Liposomal Cyclosporine A for Inhalation (L-CsA-i) to Treat Bronchiolitis Obliterans Syndrome: Novel Formulation and Drug-Specific Delivery System Improve Tolerability

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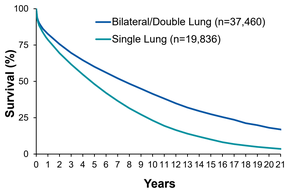
BACKGROUND

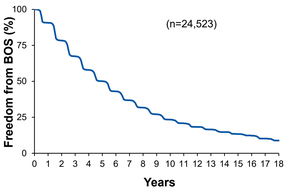
- Although lung transplantation (LTx) has become an effective treatment option for end-stage lung disease, long-term allograft viability remains a challenge to extended survival[1] (**Fig 1**)
- Following LTx, three or more immunosuppressive medications are used as standard of care to maintain the lung allograft. Regardless of maintenance regimen, bronchiolitis obliterans syndrome (BOS) is a major limitation to lung allograft survival[2,3] **(Fig 2)**

Figure 1. Patients With LTx Have Low Long-Term Survival



Adapted from Chamber DC, et al. *J Heart Lung Transplant.* 2018;37:1169-1183.

Figure 2. Patients With LTx Have a High Incidence of BOS



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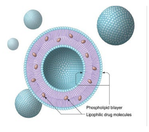
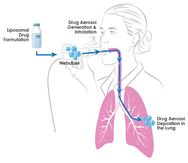
- BOS is a fatal, rapidly progressive lung disease caused by T-cell-mediated inflammation that leads to blockage of the bronchioles, resulting in respiratory failure and death[4,5]
- Currently, there is no approved therapy for the treatment or prevention of BOS[6]
- Cyclosporine A (CsA) given topically to the airways is a promising candidate to increase local immunosuppression and reduce systemic toxicity, but is highly insoluble[2,3,7,8]
  - Two different topical formulations of inhaled CsA have been clinically investigated: CsA-PG (CsA dissolved in propylene glycol) and, more recently, L-CsA-i (Liposomal Cyclosporine A for inhalation)
- L-CsA-i is a true liposome of CsA designed for inhaled delivery to the lungs (administered via the high-performance PARI eFlow® Nebulizer System) (**Fig 3**)

Figure 3. 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

METHODS

- Retrospective comparison of *in vitro* data and clinical data from prospective randomized clinical trials
  - CsA-PG (62.5 mg/mL) was dosed 300 mg/5 mL 3-times-weekly and was compared to L-CsA-i (lyophilisate reconstituted in 0.25% saline; 4 mg/mL) in doses of 5 mg/1.25 mL (single lung transplantation [SLTx]) or 10 mg/2.5 mL (double lung transplantation [DLTx]) per twice-daily inhalation
  - CsA-PG was delivered by a Sidestream Disposable Nebulizer and Mobilaire Compressor; L-CsA-i was delivered by the L-CsA-i eFlow®
  - Premedication with lidocaine and albuterol was necessary to improve tolerability with CsA-PG; reported tolerability rates for CsA-PG reflect the use of premedication
  - No premedication was used in the L-CsA-i studies
- Blood samples for PK analysis were collected before inhalation and after inhalation, at 15, 30, and 60 mins post dosing and 2, 4, 8, 12, and 24 hrs post dosing

RESULTS

- Tolerability data were assessed from 373 patient-months drug exposure to CsA-PG and 1068 patient-months exposure to L-CsA-i
  - Select symptoms of airway irritation are reported in **Table 1**

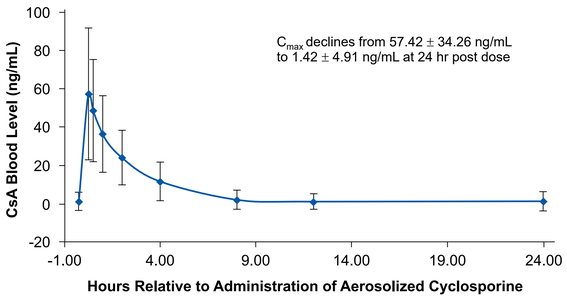
Table 1. Symptoms Associated With Airway Irritation Were Less Frequently Reported for L-CsA-i Compared to CsA-PG

	L-CsA-i	CsA-PG
Pharyngeal soreness	1%	43%
Cough	22%	36%
Dyspnea	7%	25%
Wheezing	1%	7%
Discontinuation due to symptoms of aerosol administration	0%	7%

