Clinical Study Protocol

Protocol Title:	**A Phase IIa, Randomized, Double-blinded, Placebo-controlled, Dose-finding Study for Single-dose Administration of TLC599 in Patients with Osteoarthritis (OA) of Knee**
Protocol Number:	**TLC599A2003**
Date of Protocol/Version No.:	**03 Aug 2018 / Version 7.0**
Product:	**TLC599**
Study Phase:	**IIa**
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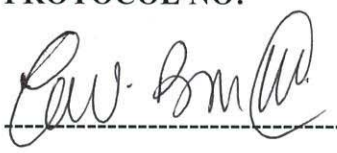
Signatures

PROTOCOL TITLE: A Phase IIa, Randomized, Double-blinded, Placebo-controlled, Dose-finding Study for Single-dose Administration of TLC599 in Patients with Osteoarthritis (OA) of Knee

PROTOCOL NO: TLC599A2003



03 AUG 2018

Sponsor's Representative **Date**

Carl Brown, PhD
Director, Medical Science Department
Product Development Division
Taiwan Liposome Company, Ltd.

SYNOPSIS

Name of Sponsor/Company:	Taiwan Liposome Company, Ltd. (TLC)
Name of Finished Product:	TLC599
Name of Active Ingredient:	Dexamethasone sodium phosphate (DSP)
Title of Study:	A Phase IIa, Randomized, Double-blinded, Placebo-controlled, Dose-finding Study for Single-dose Administration of TLC599 in Patients with Osteoarthritis (OA) of Knee
Protocol No:	TLC599A2003
Study Sites:	Global study, around 8 to 13 sites
Study duration: The study will be conducted for approximately 27 weeks including a 21-day screening period and a 24-week follow-up period.	**Phase:** IIa
Objectives: Primary: The primary objective is to evaluate the treatment efficacy of different test doses of TLC599 in patients with OA pain of knee. Secondary: The secondary objective is to evaluate the safety of different test doses of TLC599 in patients with OA of knee. Pharmacokinetics: The concentrations of dexamethasone and dexamethasone 21-phosphate in the synovial fluid at the end of study (EOS) or early termination (ET).	
Methodology: This is a Phase IIa, multi-center, double-blind, prospective, randomized, placebo (normal saline)-controlled study, intending to explore the treatment efficacy of 2 different dose levels of TLC599 compared to the placebo in patients with OA of the knee.	
Planned number of patients:	Approximately 24 patients in each of 3 different study groups (a total of approximately 72 patients) will participate in the study.
Diagnosis and main criteria for inclusion:	**Main Criteria for inclusion** Before the start of any screening procedure, all patients must have signed an informed consent form and be willing to follow the procedures as described in the protocol. (1) Male or female patients, at least 50 years of age. (2) Has any symptoms associated with OA of the knee for at least 6 months prior to the screening visit and confirmation of OA based on the clinical and radiological criteria of American College of Rheumatology Criteria for Classification of Idiopathic OA of the knee (standing fixed-flexion posteroanterior X-ray of the knee of approximately 20 degrees) within 6 months prior to the screening visit or during the screening period. (3) The study knee has OA with Grade 2 to 3 severity based on the Kellgren-Lawrence grades according to confirmatory X-ray result in inclusion criterion 2. (4) Patients with patient related visual analogue scale (VAS) score of 5.0 to 9.0 of study knee prior to the study drug administration at

