SINGLE INTRA-ARTICULAR INJECTION OF TLC599 PROVIDED SUSTAINED PAIN RELIEF THROUGH 24 WEEKS IN PARTICIPANTS WITH SYMPTOMATIC KNEE OSTEOARTHRITIS

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**Abstract:**
**Purpose:** Osteoarthritis (OA) is the most common form of arthritis and the leading cause of chronic disability and reduced activity in people older than 50 years. Intra-articular (IA) corticosteroid injections, such as dexamethasone sodium phosphate (DSP), provide effective short-term pain relief for knee OA for 2-4 weeks; however, more sustained relief is needed in this chronic disease. TLC599 is an investigational drug designed to prolong the local residence time of DSP in the knee joint through liposomal formulation and it is designed to provide immediate as well as sustained pain relief for 24 weeks. Due to its durable effect, TLC599 is capable of reducing intra-articular injection frequency to maximize the clinical benefit. The current trial evaluated the efficacy and safety of two dose levels of TLC599 in participants with knee OA.

**Methods:** This trial was a Phase 2a, double-blinded, randomized and placebo-controlled study conducted in Australia and Taiwan. Participants of 50 years old or older, with Kellgren-Lawrence Grade 2-3 knee OA and pain severity of 5-9 on visual analog scale (VAS), were randomized to receive a single IA injection of TLC599 12 mg (12 mg DSP with 100 µmol phospholipid), TLC599 18 mg (18 mg DSP with 150 µmol phospholipid), or saline placebo. For each patient, only one knee was selected for study drug injection. All participants were scheduled for a follow-up of 24 weeks after the single injection. The primary endpoint was the change in Western Ontario and McMaster Universities (WOMAC) pain (0-4) through Week 12; secondary endpoints included change in WOMAC pain and VAS scores at time points up to Week 24, proportion of clinical responders, total consumption of acetaminophen and safety/tolerability.

**Results:** A total of 149 participants were screened and 75 received treatment, with mean age 63.9 years; 2/3 were female. Around two-thirds of the treated participants had bilateral knee pain (61.3%). The mean WOMAC (0-4 scale) / VAS (0.0 - 10.0 scale) pain scores at baseline in placebo, TLC599 12 mg and TLC599 18 mg were 1.6 / 6.6, 1.5 / 6.5 and 1.7 / 6.9, respectively. Although both placebo- and TLC599-treated subjects displayed a reduction in WOMAC pain score, those treated with TLC599 12 mg displayed a significantly greater reduction than placebo through all specified time points, including Weeks 12, 16, 20 and 24 (p<0.05). This demonstrated the sustained duration of pain control by TLC599 for at least 6 months (**Figure 1**). A majority of the TLC599 12 mg group had a durable response, maintaining at least 30% pain relief at all visits from Week 1 through Week 12 (56% vs 29% in placebo; p=0.0104) and further through Week 24 (52% vs 22% in placebo; p=0.0143) (**Figure 2**). The onset of pain relief started as early as Day 3 post-dose, with no sign of loss in pain relief noted at Week 24. Reductions in pain with TLC599 18 mg were not as great as with TLC599 12 mg. Similar trends were observed in VAS pain scores. In addition, a trend of lower total consumption of acetaminophen was observed in the TLC599-treated groups compared to the placebo group through Week 24. Treatment-related adverse events were reported in 4 participants (16%) receiving placebo and in 7 participants (27%) receiving TLC599 12 mg; most were mild to moderate in severity. No treatment-related serious adverse events were reported in any group.

**Conclusions:** The current clinical study demonstrated that TLC599 12 mg was capable of providing clinically and statistically significant durable pain relief in participants with knee OA through 24 weeks with good tolerability. Furthermore, over half of participants treated with TLC599 12 mg maintained at least a 30% reduction in pain throughout the 6-month study (more than twice as many as placebo).
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