# Pediatric Patients with Bronchiolitis Obliterans Syndrome (BOS): Dosing and Breath Simulation Experiments of Liposomal Cyclosporin A for Inhalation (L-CsA-i)

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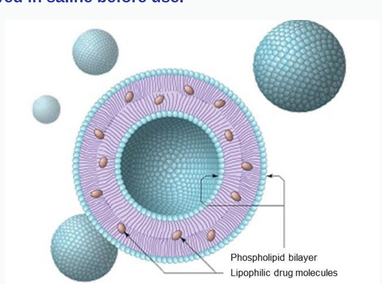
## Introduction

- Bronchiolitis obliterans syndrome (BOS) is a severe lung condition commonly occurring after lung transplant[1] or allogeneic hematopoietic stem cell transplantation[2] but is also seen as a result of other types of airway injury. The condition can affect patients at all ages and is recognized as a rare but debilitating condition in pediatric patients.[3-5]
- Regardless of preceding injury, BOS is characterized by T-cell–mediated inflammation and fibrosis of bronchiolar walls that reduces the diameter of the bronchioles and results in progressive and irreversible airflow obstruction[6]
- Currently, there are no approved therapies for BOS, and off-label use of oral therapies is limited by side effects and unproven efficacy[1]
- Cyclosporine is a potent anti-inflammatory agent that targets T cells.[7] When given systemically, however, it achieves low levels in the airways of the lungs,[8] and systemic administration is associated with renal[7] and hepatic toxicity[8]
- L-CsA-i, (**Figure 1**) a liposomal formulation of cyclosporin A, is being investigated for the treatment of BOS in two pivotal clinical trials: BOSTON-1 (NCT03657342) and BOSTON-2 (NCT03656926)

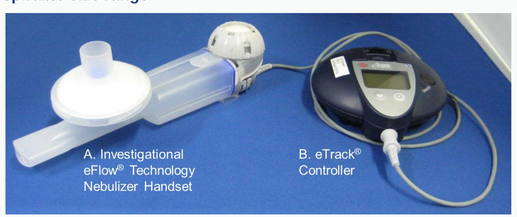
**Figure 1. Investigational liposomal cyclosporin A (L-CsA-i): Lipophilic drug molecules are contained within the phospholipid bilayer. Lyophilized L-CsA-i, which is stable at room temperature, is dissolved in saline before use.**




- L-CsA-i is administered as an aerosolized drug via an investigational eFlow® Technology nebulizer (PARI Pharma GmbH), optimized for the delivery of L-CsA-i (**Figure 2**). The aerosol characteristics have been previously described for adult users (Breath Therapeutics, data on file).
- Lungs grow in size as children mature. Beginning at about 10 years of age, lung function, structure, and surface area are comparable to that of adults.[9-11]
- A 5-mg dose of L-CsA-i is being considered for children aged 6-11 years on the basis of comparisons of lung weight from toxicology studies of animals and children, as well as data from clinical trials in children aged 6 to 11 years
  - Although the safety of L-CsA-i has not been investigated in this age group, limited adverse events have been reported for 5 mg and 10 mg doses in adults[12]
- The objective of this simulation study was to characterize and support dose selection for future studies of L-CsA-i for the treatment of BOS in pediatric patients

## Introduction (cont'd)

**Figure 2. The investigational eFlow® Technology nebulizer handset (A), optimized for L-CsA-i, and eTrack® Controller (B). The eFlow® Technology nebulizes liquid drugs with a perforated vibrating membrane, generating an aerosol with a high percentage of droplets in a respirable size range.**




## Methods

- Investigational eFlow® Technology nebulizer handsets (N=5), along with 1 eTrack® Controller (**Figure 3**) were tested with two dose strengths (5 mg and 10 mg) of L-CsA-i for breath simulation experiments and laser diffraction measurements using a child breathing pattern (according to Ph. Eur. monograph 2.9.44), compared with L-CsA-i 10 mg for the adult breathing pattern[13]
  - Reported parameters included delivered dose, respirable dose, and mass median diameter[13,14]
- Accepted assumptions for child versus adult breathing patterns were evaluated and are summarized in **Table 1**.

**Figure 3. Setup for Breath Simulation Experiments**

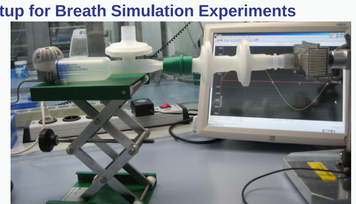


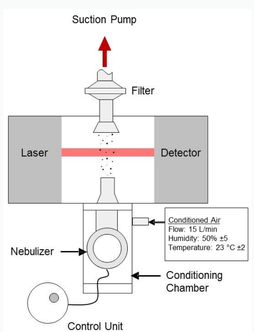
**Table 1. Comparison of Child and Adult Simulated Breathing Patterns**

| | Child Breathing Pattern[13] | Adult Breathing Pattern |
|---|---|---|
| **Tidal volume** | 155 ml | 500 ml |
| **Frequency** | 25 cycles/min | 15 cycles/min |
| **Waveform** | Sinusoidal | Sinusoidal |
| **Inhalation/exhalation ratio** | 1:2 | 1:1 |