	baseline. The VAS score of study knee should be equal or higher than non-study knee. Note: If the patient has been confirmed to have OA for one knee but the VAS score of this knee is lower than the other knee which was not diagnosed with OA, the patient should be excluded and screened failure. (5) Willing and able to comply with study procedures and provide written informed consent. **Main Criteria for exclusion** (1) Patients who received systemic corticosteroids within the last 30 days prior to study drug administration. (2) Patients who start new rehabilitation or exercise program during screening period. (3) Patients using glucosamine or chondroitin or dietary supplement with unstable dose or frequency within 4 weeks before screening visit. (4) Patients who use prohibited medications within 7 days prior to study drug administration or any pain control medication including acetaminophen within 48 hours prior to study drug administration. (5) Patients who use prohibited medications other than acetaminophen and oral NSAIDs from screening visit to 7 days prior to study drug administration. (6) Documented history and confirmed autoimmune disease including but not limited to secondary OA, Reiter's syndrome, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, inflammatory myositis, mixed connective tissue disease, palindromic rheumatism, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Bechet's disease, arthritis associated with inflammatory bowel disease, sarcoidosis, vasculitis, cryoglobulinemia, or amyloidosis. (7) Evidence of intra-articular bleeding of the study knee at baseline prior to study drug administration. (8) History of infective arthritis in the study knee, or suspected / concurrent infection in the study knee at baseline prior to study drug administration. (9) Documented gout attack in study knee within 6 months, evidence of tophi formulation, or active gouty arthritis attack prior to the baseline. (10) Patient with any amputation in any lower limb. (11) Any condition that could possibly confound the patient's assessment of study knee pain in judgement of the investigator (i.e., ipsilateral hip OA, radicular low back pain, and hip pain refer to the study knee).

	(12) Unstable study knee joint as determined by the investigator based on physical examination (with or without buckling or giving way) due to an acute injury (defined as injury within 6 months, eg. anterior cruciate ligament injury or tear); OR any surgery or arthroscopy in the study knee within the 12 months prior to the screening visit. (13) Clinical symptoms and signs of acute infection or infection-related inflammation in the other knee before study drug administration. (14) Use of IA corticosteroid, hyaluronic acid, or other IA injection in the study knee within 3 months prior to the screening visit. (15) Any skin lesion / breakdown at the anticipated injection site or any condition that impairs penetration of the study knee joint space. (16) Patient with body mass index > 40 kg/m^2 at the screening visit. (17) Platelet count < 80,000/μL, or blood coagulation disorders, including patients with hemophilia, decompensated liver cirrhosis or uremia at the screening visit. (18) History of acquired or congenital immunodeficiency diseases. (19) Concurrent systemic active or uncontrolled infectious disease. (20) A history of treated malignancy which is disease free for ≤ 5 years prior to the screening visit, except basal-cell carcinoma of skin or carcinoma-in-situ of the uterine cervix. (21) Stroke or myocardial infarction within 3 months prior to the screening visit. (22) Uncontrolled and unstable concurrent medical or psychiatric illness, including but not limited to, poorly controlled diabetes (defined as HbA1c > 9.0%), poorly controlled hypertension (mean arterial pressure [2/3 diastolic blood pressure + 1/3 systolic blood pressure] > 110mmHg), severe dementia, schizophrenia, or bipolar disorder, that will jeopardize the safety of the patient, interfere with the objectives of the protocol, or affect the patient compliance with study requirements, as determined by the investigator. (23) Patients with a condition or in a situation which, in the assessment of the investigators, will interfere with the patient's ability to comply or cooperate with the dosing and visit schedules and the protocol evaluations or may not be suitable for this study (e.g. illiterate). (24) Use of any chemotherapeutic or systemic immunosuppressant agents for inflammatory diseases within 6 months prior to the screening visit. (25) Current use of anticoagulants, including warfarin, heparin, low-molecular weight heparin, or dabigatran. (26) Use of any investigational agent within 4 weeks prior to study drug administration or within 5 half-lives of the product, whichever is

