-503. Available from: https://doi.org/10.1183/09031936.00107514.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.