INTRODUCTION

Osteoarthritis (OA) is the most prevalent degenerative joint disorder worldwide, characterized by progressive articular cartilage destruction. Due to the lack of self-healing capacity of articular cartilage, there is no cure, and limited long-lasting treatment options are available. Among available pharmacologic therapies for OA, corticosteroids have been recommended by guidance of international societies as the golden standard.1 While there are various steroid formulations on the market, intra-articular (IA) injections must be administered frequently due to the short-term symptomatic relief they provide.2 An extended-release (ER) steroid triamcinolone acetonide (TA) for knee OA pain was recently approved by the FDA. However, ER-TA has been shown to result in local adverse effects similar to TA,3 which include chondrotoxicity and related cartilage damage.4

To circumvent these issues, TLC599, a novel sustained-release liposomal formulation of dexamethasone sodium phosphate (DSP) was developed. DSP is the proof of dexamethasone sodium phosphate’s synthetic glucocorticoid approved by the FDA over 50 years ago for the treatment of multiple conditions, including rheumatic diseases. DXR inhibits the expression of inflammatory mediators which cause inflammatory diseases such as OA. The safety profile of DXR has been well characterized in clinical studies to support its use in the management of OA via intra-articular injection.5

In numerous studies, TLC599 showed a sustained-release profile in local joint with low systemic exposure, indicating the potential as new OA treatment with reduced treatment frequency and fewer side effects than other commercially available steroid-formulation drugs.

MATERIALS AND METHODS

TLC599

TLC599, a BioSeizer® formulation of DSP (Figure 1), is designed to provide sustained pain management for an extended period of up to six months. The BioSeizer® technology uses multilayer lipid membranes to entrain DSP, providing an exceptionally long duration of release period by the constant collapse of lipid layers.

Study Designs for Pharmacokinetic and Toxicokinetic Study

In two pharmacokinetic (PK) and toxicokinetic (TK) studies (Table 1), dexamethasone phosphate (DP) was quantified using the combination of liquid chromatography with mass spectrometry (LC-MS/MS). The PK/TK profile and parameters were calculated by Phoenix WinNonlin. DSP is the sodium salt form of DP.

RESULTS

The TK profile of DP in synovial fluid following a single IA injection is shown in Figure 2a. DP concentration remained at high levels in synovial fluid between 2.5 to 48 hours, and lasted through 360 hours.

The TK profile of DP in synovial fluid following single or multiple IA injections is shown in Figure 3. DP concentration increased with the increase in dose levels from 8 to 36 mg/animal. System exposure in terms of Cmax and AUC0-t were generally dose proportional.

CONCLUSIONS

• TLC599, a novel formulation of dexamethasone sodium phosphate, showed sustained-release profile in dog joints after a single intra-articular injection. Drug levels were maintained locally for up to 120 days.

• No accumulation of dexamethasone phosphate was observed in dog plasma following multiple-dose administration of TLC599, supporting the possibility for repeated dosing in humans.

• Systemic exposure after intra-articular injections of TLC599 is minimal and generally dose proportional.

• All animal studies indicate that TLC599 could be an effective and a safe chronic treatment for osteoarthritis.

REFERENCES


Table 1. Pharmacokinetic and Toxicokinetic Study

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Species</th>
<th>Study Designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>8338151</td>
<td>Dogs</td>
<td>TLC599 was administered at dose levels of 4 and 18 mg/knee (8 and 36 mg/animal) as a single (once on Day 1) and multiple (once on Day 1, 92, 183, and 274) IA injections in both knees. Synovial fluid samples were collected at 2.5, 48, 96, 368, and 360 hours post-dose; plasma samples were collected at 0.25, 0.75, 1.25, 2, 4, 6, 24, 48, 96, and 168 hours post-dose.</td>
</tr>
<tr>
<td>8388198</td>
<td>Dogs</td>
<td>TLC599 was administered at the dose level of 18 mg/knee as a single IA injection in both knees (36 mg/animal). Synovial fluid samples were collected at 15, 30, 45, 90, and 120 days post-dose.</td>
</tr>
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</table>

Table 2. Ratio of DP Parameters in Dog Plasma between First Dose (Day 1) and Month-End Dose (Day 274)

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Dose Level (mg/animal)</th>
<th>Cmax Ratio (Day 274/Day 1)</th>
<th>AUC0-t Ratio (Day 274/Day 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP</td>
<td>8</td>
<td>90%</td>
<td>100%</td>
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</tbody>
</table>

Table 3. Ratio of DP Concentration in plasma to synovial fluid*

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Plasma to Synovial Fluid Ratio</th>
<th>Dose Level (mg/animal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP</td>
<td>0.000133%</td>
<td>36</td>
</tr>
</tbody>
</table>

* Plasma concentrations at 3 hours were compared with synovial fluid concentrations at 3 hours.

Figure 1. Electron microscopic image of TLC599, a multi-layer vesicle structure

Figure 2a. DP Concentration in Dog Synovial Fluid

Figure 2b. DP Concentration in Dog Synovial Fluid Following a Single IA Injection at 130/84 mg/ml into both knees of dogs (study #8388198).

Figure 2c. Synovial Fluid TK/PK profile of TLC599 following a single IA injection at 130/84 mg/ml into both knees of dogs (study #8388198).

Figure 2d. Mean (± SD) Concentration of DP in Dog Synovial Fluid

Figure 3. Mean (± SD) Concentration of DP in Dog Plasma

Figure 4. Plasma PK profile of TLC599 following single or multiple IA injections at dose levels 8 mg and 36 mg/animal into both knees of dogs (study #8351851).