

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 50 μ mol phospholipid)
 - **Group B**, n = 20 (12mg DSP with 100 μ mol 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

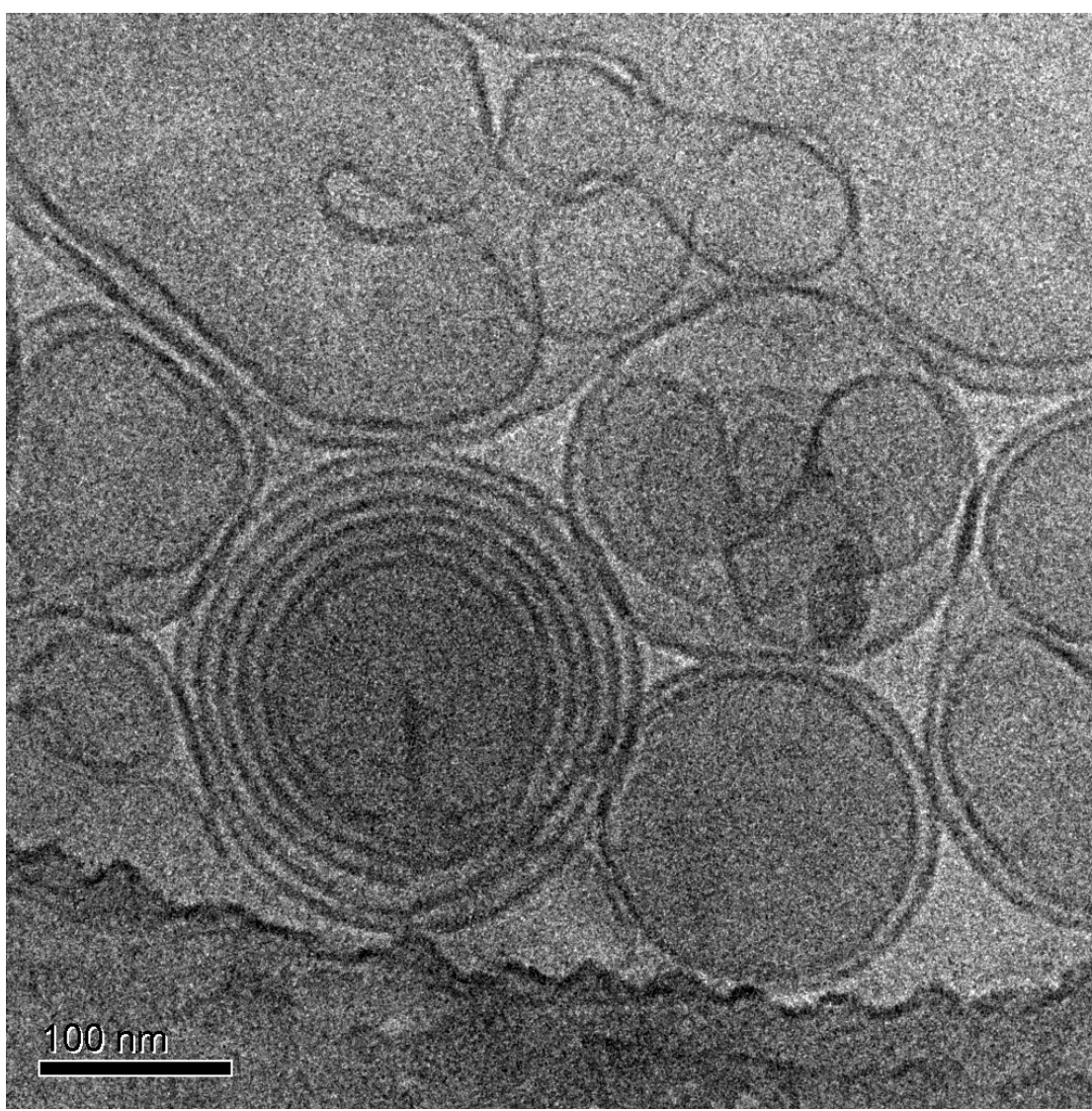


