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

**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. (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 survival1. (Fig 2)
- 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. A
- Currently, there is no approved therapy for the treatment or prevention of BOS.
- Cyclosporine A (CsA) given topically to the airways is a promising candidate to increase local immunosuppression and reduce systemic toxicity, but is highly insoluble2,3,7,8 (Fig 3). 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 specifically for use with Breath Therapeutics’ eFlow® Nebulizer System.

**METHODS**

- Retrospective comparison of in vitro 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 (liposome reconstituted in 0.25% saline, 4 mg/mL) in doses of 5 mg/0.25 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 Multidose Compressor. L-CsA-i was delivered by the L-CsA-i eFlow Nebulizer System.
- 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 exposure to CsA-PG and 198 patient-months exposure to L-CsA-i.
- Select symptoms of airway irritation were reported in Table 1.

**RESULTS (CONT’D)**

- 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.

**CONCLUSIONS**

- L-CsA-i is an investigational compound and its safety and efficacy have not been established.

**REFERENCES**


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**Disclosure:** L-CsA-i is an investigational compound and its safety and efficacy have not been established.