BACKGROUND
Osteoarthritis (OA) is a degenerative joint disorder with limited long-lasting treatment options. Pro-inflammatory cytokines such as IL-1 and TNF-α which cause synovial inflammation and further mediated cartilage damage are believed to be one of the causes of OA, thus, corticosteroids are an ideal option for effective treatment in addition to nonsteroidal anti-inflammatory drugs. 1 Various steroid formulations on the market are effective but require frequent intra-articular (IA) injections due to short-term symptomatic relief. 2 An extended-release steroid, triamcinolone acetonide (ER-TA), for knee OA pain was recently approved by the FDA, however, both TA and ER-TA have been associated with chondrotoxic and related cartilage damage. 3,4

Dexamethasone sodium phosphate (DSP), a synthetic glucocorticoid, is the prodrug of dexamethasone (DEX) that was approved by the FDA over 30 years ago for the treatment of multiple conditions by multiple routes. DSP/DEX inhibits processes involved in inflammatory disease such as OA. The safety profile of DSP/DEX has been well characterized in nonclinical and clinical studies to support its use in the management of OA following IA injection. 5,6

TLC599, a novel sustained-release liposome formulation of DSP, resulted in reduced treatment frequency, fewer side effects, and significantly less toxicity than other commercial extended release formulation treatments for OA.

OBJECTIVES
• To evaluate cartilage damage by TLC599 in comparison to current steroid treatment such as TA and ER-TA
• To evaluate toxicokinetic (TK) and pharmacokinetic (PK) profiles of TLC599 following a single IA injection in five preclinical studies in healthy dogs and rabbits.

MATERIALS AND METHODS
TLC599
TLC599, a BioSeizer® formulation of DSP, is designed to provide sustained pain management over an extended period of up to six months. BioSeizer® technology uses multi-layer lipid membranes to provide prolonged local exposure in the joint.

Toxicity and Toxicokinetic Study Designs
In four toxicity studies, cartilage histology was examined following IA injection of TLC599 or other test articles. Proteoglycan loss was evaluated by the intensity of toluidine blue, a cationic dye which stains proteoglycans. A reduction in proteoglycan staining intensity would suggest cartilage damage and underlying chondrotoxicity. In two TK/PK studies, dexamethasone phosphate (DP) concentration was quantified and the TK/PK profile was evaluated (Table 1). DSP is the sodium salt form of DP.

RESULTS
Following IA injection of TLC599, the concentration of DP in synovial fluid maintained in high levels between 2.5 to 48.0 hours, and lasted through 360 hours (Figure 1a). DP maintained at similar levels from 30 days to 120 days post-dose (Figure 1b), demonstrating the prolonged local exposure in the joint.

TLC599 demonstrated comparable proteoglycan level to saline at 30 days post treatment, while high dose TA and ER TA showed significant proteoglycan loss compared to saline, and low dose ER TA showed significant proteoglycan loss compared to its equipotent dose of TA, as well as saline (Figure 3).

No intensity change in toluidine blue staining or morphology change in Hematoxylin and Eosin (H&E) staining were observed in either dogs or rabbits studies (Figure 2), indicating neither proteoglycan loss nor cartilage damage even after repeat dosing.

REFERENCES