LUNG DELIVERY OF A NEW TOBRAMYCIN NEBULIZER SOLUTION (150 MG/1.5 ML) BY A CUSTOMIZED eFlow® NEBULIZER IS THE EQUIVALENT OF TOBI® BUT IN A FRACTION OF THE TIME

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Introduction and Objective
Adherence to recommended therapy in CF has always been a challenge, in part, due to the time demands of the daily therapy. While twice daily inhaled tobramycin for those infected with Pseudomonas aeruginosa (PA) has become an accepted standard of care, as much as 40 minutes a day may be consumed inhaling 300 mg in 5 mL of tobramycin (TOBI®, 60 mg/mL) from the PARI LC PLUS® breath enhanced jet nebulizer (Figure 1) [1].

The purpose of this study was to determine if equivalent levels of pulmonary deposition could be achieved in a much shorter time period using 1.5 mL of a more concentrated (100 mg/mL) tobramycin solution delivered by a customized investigational eFlow® nebulizer configuration (Figure 2) (both developed by PARI Pharma, Munich, Germany) generating a fine aerosol mist via a perforated vibrating membrane [2].

Methods
The subjects were 8 boys aged between 10 and 17 years and 8 adult males, all with an FEV₁ > 50% predicted and stable CF. All were receiving inhaled tobramycin for positive sputum cultures of Pseudomonas aeruginosa (PA). Following pretreatment with albuterol, they inhaled both preparations on two occasions with 99mTc-DTPA added to the tobramycin. In vitro preliminary work demonstrated that the radioactive tracked with both formulations of tobramycin [3]. Deposition was measured by a gamma camera taking both tissue attenuation and mucociliary clearance during nebulization into account. In order to have a continuous rate of deposition, the PARI LC PLUS® was run for a timed 10 minutes and then both the total deposition and time of nebulization “scaled up” from in vitro testing when the nebulizer was run to dryness. This was done by multiplying the deposition by the total output when run to dryness divided by the total output in 10 minutes. The rate of output per minute was calculated from the 10 minute run and the total time was total output from in vitro testing divided by the rate of output. The eFlow® provides a continuous output and stops automatically at dryness. Quality assurance was the agreement (within 10%) between total radioactivity pre nebulization (in the nebulizer) and post which included the subject, the nebulizer, the connectors and the expiratory filter. Experimental details were described previously by Coates et al. [3].

Results
The PARI LC PLUS® delivered 46.2 ± 10.3 (mean ± SD) mg in 17.0 ± 2.2 minutes which was similar to 46.6 ± 9.9 mg in 4.0 ± 1.0 minutes for the eFlow® (Bland and Altman Limits of Agreement, see Table 1 and Figure 1. Only the time of delivery was significantly different with p=0.0001 (paired t-test).

Tolerance of the treatment was comparable for both inhalation regimes, but the shorter treatment was preferred by all patients. There was a correlation between the deposition (R=0.57, p< 0.05) suggesting that individual patient factors played a role. The deposition did not correlate with the FEV₁.

Conclusions
- In 8 adults and 8 children with CF, the lung deposition was similar between the two formulations and devices but an investigational customized eFlow® with 150 mg/1.5 mL (Tobramycin PARI) was very much faster than the PARI LC PLUS® with TOBI®.
- While there was a significant correlation of deposition between the two systems, there was also a lot of scatter.
- The distribution of tobramycin within the lung was much less homogeneous than that seen in healthy volunteers suggesting that there will be areas of high concentration and areas of much lower concentration [3].
- The new system using an investigational eFlow® and Tobramycin PARI would result in an equivalent lung dose and considerable saving of time spent doing therapy and could improve adherence to recommended therapy.

References

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Table

<table>
<thead>
<tr>
<th>Summary of Key Results</th>
<th>Tobramycin PARI® 100 mg / mL [Mean ± SD]</th>
<th>TOBI® 60 mg / mL [Mean ± SD]</th>
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</thead>
<tbody>
<tr>
<td>Lung deposition all ages</td>
<td>46.6 ± 9.9 mg</td>
<td>46.2 ± 10.3 mg</td>
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<tr>
<td>Lung deposition adults (≥18 years)</td>
<td>47.0 ± 10.3 mg</td>
<td>47.5 ± 10.2 mg</td>
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<tr>
<td>Lung deposition children (0-17 years)</td>
<td>46.3 ± 10.2 mg</td>
<td>44.8 ± 10.8 mg</td>
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<td>Peripheral-to-Central Ratio</td>
<td>0.45 ± 0.04</td>
<td>0.44 ± 0.04</td>
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<td>Nebulization time</td>
<td>4.0 ± 1.0 min</td>
<td>17.0 ± 2.2 min</td>
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Figure 1: LC Plus® with the PRONEB Ultra® compressor
Figure 2: Base unit and customized handset of an investigational eFlow®