Liposomal Cyclosporine A for Inhalation (L-CsA-i) to Treat Bronchiolitis Obliterans Syndrome (BOS): Novel Formulation With Therapeutic Potential for Patients With BOS Following allo-HSCT

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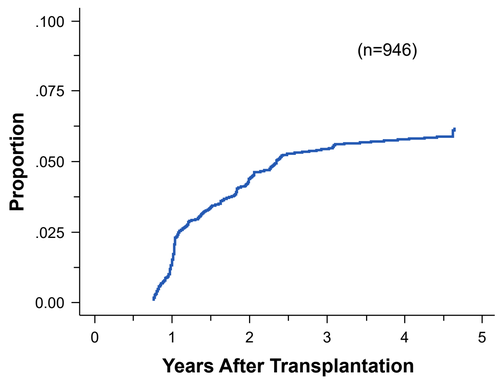
BACKGROUND

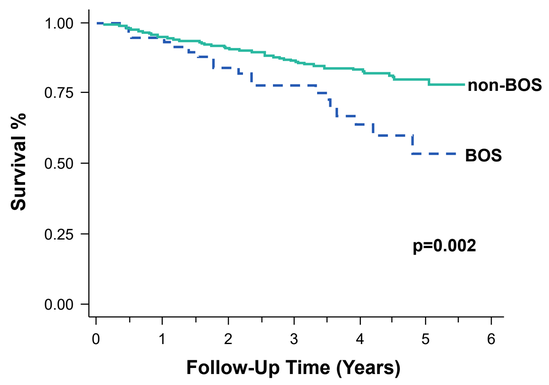
- Bronchiolitis obliterans syndrome (BOS) is a fatal, rapidly progressive lung disease caused by T-cell-mediated inflammation that leads to blockage of the bronchioles, resulting in respiratory failure and death[1,2]
- Approximately 4% to 10% of patients who undergo allogeneic hematopoietic stem cell transplantation (allo-HSCT) will develop BOS[1,3] (**Fig 1**)
  - 72% to 100% develop BOS as a respiratory form of chronic graft-versus-host disease (cGVHD)
  - Median time to BOS diagnosis ranges from 273 to 547 days post-transplant in literature
  - A diagnosis of BOS confers a significant increase in the risk of transplant-related mortality[1,4] (**Fig 2**)

Figure 1. The Overall Prevalence of BOS in Patients With allo-HSCT Has Been Found to Be Between 4% and 10%



Adapted from Au BKC, et al. *Biol Blood Marrow Transplant*. 2011;17:1072-1078.

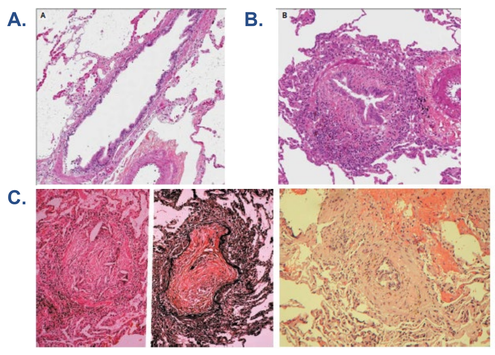
Figure 2. BOS Is Associated With Increased Mortality in Patients With allo-HSCT



Adapted from Au BKC, et al. *Biol Blood Marrow Transplant*. 2011;17:1072-1078.

- The histopathology of BOS after allo-HSCT and lung transplantation (LTx) is identical[2,5,6] (**Fig 3**)

Figure 3. The Histopathology of BOS After allo-HSCT and Lung Transplantation Is Identical



Histopathology of:

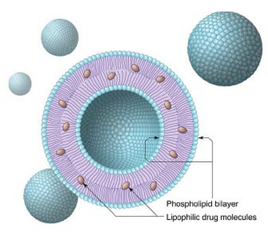
A. Bronchiole of a healthy subject[1]
B. Bronchiole of a BOS patient after LTx[1]

C. Bronchiole of a BOS patient after HSCT[2,3]

1. Barker AF, et al. *N Engl J Med*. 2014;370:1820-1828; 2. Yoshihara S, et al. *Biol Blood Marrow Transplant*. 2007;13:749-759; 3. Afessa B, et al. *Bone Marrow Transplant*. 2001;28:425-434.