	longer. (27) Known allergy or hypersensitivity to the study drug or its components. (28) Female patients who are pregnant, nursing, planning to become pregnant, or who are of childbearing potential (defined as all the female patients after puberty, unless they have been post-menopausal for at least 2 years, are sterile based on a documented ovarian failure, or are surgically sterile, such as after hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and not using reliable means of contraception (e.g. established use of oral, transdermal, injected or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, barrier methods of contraception, male sterilization, total abstinence, etc.). (29) Abnormalities of laboratory parameters as described below will qualify for exclusion at the screening visit: • hemoglobin < 8 g/dL; • total white blood cell count < 4000/ μL; • serum bilirubin/ alanine aminotransferase/ aspartate aminotransferase > 2 times upper limit of normal (ULN) for the laboratory reference ranges; • eGFR <30 ml/min; • prothrombin time / International Normalized Ratio > ULN for the laboratory reference range. (30) Contraindication to undergoing magnetic resonance imaging (MRI) for both knees including but not limited to pacemaker, metal sutures, presence of shrapnel or iron filings.
Test product, dose and mode of administration:	Test product: TLC599 (1) low-dose group: 12 mg DSP with 100 μmol PL (1.0 mL) via intra-articular injection; (2) high-dose group: 18 mg DSP with 150 μmol PL (1.5 mL) via intra-articular injection.
Reference therapy, dose, and mode of administration:	Placebo group: Normal saline 1.5 mL via intra-articular injection

Criteria for evaluation:

Primary Endpoint:

The primary endpoint is to evaluate the change from baseline by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale through Week 12.

Secondary Endpoints:

(1) Change from baseline to Weeks 1, 4, 8, 12, 16, 20, and 24 in the patient rated visual analogue scale (VAS), and pain / function subscales of WOMAC.

(2) Change from baseline through Weeks 12, 16, 20 and 24 in VAS, and pain / function subscales of WOMAC

(3) Area under the effect curve (AUEC) of the VAS from baseline to Week 12, 16, 20 and 24.

(4) Area under the effect curve of the WOMAC pain subscale from baseline to Week 12, 16, 20 and 24.

(5) Proportion of responders by a decrease of > 30% or > 50% in patient-rated VAS from baseline to Weeks 1, 4, 8, 12, 16, 20, and 24.

(6) Proportion of responders by a decrease of > 30% or > 50% in WOMAC pain subscale from baseline to Weeks 1, 4, 8, 12, 16, 20, and 24.

(7) Proportions of durable responders with persistent response since Week 1till Weeks 12, 16, 20, and 24, respectively, by pain relief > 30% in VAS.

(8) Proportions of durable responders with persistent response since Week 1 till Weeks 12, 16, 20, and 24, respectively, by pain relief > 30% in WOMAC pain subscales.

(9) Proportions of durable responders with persistent response since Week 1 till Weeks 12, 16, 20, and 24, respectively, by outcome measured in rheumatology- Osteoarthritis Research Society International set of responder criteria.

(10) Change from baseline to Weeks 1, 4, 8, 12, 16, 20, and 24 in EuroQol-5 Dimension questionnaire.

(11) Total consumption of acetaminophen at Weeks 1, 4, 8, 12, 16, 20, and 24.

(12) Safety and tolerability.

Pharmacokinetic Endpoints:

The concentrations of dexamethasone and dexamethasone 21-phosphate in synovial fluid of the study knee joint at end of study or early termination.

Statistical methods:

Sample size calculation:

This is an exploratory study and there is no formal sample size evaluation. It is expected to have approximately 20 patients in each study groups completing 24-week follow-up period after study drug administration. Given a drop-out rate of 15%, approximately 24 patients in each study group will be enrolled and a total of approximately 72 patients will be randomly assigned.

General statistical considerations:

All efficacy and safety variables will be summarized using descriptive statistics. Continuous variables will be presented as number of observations, mean, standard deviation, median and range; while categorical variables will be presented as number of observations, count, and percentage in frequency table.

In this study, safety population is used for any safety analysis. The intent-to-treat (ITT), modified Intent-to-treat (mITT) and per-protocol (PP) populations will be used in analysis of efficacy variables, but the major efficacy conclusion will be based on the results obtained from mITT population. The analysis of

dexamethasone and dexamethasone 21-phosphate concentrations in the synovial fluid will be conducted based on the pharmacokinetic (PK) population.

Unless otherwise specified, all statistical assessments will be 1-sided and evaluated at the 5% level of significance.

All analyses, summaries, and listings will be performed using statistical analysis software (Version 9.2 or higher).