## Methods (cont'd)

- Droplet size measurements for the calculation of respirable dose were performed by laser diffraction (Helos BR-OM, Sympatec). A schematic diagram of the setup is presented in **Figure 4.**
  - Ambient temperature: 23.0 °C ± 2.0
  - Ambient humidity: 50.0% ± 5.0
  - Inspiratory flow: 15.0 L/min ± 0.5
  - 2 min nebulization time; start of measurement after 1 min; measurement time 1 min
- Fill volumes (L-CsA-i): 1.25 mL (5 mg dose); 2.50 mL (10 mg dose)
- Breath simulation measurements:
  - Delivered dose (mg and %)
  - Exhaled drug amount (mg and %)
  - Residue in nebulizer (mg and %)
  - Recovery (%)
  - Nebulization time (end of aerosol production and automatic shut-off,
- Laser diffraction measurements
  - Mass median diameter (µm)
  - Respirable fraction: droplets <5 µm (%)
  - Total output rate (mg/min)
- The following parameter was calculated:
  - Respirable dose (<5 µm) = delivered dose (mg) x respirable fraction <5 µm

**Figure 4. Schematic Diagram of Particle Size Determination by Laser Diffraction (Helos BR-OM, Sympatec)**




## Results

- For the 10 mg L-CsA-i dose with the child breathing pattern, delivered dose and respirable dose were slightly lower than that was seen in the adult pattern (**Table 2** and **Figure 5**)
- The 5 mg L-CsA-i dose had a corresponding 50% reduction in delivered dose and respirable dose, compared with 10 mg
- Mass median diameter for each dose was <3 µm
- Nebulization time (and volume) was increased for the higher dose but remained under 10 minutes in all simulations, with the lower dose having the fastest inhalation time

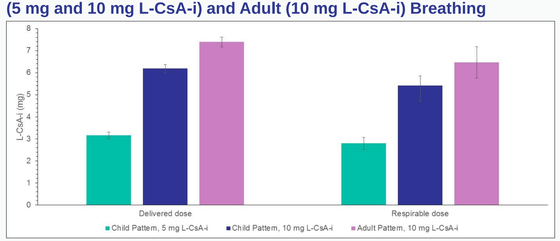
**Table 2. Summary of Breath Simulation Experiment Results**

| | 6-11 year-olds Child Pattern 5 mg L-CsA-i | 12-17 year-olds Child Pattern 10 mg L-CsA-i | 18+ year-olds Adult Pattern 10 mg L-CsA-i |
|---|---|---|---|
| **Fill volume, mL** | 1.25 | 2.5 | 2.5 |
| **Delivered dose, mg (SD)** | 3.16 (0.15) | 6.20 (0.17) | 7.39 (0.22) |
| **Respirable dose (<5 µm), mg (SD)** | 2.79 (0.28) | 5.42 (0.43) | 6.47 (0.71) |
| **Mass median diameter, µm (SD)** | 2.95 (0.45) | 2.90 (0.69) | 2.90 (0.69) |
| **Nebulization time, minutes (SD)** | 6.08 (1.08) | 9.11 (2.08) | 9.72 (2.61) |

**Abbreviation**: SD, standard deviation.

## Results (cont'd)

**Figure 5. Delivered and Respirable doses of L-CsA-i using Child (5 mg and 10 mg L-CsA-i) and Adult (10 mg L-CsA-i) Breathing**




## Conclusions and Implications

- **Administration of 10 mg L-CsA-i with the child and adult patterns of breathing yielded similar delivered doses**
  - **Administration of half that dose (5 mg L-CsA-i) with the child pattern of breathing yielded about half the delivered dose**
  - **Given that alveolar surface area is smaller in children than in adults, a lower dose is believed to be appropriate**
- **L-CsA-i particle size (measured as mass median diameter) delivered by the investigational eFlow® Technology nebulizer system for L-CsA-i was about 3 µm, consistent with the ideal particle size for drug deposition in the small airways of the lungs (1-5 µm),[15] which are most directly affected by BOS[1]**
  - **Nebulization time was in the range well accepted by patients in previous clinical trials**
- **L-CsA-i must be used with the investigational eFlow® Technology nebulizer system to achieve these results**
- **Delivery of L-CsA-i using the investigational eFlow® Technology nebulizer system has the potential to achieve high drug concentrations in the bronchioles with low systemic exposure**

## References

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## Author Disclosures

J. Paulukat is a current employee of Breath Therapeutics, a Zambon company. N. R. Henig and A. Copans are former employees of Breath Therapeutics, a Zambon company. A. Bucholski is a current employee of PARI Pharma GmbH. A. Moreno Galdo has no disclosures.

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