Table 1. Subject demographics

		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

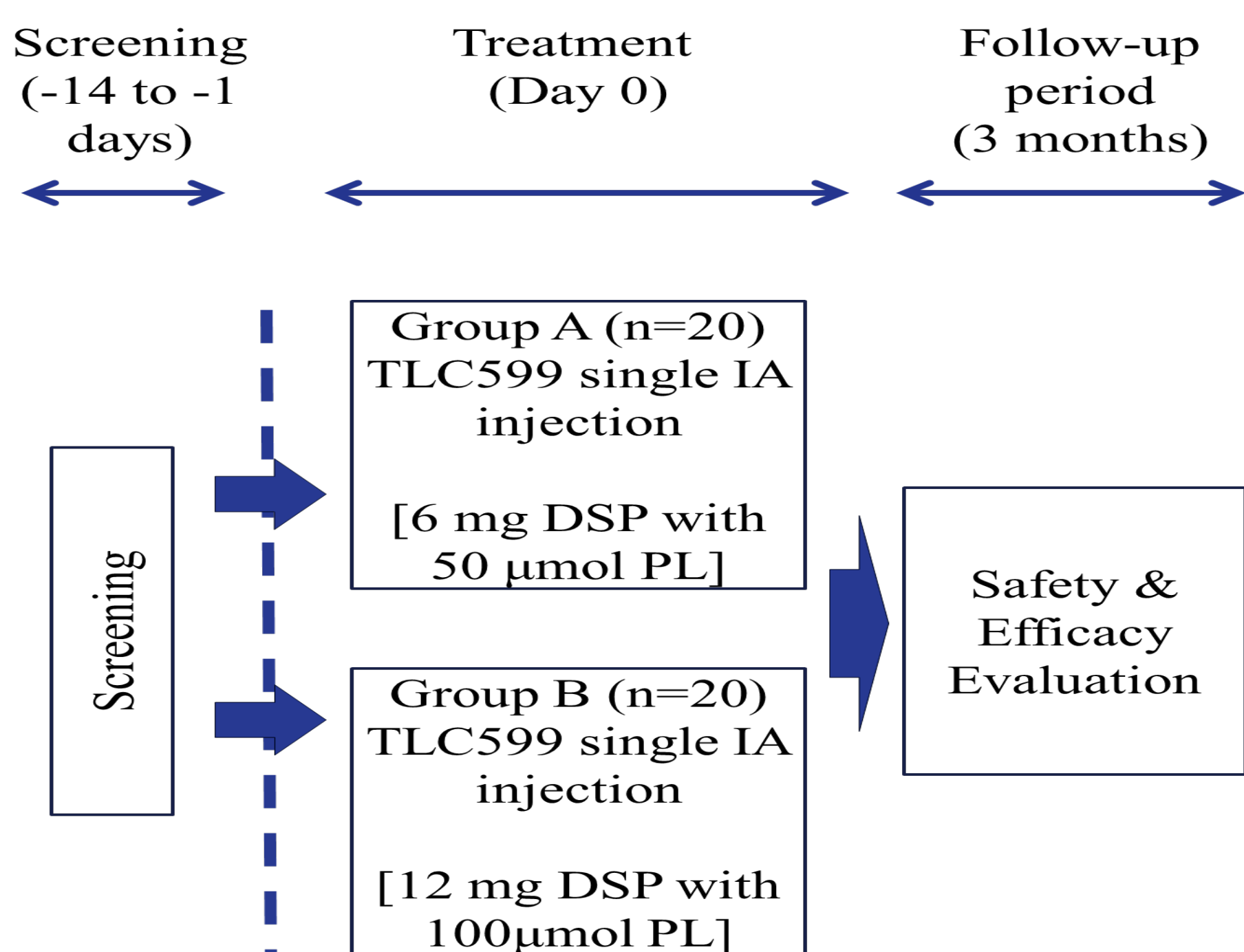


Figure 3. Mean plasma cortisol was within normal range after dosing through 12 weeks