Further details regarding the definition of analysis variables and analysis methodology will be specified in a statistical analysis plan (SAP) to address all study objectives. The SAP will be developed and approved before database lock.

Analysis population:

The populations for analysis applied into this study are defined as follows:

(1) Intent-to-treat population: all enrolled and randomized patients.

(2) Safety population: All patients who receive any dose of study drug administration will be included in the safety population.

(3) Modified Intent-to-treat population: The mITT population indicates all enrolled patients who receive one complete dose of study drug administration and have at least one complete efficacy evaluation after study drug dosing.

(4) Per-protocol population: The PP population is a subset of mITT population fulfilling evaluable criteria without any major protocol deviation and has evaluation at baseline, Week 12 and at least 2 other evaluation within 12 weeks.

(5) Pharmacokinetics population: All ITT patients who receive any dose of study drug, and those who consented for synovial fluid collection from the study knee at the end of study (EOS)/early termination (ET) visit.

Efficacy analysis:

All efficacy analyses will be conducted for the mITT and PP populations as well as ITT population.

For the primary efficacy analysis, the overall change from baseline in WOMAC pain subscale over 12 weeks will be analyzed using a mixed-effects model for repeated measures (MMRM) with restricted maximum likelihood estimation. The model will include factors of treatment, visit (as a categorical variable), baseline value of the WOMAC pain subscale score as fixed factors, site as random factor, and treatment-by-visit as interaction terms. This methodology will be used to compare treatment groups for change from baseline through Week 12. The model estimates by treatment group, contrast estimates for between-group (pairwise) comparisons, standard errors, 90% CIs, and p-values will be presented.

An MMRM model as described for primary efficacy analysis will be used to analyze the overall change from baseline in WOMAC pain / function subscale and VAS over 12, 16, 20 and 24 weeks as well as the change from baseline in WOMAC pain / function subscale and VAS at each scheduled visit.

Analysis of covariance (ANCOVA) is to be used for secondary efficacy endpoints measured in continuous scale, including treatment group, and the baseline value of that endpoint and the study sites as covariate if appropriate. Within each treatment group, the total consumption of acetaminophen, changes from baseline in patient-rated VAS, WOMAC pain subscale, WOMAC function subscale, and EQ-5D at scheduled time points, and AUEC of VAS/WOMAC pain subscale will be summarized using descriptive statistic and estimated using the least squares mean. The 2-sided 90% confidence interval for LSM will be reported for each treatment arm.

The frequency and percentage will be used to summarize patients achieving the response criteria at scheduled time points and patients achieving the durable response criteria and will be presented by treatment group. Treatment comparisons of each TLC599 dose treatment with placebo will be made using a logistic regression analysis with treatment group, study site, and the baseline value of that endpoint as covariate in the model.

Explorative univariate models will be used to identify the possible prognostic factors associated with

WOMAC pain subscale and VAS, e.g. age, gender, race, unilateral or bilateral knee pain, and baseline severity by VAS or pain score and Kellgren-Lawrence grades. The subgroup analysis will be performed according to the results of regression model.

Safety analysis:

The assessment of safety will be based mainly on the frequency of adverse events (AEs), which includes all serious AEs (SAEs) and AEs, clinical laboratory data, vital signs, physical examination, electrocardiogram (ECG) result, articular cartilage assessment by MRI, and other safety findings.

All safety variables will be summarized using descriptive statistic based on the safety population. No inferential statistics are planned.

Pharmacokinetics analysis:

The concentrations of dexamethasone and dexamethasone 21-phosphate in the synovial fluid of the study knee at EOS will be summarized by treatment group using descriptive statistics.

