In Vivo Tissue Distribution and Elimination of DUR-928, a First in Class Therapeutic for Treatment of Hepatic and Renal Disease


INTRODUCTION

DUR-928 [5-cholesten-3β,25-diol 3-sulfate (25HC3S)] is a recently discovered endogenous sulfated oxysterol that has been shown to be an intracellular regulatory molecule in lipid metabolism, inflammatory responses, cell survival, and tissue regeneration. This first-in-class molecule is being developed for the treatment of hepatic and renal diseases.

MATERIALS & METHODS

The absorption, distribution, metabolism, and excretion (ADME) of [4-14C]-DUR-928-derived radioactivity were studied in rats. The plasma pharmacokinetics (PK), the routes of elimination and excretion, mass balance, tissue distribution, and tissue PK were determined using quantitative whole body autoradiography methods in male Sprague-Dawley (N=19) and male Long-Evans (N=9) rats following a single intravenous bolus dose of (4-14C)-DUR-928 at 10 mg/kg. Blood samples were collected for PK up to 72 hours post-dose. Urine and feces were collected through 168 hours (h) post-dose. Following blood collection, animals were euthanized by CO2 inhalation and carcasses frozen for processing.

CONFLICT OF INTEREST DISCLOSURE

• The authors are employees of DURECT Corporation and may hold company stock/options.
• This presentation includes discussion of an investigational drug product in phase 2 development.

RESULTS

Pharmacokinetic Parameters of DUR-928 Equivalents in Plasma and Selected Tissues of Male Sprague-Dawley Rats Following an Intravenous Dose of 4-14C-DUR-928 at 10 mg/kg

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Cmax (ng.equiv./g)</th>
<th>Tmax (h)</th>
<th>T1/2 (h)</th>
<th>AUC(0-∞) (ng.equiv.l/g)</th>
<th>Tissue/Plasma AUC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>12,400</td>
<td>0.083</td>
<td>26.6</td>
<td>27,900</td>
<td>1.00</td>
</tr>
<tr>
<td>Kidney</td>
<td>44,000</td>
<td>0.083</td>
<td>11.1</td>
<td>73,700</td>
<td>2.32</td>
</tr>
<tr>
<td>Liver</td>
<td>87,900</td>
<td>0.083</td>
<td>48.4</td>
<td>364,000</td>
<td>11.4</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>19,800</td>
<td>0.5</td>
<td>91.0</td>
<td>241,000</td>
<td>7.58</td>
</tr>
</tbody>
</table>

SUMMARY

• 100.2% of the administered dose was recovered in urine, feces, and cage rinse over the 168 hour collection period.
• DUR-928 and/or its metabolites were broadly distributed and detected by quantitative whole body autoradiography in all tissues except the eye (lens).
• 83% of the recovered radioactivity was in feces indicating that biliary excretion is the primary route of excretion in rats, with 84% of the dose recovered in the first 48 hours.
• Liver and small intestine wall had the highest AUCs for DUR-928-derived radioactivity relative to plasma.
• Notable exposures were measured in the kidney.
• DUR-928-derived radioactivity was below quantitation limit in most tissues by 168 hours postdose.

CONCLUSIONS

The current ADME study results highlight the preferential uptake of DUR-928 in selected target organs and support the continued development of DUR-928 for organ injury and disease involving the liver and kidney.

ACKNOWLEDGEMENTS

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