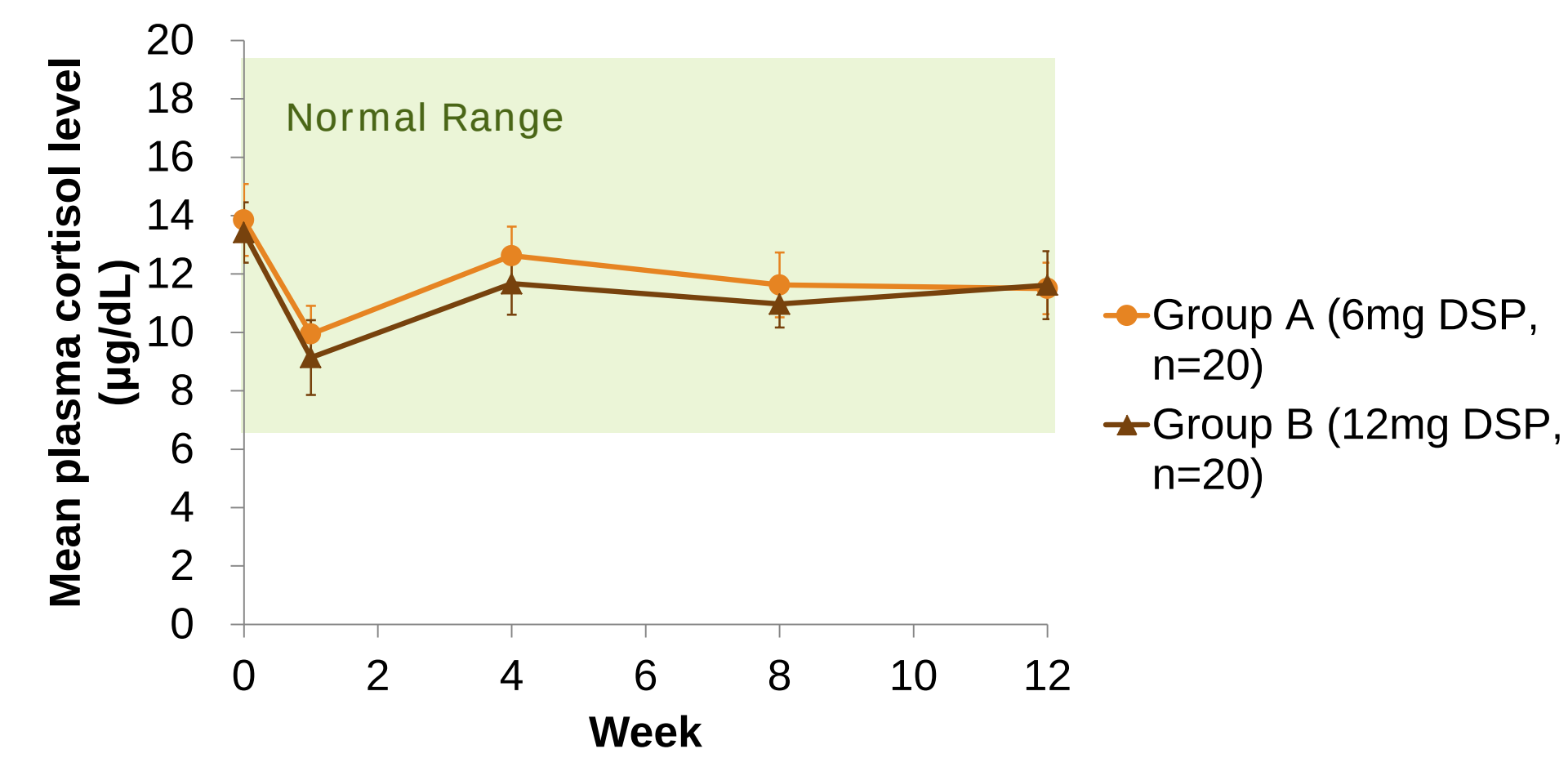


Figure 4. Mean subject-reported VAS throughout 12 weeks (ITT population)

