L-CsA-i, a Liposomal Formulation of Cyclosporine, Demonstrates Therapeutic Potential for Bronchiolitis Obliterans Syndrome (BOS)

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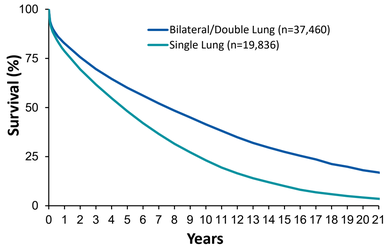
BACKGROUND

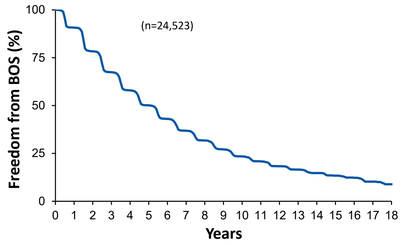
- Although lung transplantation (LTx) has become an effective treatment option for end-stage lung disease, long-term allograft viability remains a challenge to extended survival in patients with LTx[1] (**Fig 1**)
- Following LTx, three or more immunosuppressive medications are used as standard of care to maintain the lung allograft. Regardless of maintenance regimen, bronchiolitis obliterans syndrome (BOS) is a major limitation to long 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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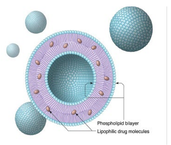
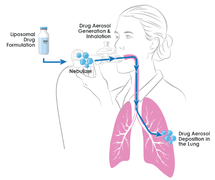
- BOS is a fatal, rapidly progressive lung disease caused by T-cell-mediated inflammation that leads to blockage of the bronchioles, resulting in respiratory failure and death[4,5]
  - Currently, there is no approved therapy for the prevention or treatment of BOS[6]
- Prior studies with inhaled propylene glycol-based cyclosporine demonstrated that acute rejection was not prevented but that there was significant BOS-free survival[7]
  - Propylene glycol-based cyclosporine is poorly tolerated and poorly aerosolized (CYCLIST trial)[8]
- 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 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

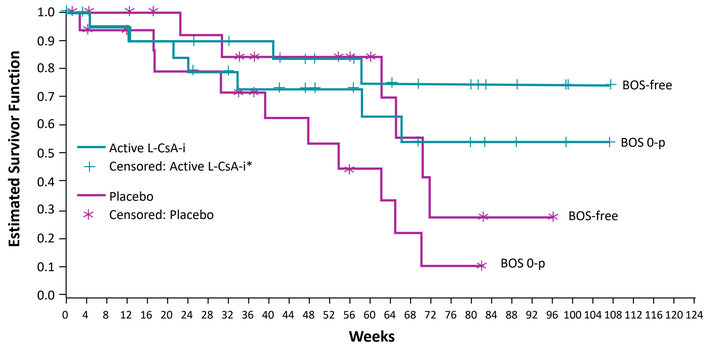
METHODS

- A study of L-CsA-i for the prevention of BOS in LTx recipients was conducted from 2009 to 2013 at 11 European lung transplant centers
  - Patients received either L-CsA-i (n=74) 5 mg (single LTx [SLTx]) or 10 mg (double LTx [DLTx]) twice daily via inhalation vs placebo (n=56)
  - The primary endpoint was BOS-free survival, defined as time to development of BOS ≥stage 1 or re-transplantation or death
  - The BOS prevention study was terminated after 130 of 180 patients were enrolled by decision of the original study sponsor for economic reasons unrelated to any safety or efficacy concerns
- Due to the shortened observation period, a post-hoc analysis was performed to predict the occurrence of BOS ≥stage 1
  - The predefined endpoint of development of BOS stage 1 was changed to BOS stage 0-p (BOS 0-p) within the composite primary endpoint for the post-hoc analysis
  - BOS 0-p is a predictor for deterioration of lung function and the development of BOS stages 1-3