  - Adherence to investigational therapy (L-CsA-i vs CsA-PG) was 80% vs 60%, respectively
  - The tolerability of CsA-PG without premedication was worse than with premedication
- PK models predict a constant drug level in the lung with twice-daily inhalation of L-CsA-i compared to 3-times-weekly inhalations of CsA-PG
- Maximum serum CsA concentration was 57.42 ± 34.26 ng/mL with inhaled L-CsA-i; trough levels for up to 2 years of daily administration were 4-5 ng/mL (systemic CsA target levels are 200-300 ng/mL) (**Figs 4 & 5**)
  - High peak and low trough levels were observed with inhaled CsA-PG[9] (**Fig 6**)
- L-CsA-i requires a shorter total inhalation time to achieve target dose compared to CsA-PG
  - Inhalation time was 60 mins for CsA-PG 300 mg vs 6-10 mins and 8-13 mins for L-CsA-i 5 mg (SLTx) and 10 mg (DLTx) doses, respectively
  - CsA-PG necessitated titration from 100 mg to 300 mg to achieve the target dose; no titration was needed with L-CsA-i

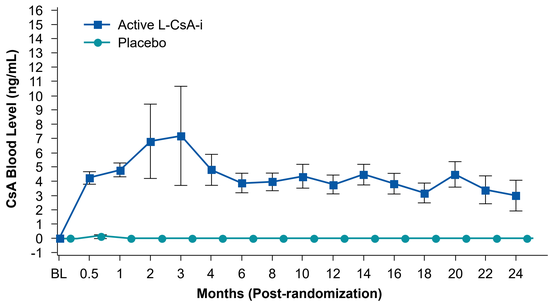
RESULTS (CONT'D)

Figure 4. CsA Blood Concentrations Following Inhalation of L-CsA-i Are Far Below Therapeutic Target Levels of Systemically Administered CsA



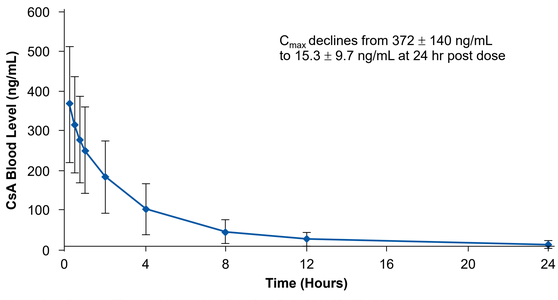
From Study AI001, Clinical Study Report 2017.

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. High Peak CsA Blood Concentrations Are Observed After Inhalation of CsA-PG

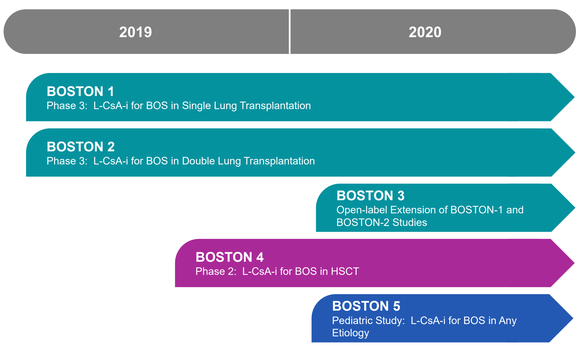


Adapted from Corcoran TE, et al. *J Aerosol Med Pulm Drug Deliv.* 2014;27:178-184.

CONCLUSIONS

- L-CsA-i has improved tolerability and may increase adherence compared to inhaled CsA-PG
- L-CsA-i uses lower total dose exposure to achieve constant levels of drug in the airway compared to inhaled CsA-PG
- L-CsA-i is administered more frequently, but the total inhalation time per week is about 40% that of CsA-PG, which is an important reduction in treatment burden
- Improved PK and tolerability profiles for L-CsA-i provide several advantages over other inhaled CsA formulations, and warrant further study. 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**)

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 Nebulization.

REFERENCES

1. Chambers DC, et al. *J Heart Lung Transplant.* 2018;37:1169-1183. 2. Study AI001, 2017, submitted. 3. Study 12011.201, Clinical Study Report, 2015. 4. Au BKC, et al. *Biol Blood Marrow Transplant.* 2011;17:1072-1078. 5. Barker AF, et al. *N Engl J Med.* 2014;370:1820-1828. 6. Walters EH, et al. *Eur Respir J.* 2007;30:574-588. 7. Guada M, et al. *J Control Release.* 2016;225:269-282. 8. Iacono AT, et al. *N Engl J Med.* 2006;354:141-150. 9. Corcoran TE, et al. *J Aerosol Med Pulm Drug Deliv.* 2014;27:178-184.

ACKNOWLEDGEMENTS

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Disclosure: L-CsA-i is an investigational compound and its safety and efficacy have not been established. It is not approved for use by any regulatory authority.

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