**PHARMACOKINETIC AND TOXICITY PROFILE OF OTO-104:**
**A SUSTAINED RELEASE DEXAMETHASONE HYDROGEL FOR INNER EAR DELIVERY**

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**INTRODUCTION**

In recent years, intratympanic drug delivery has been investigated as a route of administration to treat a variety of inner ear disorders, such as Meniere’s disease and Sudden Sensorineural Hearing Loss. While constituting an improvement in safety and efficacy over the traditional systemic dosing approach (oral, intravenous), multiple issues still remain to be addressed: large differences in dosing schedules and regimens, as well as high variability in clinical outcomes and patient acceptance. These disparities are primarily the result of the current formulations, namely drug solutions with short residence time and rapid elimination from the middle and inner ear.

OTO-104, a dexamethasone suspension in a poloxamer-based hydrogel, was developed. Poloxamers are tri-block co-polymers (PEO-PPO-PEO) with mucoadhesive and thermoreversible properties that behave as sustained release drug delivery vehicles. OTO-104 was administered to guinea pigs via intratympanic injection and its pharmacokinetic and toxicity profile was examined.

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**IN VITRO RELEASE PROFILE**

Dissolution rate experiments were performed at 37°C in a sinker of 6.5 mm diameter polycarbonate membrane with a pore size of 0.4 µm. Briefly, 0.2 ml of the test article was deposited into the snapwell; 0.5 ml of the buffer solution (10mM PBS buffer) was placed into the reservoir and shaken at 70 rpm. Samples were taken at indicated times, where 0.1 ml was withdrawn and replaced with the equivalent volume of pre-warmed buffer.

**Dissolution time (h) vs. % Release**

![Graph showing dissolution time (h) vs. % Release](Image)

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**INNER EAR PHARMACOKINETICS**

**Pharmacokinetic Parameters**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Guinea pig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>DSP OTO-104</td>
</tr>
<tr>
<td>AUC (µg.h/mL)</td>
<td>57</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>DSP OTO-104</td>
</tr>
<tr>
<td>TET (d)</td>
<td>20% OTO-104</td>
</tr>
</tbody>
</table>

**IN VITRO RELEASE PROFILE**

Female guinea pigs (n=4 per group) received a single 50µl intratympanic injection directed towards the round window niche. In the isolated transtympanic, perilymph from the base of the cochlea was collected and dexamethasone quantified by LC-MS. AUC: Area Under the Curve, MRT: Mean Residence Time; TET: Terminal Exposure Time (time during which therapeutic drug levels (>40 ng/ml) are present in the inner ear).

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**CONCLUSIONS**

* In vitro, OTO-104 displays a significantly longer residence time than a 2% DSP solution, up to several orders of magnitude.
* In guinea pigs, OTO-104 achieves therapeutic levels of dexamethasone in the inner ear for up to 3 months following a single intratympanic injection.
* Administration of OTO-104 is associated with a small and transient shift in hearing threshold, probably of conductive nature.
* As determined by histological assessment of middle ear inner tissues, the minimal histological changes observed were no different in the saline, vehicle and OTO-104 treated groups.
* No hair cell loss was observed following administration of OTO-104.

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**AUDITORY FUNCTION**

**ABR Hearing Threshold (dB SPL)**

<table>
<thead>
<tr>
<th>Days post IT injection</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>29</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>29</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>29</th>
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</thead>
<tbody>
<tr>
<td>RWN</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>29</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>29</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td>Vehicle</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>29</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>29</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td>20% OTO-104</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>29</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>29</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>29</td>
</tr>
</tbody>
</table>

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**HISTOLOGY**

Harnessed cochleae were decalcified in EDTA for 2 weeks. Following thorough rinsing with water, cochleae were further dissected, trimmed and balanced on their ventral surface. Embedding was performed in a Autotechnicon using the following cycle: ethanol 70% 90min, ethanol 95% 120min (3X), ethanol 100% 120min (3X), histoclear 30min (3X), paraffin 120min (2X), paraffin 12-18h in a vacuum oven. Sectioning of the cochlear preparations were carried out taking 7 µm sections. Slides were stained using a standard hematoxilin / eosin protocol before being photographed and measured.

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**CYTOCOCHLEOGRAMS**

Hair cell status was quantitatively assessed by photomicroscopic surface projections of the cochlear spiral and plotted from apex to base as cytocochleograms. Normal, flattened hair cell loss under 35% and occasional scattered larger losses of hair cell loss minimal, few regions and a few rows of OHCs with 10-35% loss. Moderate, many regions of loss over 25%. Severe, many regions of loss over 60%. Data was generated by R. Altschuler, Kresge Institute, Ann Arbor, Michigan.

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* OTO-104 = 2% DSP Sol.
* DSP OTO-104 = 2% DSP Sol. containing OTO-104
* 0.6% OTO-104 = 2% DSP Sol. containing 0.6% OTO-104
* 6% OTO-104 = 2% DSP Sol. containing 6% OTO-104
* 20% OTO-104 = 2% DSP Sol. containing 20% OTO-104

**MDT = nK-1/n / n + 1**

* In guinea pigs, OTO-104 achieves therapeutic levels of dexamethasone in the inner ear for up to 3 months following a single intratympanic injection.

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**ACKNOWLEDGMENTS**

No conflicts of interest.

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**REFERENCES**

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**CONTACT**

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