Evaluation of the Pharmacokinetic Profile of a Novel Ophthalmic Formulation of Loteprednol Etabonate

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Loteprednol Etabonate Mucus Penetrating Particles (LE-MPP)

- Nano-suspension of loteprednol etabonate (LE) with particle size of 200-500 nm
- Formulated with Kala proprietary coating to allow penetration through mucus of tear film
- Can provide increased penetration and duration in ocular tissues
How do MPPs work?

**Conventional Particles (CP)**

1. Muco-adhesive particles are **rapidly cleared** from mucus through mucus turnover
2. Particle aggregation and mucus adherence leads to **poor distribution**

**Mucus Penetrating Particles (MPP)**

1. Muco-inert particles penetrate through tear film mucus layer
2. Mobility leads to **uniform distribution** across the mucosal epithelia
Previously Demonstrated Significant Corneal Delivery and Duration

Kala MPPs

1 dose
2hr
4hr

Control Nanoparticles

MPPs – inert nanoparticles with Kala’s proprietary coating
Control nanoparticles - same size and composition as the MPPs but without the proprietary coating

Schopf, L et. al., Poster Presentation ARVO 2013
### Study Design

<table>
<thead>
<tr>
<th>Number of NZW Rabbits</th>
<th>Test Article</th>
<th>Dosing</th>
<th>Terminal Time Points (Post-dose)</th>
<th>Tissues and Fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 per time point (n=6 eyes)</td>
<td>Lotemax® Gel (0.5% LE)</td>
<td>35 µL -QD</td>
<td>0.083, 0.25, 0.5, 1, 3, 6, 9, and 12hr</td>
<td>Cornea</td>
</tr>
<tr>
<td></td>
<td>LE Test Formulation (0.4% LE-MPP)</td>
<td></td>
<td></td>
<td>Aqueous humor</td>
</tr>
</tbody>
</table>

- The test formulations were well tolerated. No abnormal observations were noted in any rabbits following administration of the test formulations.

- Animals were euthanized by intravenous barbiturate overdose post-dose

- Both eyes were harvested with the collection of aqueous humor and dissection of cornea

\[ T_{\text{max}}, C_{\text{max}}, t_{1/2}, \text{AUC}_{0-\text{last}}, \text{and AUC}_{0-\text{inf}} \] were determined using Pharsight’s Phoenix WinNonlin software (v.6.2.1) for all collected matrices. The log-linear trapezoidal rule was used for calculating AUC. \( T_{1/2} \) was calculated using the “best-fit” or a minimum of the three last data points. If the calculated \( r^2 \) for the regression was <0.6, the value was not reported. Prior to the calculation, any mean data points with a %CV >100 were checked for outliers at the p<0.01 level using the Grubbs’ Test. If indicated as an outlier, the value was excluded prior to calculating any pharmacokinetic parameter.
Comparison of Lotemax gel, 0.5% and LE-MPP, 0.4%

LE-MPP 1.6-fold greater AUC$_{0-3}$ Compared to Lotemax Gel in Aqueous Humor

In this study, at a 20% lower dose strength, LE-MPP provided equal or better drug levels than Lotemax® gel formulation.
## Comparison of Lotemax gel, 0.5% and LE-MPP, 0.4%

<table>
<thead>
<tr>
<th>Loteprednol Pharmacokinetic Parameters</th>
<th>Aqueous Humor (Lotemax® gel, 0.5%)</th>
<th>Aqueous Humor (LE-MPP, 0.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_{\text{max}} ) (hours)</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/g or ng/mL)</td>
<td>12.7</td>
<td>30.3</td>
</tr>
<tr>
<td>( t_{1/2} ) elimination (hours)</td>
<td>2.9</td>
<td>2.6</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\text{last}} ) (ng<em>h/g or ng</em>h/mL)</td>
<td>28.7</td>
<td>42.6</td>
</tr>
</tbody>
</table>
## Study Design

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<th>Terminal Time Points (Post-dose)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>3 per time point (n=6 eyes)</td>
<td>LE-MPP</td>
<td>50 µL-QID</td>
<td>0.5, 1, 2, 4, and 8hr</td>
<td>Cornea</td>
</tr>
<tr>
<td></td>
<td>LE-MPP</td>
<td>50 µL-BID</td>
<td></td>
<td>Aqueous humor</td>
</tr>
</tbody>
</table>

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LE-MPP: Twice-a-day (BID) compared to Four-times-a-day (QID)

<table>
<thead>
<tr>
<th>Loteprednol Pharmacokinetic Parameters</th>
<th>Cornea LE-MPP, 0.5% BID</th>
<th>Cornea LE-MPP, 0.5% QID</th>
<th>Aqueous Humor LE-MPP, 0.5% BID</th>
<th>Aqueous Humor LE-MPP, 0.5% QID</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (hours)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/g or ng/mL)</td>
<td>1392</td>
<td>1672</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{last}}$ (ng<em>h/g or ng</em>h/mL)</td>
<td>2279</td>
<td>2713</td>
<td>35</td>
<td>45</td>
</tr>
</tbody>
</table>

- $T_{\text{max}}$ and $C_{\text{max}}$ values were similar regardless of dose frequency
- $\text{AUC}_{0-\text{last}}$ values were greater from the QID group than that of BID dosed group
Conclusions

• In this study, LE-MPP provides equal or better drug levels in both the cornea and aqueous humor compared to Lotemax® gel even at a 20% lower dose strength

• In a rabbit PK study comparing dose frequency of LE-MPP, 0.5%, four-times-a-day versus twice-a-day increased total drug exposure by only 15-20%

• This works supports the premise that mucus penetrating particle (MPP) technology can be used to enhance ocular exposure for topically applied therapeutics

• Further studies to assess the clinical efficacy and safety of LE-MPP are warranted
Breakthrough Solutions for Ocular Diseases