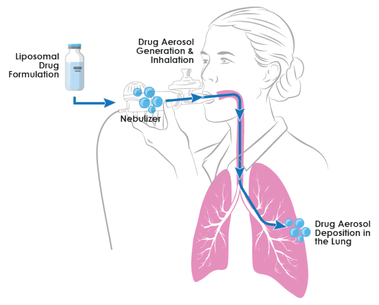
- There is no approved therapy for the treatment or prevention of BOS[7]
- Liposomal Cyclosporine A for inhalation (L-CsA-i) is a true liposome of cyclosporine A designed for inhaled delivery to the lungs (administered via the high-performance PARI eFlow® Nebulizer System) (**Fig 4**)

Figure 4. Breath Therapeutics' Drug-Device Combination Is Designed to Rapidly Deliver High Concentrations of Drugs to the Site of Action in the Lung



Liposomal Cyclosporine A for inhalation (L-CsA-i) is a true liposome of cyclosporine A designed for inhaled delivery to the lungs

The L-CsA-i eFlow® (PARI Pharma GmbH) has been specifically designed for use with Breath Therapeutics' L-CsA-i formulation



The BOSTON program combines L-CsA-i with the high-performance, drug-specific L-CsA-i eFlow® for precise and fast drug delivery into the small airway of the lungs with no or minimal systemic exposure to cyclosporine

- Early studies of L-CsA-i for the prevention of BOS in lung transplant recipients demonstrated clinical benefit[8,9]

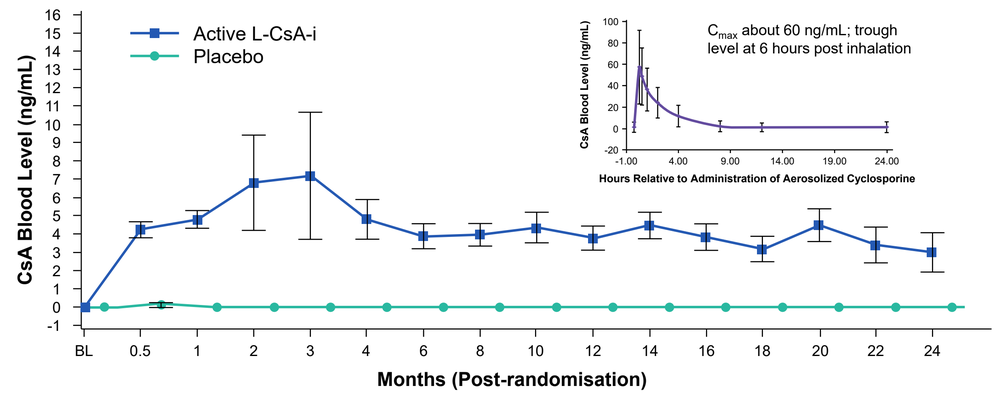
METHODS

- Retrospective review of two clinical studies of L-CsA-i (isotonic, 4 mg/mL) for BOS associated with LTx
  - Patients were randomized to receive L-CsA-i plus standard of care (SOC) vs SOC alone[8], or L-CsA-i plus SOC vs placebo plus SOC[9]
  - Patients in the L-CsA-i arms received either 5 mg (single transplant) or 10 mg (double transplant) bid via inhalation[8,9]
- Blood samples for PK analysis were collected before inhalation and after inhalation, at 15, 30, and 60 mins post dosing and 2, 4, 8, and 12 hrs post dosing
- Local and general tolerability of L-CsA-i were investigated

RESULTS

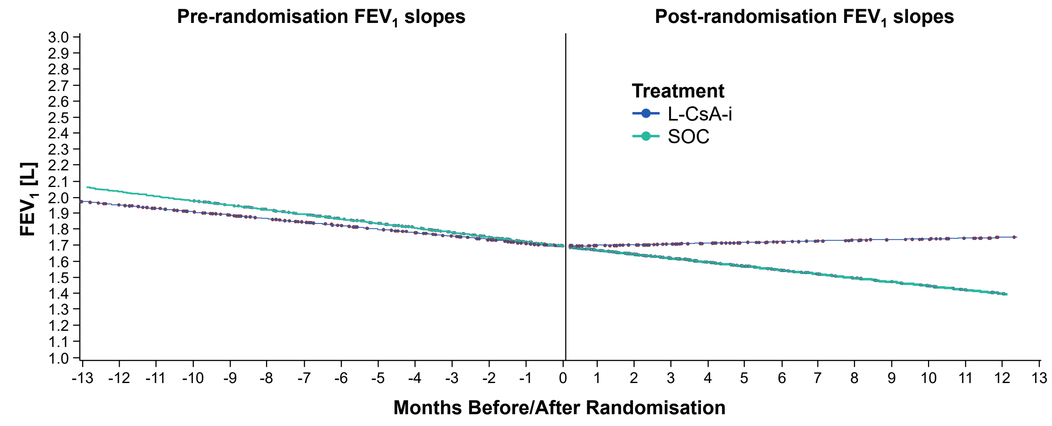
- 1068 patient-months of L-CsA-i use were collected from 85 patients with LTx
  - L-CsA-i was well tolerated and no patients discontinued due to intolerability
  - Most common reported symptoms were: cough 22%; dyspnoea 7%; pharyngeal soreness 1%; and wheezing 1%
- L-CsA-i administered 5 mg or 10 mg bid by inhalation results in nominal serum levels and does not accumulate over time (**Fig 5**)
  - Maximum serum CsA concentration was 57.42 ± 34.26 ng/mL
  - Trough levels for up to 2 years of daily administration were 4-5 ng/mL (compared to systemic CsA target levels of 200-300 ng/mL)[9]
- Lung function (FEV_1) did not continue to decline in patients with LTx who received L-CsA-i (**Fig 6**)

