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

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INTRODUCTION

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

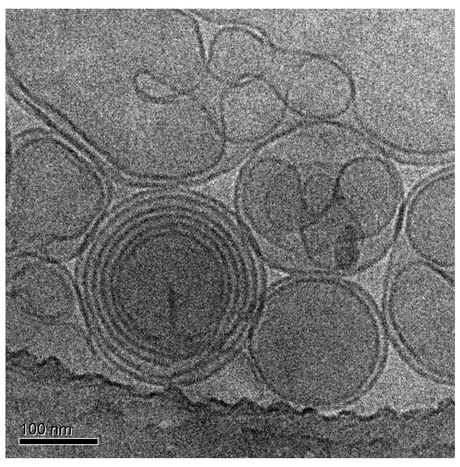

Table 1. **Subject demographics**

		Group A (6 mg DSP)	Group B (12 mg DSP)	All
Patient Number		20	20	40
East Asian (Race)		20	20	40
Gender	Male	2	6	8
	Female	18	14	32
Age	Mean	66.7	68.1	67.4
	Median	67.5	69.5	68.5
	Min	49	52	49
	Max	89	84	89

Figure 2. **Clinical study design**

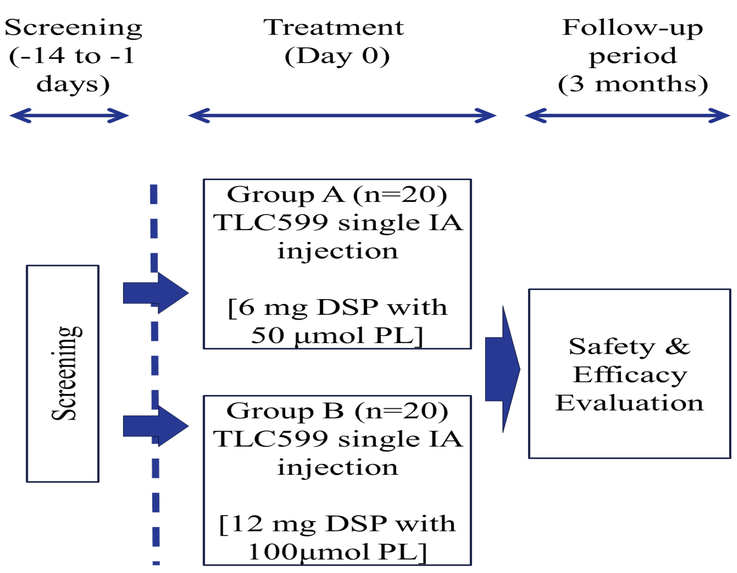

Figure 3. **Mean plasma cortisol was within normal range after dosing through 12 weeks**

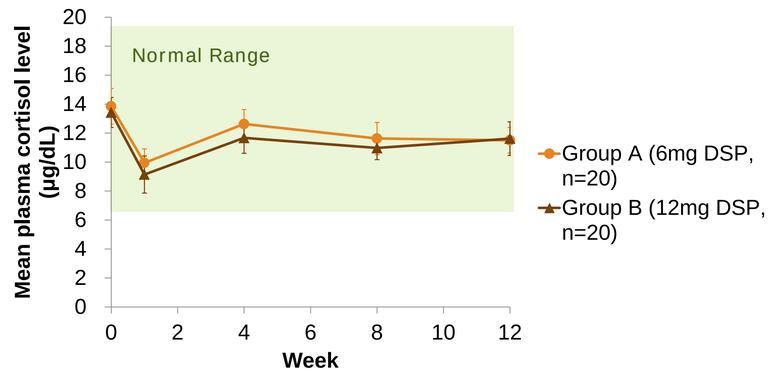

Figure 4. **Mean subject-reported VAS throughout 12 weeks (ITT population)**

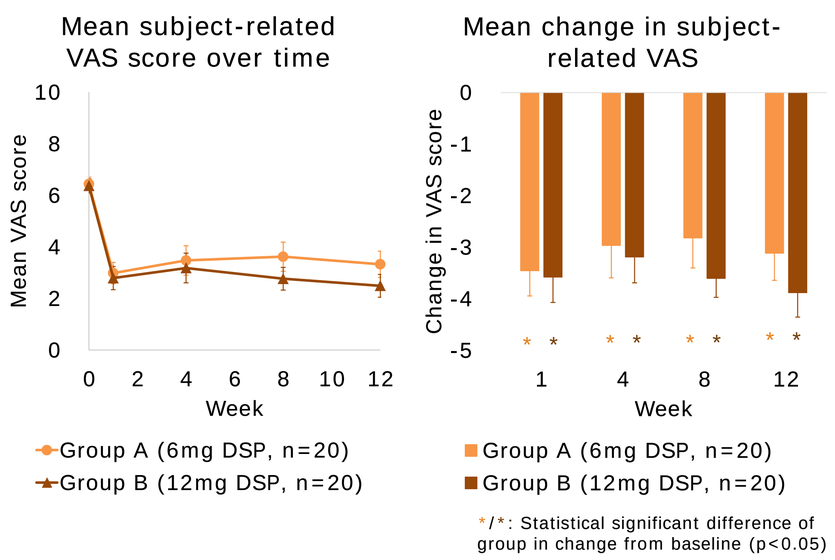

Figure 5. **Mean WOMAC pain throughout 12 weeks (ITT population)**

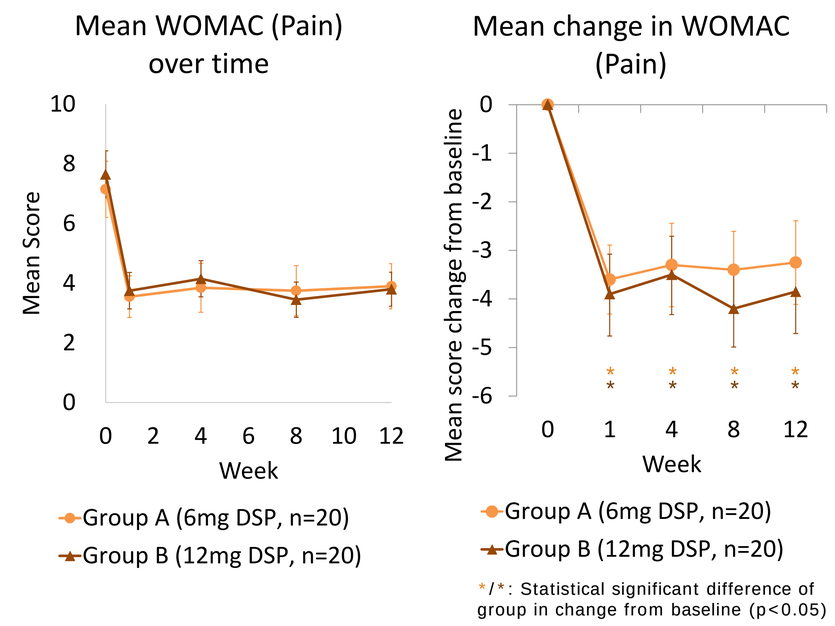

Table 2. **Percentage of Clinical responders through 12 weeks**

Responder	6mg DSP (n=20)	12mg DSP (n=20)
Week 1	70%	75%
Week 4	70%	65%
Week 8	70%	85%
Week 12	70%	75%

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

Responder is defined as

- ≥ 50% improvement and absolute improvement of ≥ 20 points from baseline in VAS or WOMAC physical function subscale.
- Subjects were also considered responders when VAS pain ≥ 20% and absolute change ≥10 with WOMAC physical function ≥20% and absolute change ≥ 10)

tlc

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