Safety, tolerability, and efficacy of a novel sustained-release liposomal formulation of dexamethasone sodium phosphate (TLC599) in patients with knee osteoarthritis

Chien-Chih Lai1, Chao-Ching Chiang1, Chyou-Shen Lee2, Chi-Ching Chang3, Hsiao-Yi Lin4, Tien-Ling Chen4, and Sheue-Fang Shih5

1 Taipei Veterans General Hospital, 2 Mackay Memorial Hospital, 3 Taipei Medical University Hospital, 4 Cheng Hsin General Hospital and 5 Taiwan Liposome Company

INTRODUCTION

- Intra-articular (IA) corticosteroid injection provides effective relief of osteoarthritis (OA) pain of the knee. Treatment efficacy mostly only lasts for 1 to 2 months.

- TLC599 is a sustained-release liposomal formulation (Figure 1) of dexamethasone sodium phosphate (DSP) for the symptom treatment of OA, through formulation with a proprietary, phospholipid-based drug delivery system (Bioseizer).

OBJECTIVE

- To evaluate safety, tolerability, and efficacy of TLC599 in subjects with knee OA

METHODS

- 40 subjects with knee OA (VAS ≥ 4, KL grade ≥2) randomized into two TLC599 dose groups by 1:1 as open-label, (Table 1) at three sites (Taipei Veterans General Hospital, Mackay Memorial Hospital and Taipei Medical University Hospital) in Taiwan

- Two TLC599 dose groups (Figure 2):
  - Group A, n=20
    - (6mg DSP with 50μmol phospholipid)
  - Group B, n=20
    - (12mg DSP with 100μmol phospholipid)

- Evaluations included:
  - Safety measurements (Primary)
    - Adverse events (AEs), changes in physical examinations, vital signs, and clinical laboratory results
  - Efficacy measurements (Secondary)
    - Pain score in visual analogue scale (VAS)
    - Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales (pain, stiffness and physical function)
    - Investigator’s global assessment of response to therapy (IGART)
  - Evaluation period is 12 weeks following a single intra-articular injection.

- ClinicalTrials.gov: NCT02803307

RESULTS

Safety:
- No serious adverse events (SAE), important adverse events (AE), or AEs leading to withdrawal occurred in this study.
- No significant changes in mean HbA1c observed in 12 weeks.
- Only two TRAEs (treatment-related adverse events) of hyperglycemia with Grade 1 reported in two Group B subjects.
- Mean plasma cortisol (Figure 3) was transiently decreased after TLC599 dosing. The decreased cortisol level was within normal range at all time points.

Efficacy:
- Mean subject-related pain (VAS) (Figure 4) and WOMAC pain subscale scores (Figure 5) showed sustained decreases from baseline in both Group A and Group B starting at Week 1 through end of study at Week 12.
- Over 50% of the patients displayed clinical response at all time points through 12 weeks for both of the dose levels (Table 2).

CONCLUSIONS

- Injection of TLC599 in OA knee was well tolerated in all subjects and a trend of pain and symptoms relief was observed in both treatment groups.
- Further blinded, placebo-controlled studies with a larger sample size and longer study duration would be required to confirm the long-term safety and efficacy of TLC599 in subjects with OA of knee (NCT03005873, report in preparation).

Figure 1. Electron cryo-microscopy of liposomal formulation

Table 1. Subject demographics

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Group A (6 mg DSP)</th>
<th>Group B (12 mg DSP)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Asian (Race)</td>
<td>20 20 40</td>
<td>20 20 40</td>
<td>40</td>
</tr>
<tr>
<td>Male</td>
<td>2 6 8</td>
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<td></td>
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<tr>
<td>Female</td>
<td>18 14 32</td>
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<tr>
<td>Mean</td>
<td>66.7 68.1 67.4</td>
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<tr>
<td>Median</td>
<td>67.5 69.5 68.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>49 52 49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>89 84 89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Percentage of Clinical responders through 12 weeks

<table>
<thead>
<tr>
<th>Week</th>
<th>Group A (6mg DSP)</th>
<th>Group B (12mg DSP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6mg DSP</td>
<td>12mg DSP</td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>70%</td>
<td>75%</td>
</tr>
<tr>
<td>Week 4</td>
<td>70%</td>
<td>65%</td>
</tr>
<tr>
<td>Week 8</td>
<td>70%</td>
<td>85%</td>
</tr>
<tr>
<td>Week 12</td>
<td>70%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Clinical responder calculated based on OMERACT-OARSI’s responder criteria (OsteoArthritis and Cartilage (2004) 12, 389–399)

Efficacy measurements (Secondary)
- Pain score in visual analogue scale (VAS)
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales (pain, stiffness and physical function)
- Investigator’s global assessment of response to therapy (IGART)

Figure 2. Clinical study design

Figure 3. Mean plasma cortisol was within normal range after dosing through 12 weeks

Figure 4. Mean subject-reported VAS throughout 12 weeks (ITT population)

Figure 5. Mean WOMAC pain throughout 12 weeks (ITT population)