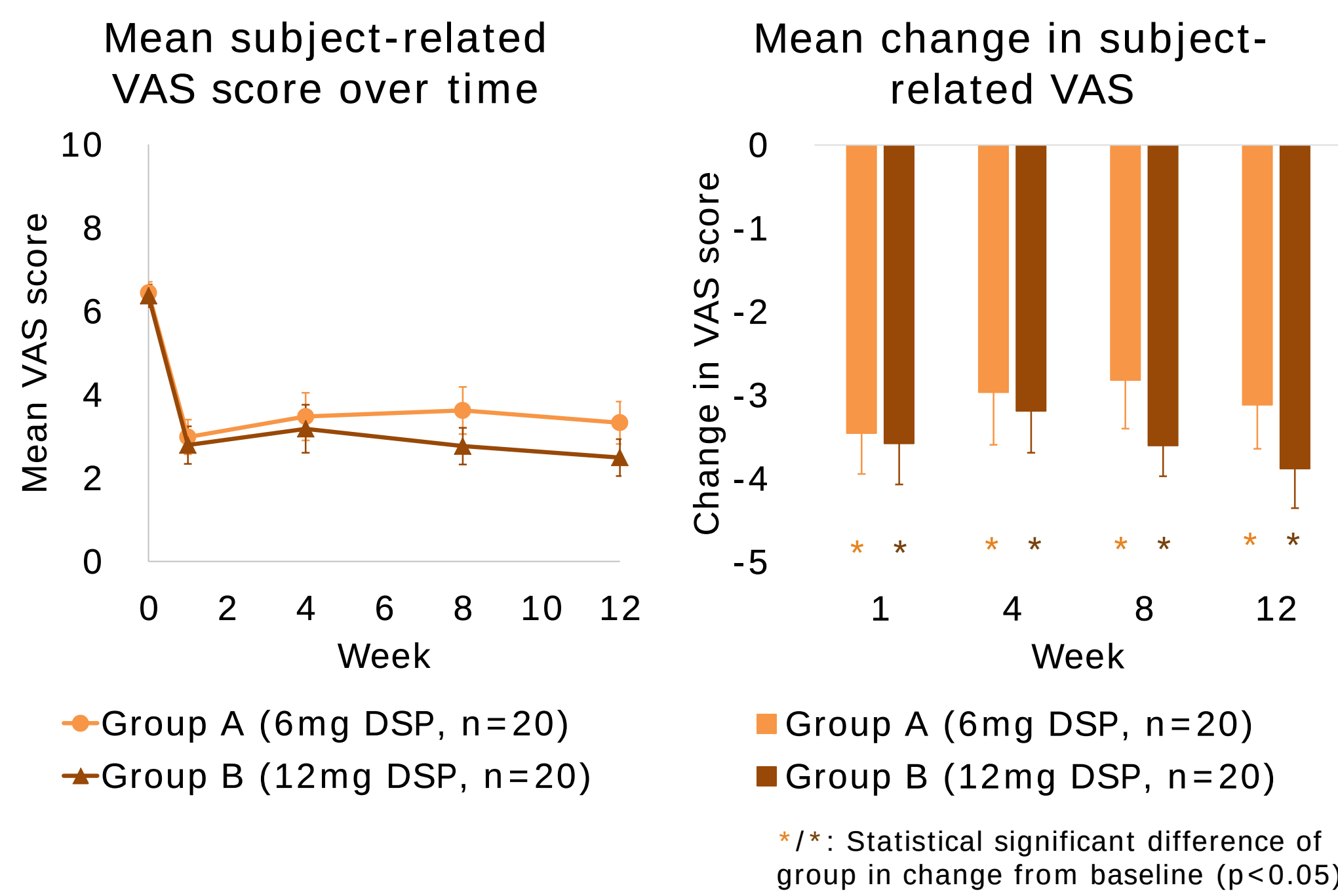


Figure 5. Mean WOMAC pain throughout 12 weeks (ITT population)