RESULTS

- Mean observation time was 13.2 months; there was no separation of cohorts in the full analysis set (FAS)
- When stratified by SLTx (n=23) vs DLTx (n=51), BOS-free survival in the FAS was not statistically different between the L-CsA-i and placebo groups in SLTx patients (p=0.191) (**Fig 4**) and in DLTx patients (p=0.643)
- In the post-hoc analysis, there was a trend towards higher BOS 0-p free survival in favor of L-CsA-i vs placebo in the SLTx cohort (p=0.062) (**Fig 4**)
  - Development of BOS 0-p was observed in 6/23 SLTx patients (26.1%) in the L-CsA-i group and 10/17 SLTx patients (58.8%) in the placebo group
  - Deterioration of lung function to BOS 0-p started earlier in the placebo group than in the L-CsA-i group

Figure 4. BOS-free and BOS 0-p Survival in SLTx Recipients (FAS)



*Censored data for primary endpoint refer to patients who did not have a BOS event, re-transplantation, or death.
From Study 12011.201, Clinical Study Report 2015.

REFERENCES

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RESULTS (CONT'D)

- Thirty-two of 74 patients (43.2%) in the L-CsA-i group and 21 of 56 patients (37.5%) in the placebo group experienced adverse drug reactions (ADR); distribution of ADR severity and relationship to treatment were similar between groups
- Most common adverse events (incidence >15%) were diarrhea (26.2%), nasopharyngitis (20.8%), cytomegalovirus infection (19.2%), cough (18.5%), peripheral edema (17.7%), increased blood creatinine (16.2%), and nausea and leukopenia (16.9%)
- Pharmacokinetic analysis of twice daily L-CsA-i showed no accumulation of cyclosporine in the systemic circulation
- L-CsA-i is not expected to have drug-drug interactions with standard of care immunosuppression in LTx recipients

CONCLUSIONS

- This post-hoc analysis suggests the addition of L-CsA-i to standard of care in SLTx recipients may lead to a clinically meaningful benefit with respect to prevention of BOS
  - There was a trend towards higher BOS 0-p free survival in favor of L-CsA-i vs placebo in the SLTx cohort
- A similar benefit was not observed in DLTx recipients in this study, likely due to the recognized difference in the longer time to onset of BOS in the DLTx population and the shortened observation period from an early terminated study
- L-CsA-i appeared to be well tolerated and did not increase the risk of nephrotoxicity or fungal infections
- BOSTON-1 and BOSTON-2, paired Phase 3 efficacy and safety studies of L-CsA-i for the treatment of BOS following LTx, are currently enrolling patients (**Fig 5**)

Figure 5. BOSTON Development Program

L-CsA-i for the Treatment of Bronchiolitis Obliterans Syndrome (BOS)

BOSTON-1
L-CsA-i for BOS following single lung transplant [Ph3] **(Initiated Q1 2019)**

BOSTON-2
L-CsA-i for BOS following double lung transplant [Ph3] **(Initiated Q1 2019)**

BOSTON-3
Extension trial of BOSTON-1 and BOSTON-2

BOSTON-4
L-CsA-i for BOS following alloHSCT*

BOSTON-5
L-CsA-i for pediatric patients with BOS

*Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT).
BOSTON, Bronchiolitis Obliterans Syndrome Treated On Nebulization.

ACKNOWLEDGEMENTS

We extend our thanks to Dr. Aldo Iacono, MD, who served as the Principal Investigator for the AI001 clinical study, and Joyce Young, PharmD, MBA, from Breath Therapeutics Inc.

DISCLOSURE

N.R. Henig is an employee of Breath Therapeutics Inc.
K. Hoffmann was a consultant for Breath Therapeutics GmbH and former employee of Chiltern (now a Covance company).
O. Denk and G. Boerner are employees of Breath Therapeutics GmbH.

Presented at ATS 2019 International Conference: May 17-22, 2019, Dallas, TX