Schedule of Events

Visit	**Screening**	**1(Baseline)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOS/ET**
Week/Day	**Day -21 ~ -1**	**Day -1 ~ 0**	**Day 3**	**Week 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**
Window (day)			**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Demographics and medical history	X									
Physical examination and vital signs[1]	X	X	X	X	X	X	X	X	X	X
X-ray examination[2]	X									
Clinical chemistry and hematology[3]	X	X	X	X	X	X	X	X	X	X
Urinalysis	X									X
12-lead ECG	X									X
HbA1c	X						X			X
Blood cortisol[4]		X	X	X	X	X	X	X	X	X
Urine pregnancy test[5]	X	X								X
VAS Score[6]		X	X	X	X	X	X	X	X	X
WOMAC score[6]		X	X	X	X	X	X	X	X	X
EQ-5D[6]		X	X	X	X	X	X	X	X	X
Randomization[6,]		X								

Visit	**Screening**	**1(Baseline)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOS/ET**
Week/Day	**Day -21 ~ -1**	**Day -1 ~ 0**	**Day 3**	**Week 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**
Window (day)			**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Excessive synovial fluid aspiration / analysis & Study drug administration [6,7,]		X								
MRI examination[8]	X									X[9]
Concomitant medication	←						→			
AE/SAE	←						→			
Diary card[10]	←						→			
Pharmacokinetics samples collection (synovial fluid) (optional)[11]										X

1. Height is measured only at screening. Weight is measured at screening, Visit 1, 4, 5, 6, 7, 8 and EOS/ET. Vital signs including BP, HR, RR, tympanic temperature will be assessed at each follow-up visit.
2. The X-ray examination will include a chest PA view and examination for both knees. Standing fixed-flexion PA X-ray of the knees of approximately 20 degrees and lateral view of X-ray examination will be performed for both knees, if it has not been performed during the 6 months prior to screening.
3. INR of PT and aPTT should be performed at the screening visit only. HbA1c should be performed at screening visit, Visit 6 and the EOS/ET visit. Other laboratory tests (clinical chemistry and hematology) at Visit 1 will be performed before study drug administration. Fasting glucose examination is not required for the screening visit, but will be required for all subsequent visits, from Visit 1 to EOS/ET visit.
4. A blood sample to measure the plasma or serum cortisol level should be collected before 10:00 am or based on local lab requirement at the scheduled visits and before study drug administration at Visit 1.
5. Urine pregnancy tests will be performed only for women with childbearing potential.
6. At Visit 1, some local sites may have facility constraint for study drug preparation. Randomization, VAS, WOMAC, and EQ-5D questionnaires should be performed at the same day. Study drug administration is allowed to be performed at the same day as randomization or one day after randomization. The day of study drug administration is defined as Day 0.
7. For patient with excessive synovial effusion, it is accepted to aspirate the excessive synovial fluid during study drug administration procedure. However, the characteristic and amount of the aspirated fluid should be recorded. The aspirated fluid can be sent for laboratory examination if there is any concern of infection, intra-articular bleeding or the OA diagnosis is questionable.
8. For the articular cartilage evaluation of the knees, all subjects should have MRI examination conducted for MOAKS grading during the screening period or prior to randomization, and at the end of study/early termination. MRI images will be performed for both knees.
9. MRI examination can be performed within 21 days prior to EOS/ET visit.

10. Use of acetaminophen will be recorded on diary card.
11. Synovial fluid from the study knee will be collected after completion of efficacy evaluation (VAS, WOMAC and EQ-5D) at EOS or within 3 days after ET visit, only if the subject has provided written informed consent for this procedure. In addition, it will only be aspired if appropriate synovial fluid volume in the study knee is ensured by local ultrasound examination and/or at the investigator's discretion prior to the aspiration.

Abbreviations: AE=adverse event; BP=blood pressure; ECG=electrocardiogram; EOS=end of study; EQ-5D=EuroQol-5 Dimension; ET=early termination; HbA1c=glycosylated hemoglobin; HR=heart rate; INR= international normalized ratio; MOAKS=MRI Osteoarthritis Knee Score; MRI=magnetic resonance imaging; PA=posterior-anterior; PT= prothrombin time; aPTT=partial thromboplastin time; RR=respiratory rate; SAE=serious adverse event; VAS=visual analogue score; WOMAC=Western Ontario McMaster Universities.