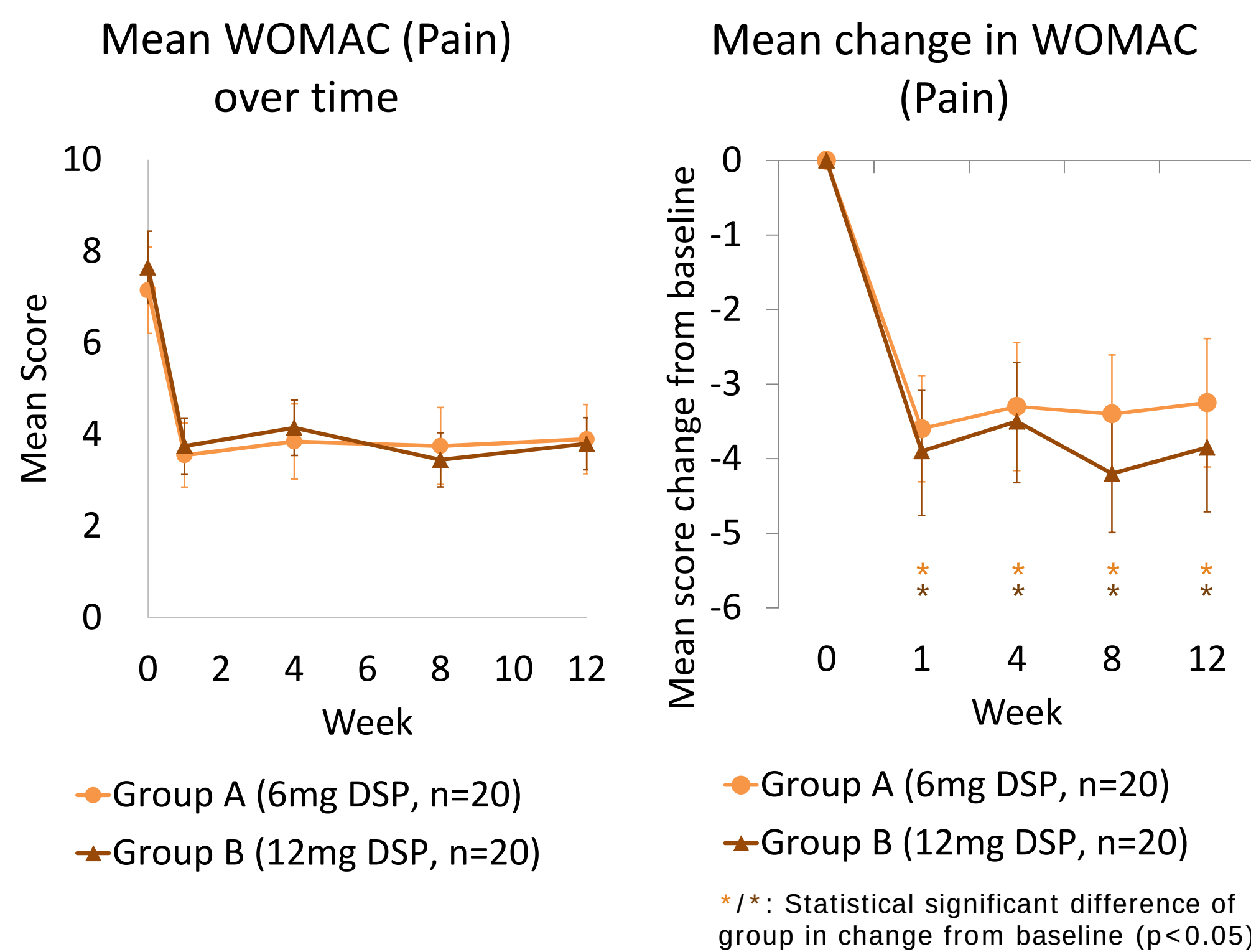


Table 2. Percentage of Clinical responders through 12 weeks

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

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