Figure 5. L-CsA-i Is Associated With Low Serum Concentrations of CsA With No Accumulation



From Study 12011.201, Clinical Study Report 2015.

Figure 6. Lung Function Is Stabilised in Patients With LTx Treated With L-CsA-i

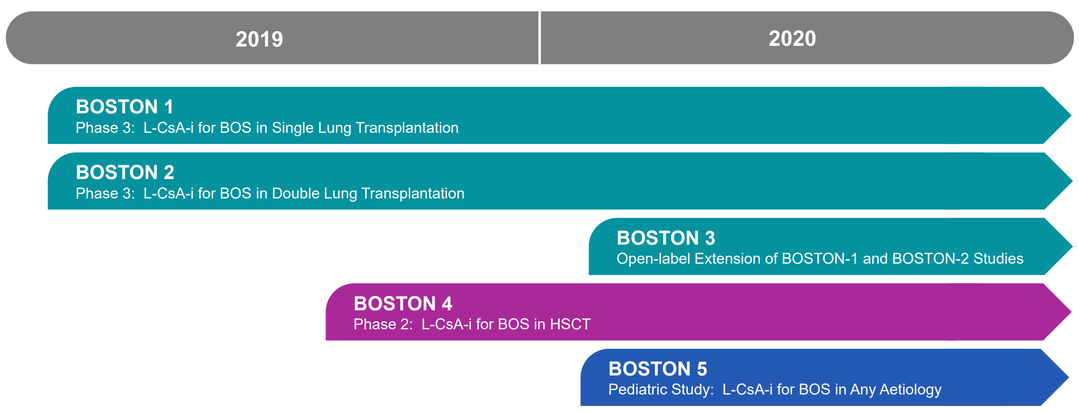


FEV_1, Forced Expiratory Volume in the first second; L, liters; SOC, standard of care.
From Study AI001, Clinical Study Report 2017.

CONCLUSIONS

- The pathophysiology of BOS is the same regardless of aetiology
- L-CsA-i is an investigational drug that to date has been demonstrated to be safe and well tolerated in >1000 patient-months of exposure
- BOSTON-1 and BOSTON-2, paired Phase 3 efficacy and safety studies of L-CsA-i for the treatment of BOS following LTx, are ongoing (**Fig 7**)
- A safety study of L-CsA-i for the treatment of BOS following allo-HSCT is planned

Figure 7. BOSTON Clinical Development Program



Ongoing and planned trials for the development of L-CsA-i to treat patients with BOS

BOSTON, Bronchiolitis Obliterans Syndrome Treated On Nebulisation.

REFERENCES

1. Au BKC, et al. *Biol Blood Marrow Transplant*. 2011;17:1072-1078. 2. Barker AF, et al. *N Engl J Med*. 2014;370:1820-1828. 3. Aguilar PR, et al. *Transplantation*. 2016;100:272-283. 4. Kulkarni HS, et al. *J Heart Lung Transplant*. 2019;38:5-16. 5. Yoshihara S, et al. *Biol Blood Marrow Transplant*. 2007;13:749-759. 6. Afessa B, et al. *Bone Marrow Transplant*. 2001;28:425-434. 7. Meyer KC, et al. *Eur Respir J*. 2014;44:1479-1503. 8. Study AI001, 2017, submitted. 9. Study 12011.201, Clinical Study Report, 2015.

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