CLINICAL STUDY PROTOCOL

A Phase I/II, Randomized, Double-blind, Comparator-controlled, Dose-escalation Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of TLC590 for Postsurgical Pain Management Following Inguinal Hernia Repair

Protocol Number:	TLC590A1001
FDA IND Number:	133171
Investigational Product:	TLC590 (Ropivacaine Liposome Injectable Suspension)
Phase:	Phase I/II
Sponsor:	Taiwan Liposome Company, Ltd. 11F-1, No. 3, Yuanqu Street, Nangang District Taipei City 115 Taiwan
Contract Research Organization:	INC Research 1030 Sync Street Morrisville NC 27560 United States
Protocol Date:	13 December 2018 (Amendment 03)
Protocol Version:	Version 4.0

3 SYNOPSIS

Protocol Number:

TLC590A1001

Title:

A Phase I/II, Randomized, Double-blind, Comparator-controlled, Dose-escalation Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of TLC590 for Postsurgical Pain Management Following Inguinal Hernia Repair

Investigational Product:

TLC590 (Ropivacaine Liposome Injectable Suspension)

Study Centers:

Approximately 2 centers in the United States (US)

Phase:

Phase I/II

Objectives:

The primary objective of this study is to evaluate the safety and tolerability of TLC590 for postsurgical pain management in subjects with inguinal hernia repair surgery.

The secondary objectives of this study are:

- To evaluate the pharmacokinetic (PK) profile and dose-exposure relationship of TLC590, as well as the bioavailability as compared with Naropin®.
- To evaluate analgesic efficacy of TLC590 compared with Naropin® for postsurgical pain management in subjects with inguinal hernia repair surgery.
- To evaluate the exposure-response relationship between PK parameters and pain management.

Study Design:

This is a Phase I/II, randomized, double-blind, comparator-controlled, dose-escalation study to assess the safety, PK, and efficacy of single postsurgical application of TLC590 compared with Naropin® via a single infiltrative local administration in adult subjects following inguinal hernia repair surgery.

The study will enroll approximately 64 evaluable subjects who meet all entry criteria across 4 cohorts. Approximately 16 subjects will be enrolled to each cohort in a 3:1 ratio. Each cohort will comprise 12 subjects receiving a dose of TLC590 and 4 subjects receiving active comparator drug (Naropin® 150 mg; [0.5%, 5 mg/mL]) in accordance with the randomization schedule (as assigned by a centralized interactive web response system [IWRS]) and dose-escalation scheme outlined in the following table.

Cohort	TLC590	Naropin®
Cohort 1 (N = 16)	N = 12: TLC590; 190 mg (10 mL)	N = 4: Naropin®; 150 mg (30 mL)
Cohort 2 (N = 16)	N = 12: TLC590; 380 mg (20 mL)	N = 4: Naropin®; 150 mg (30 mL)
Cohort 3 (N = 16)	N = 12: TLC590; 570 mg (30 mL)	N = 4: Naropin®; 150 mg (30 mL)
Cohort 4 (N = 16)	N = 12: TLC590; 760 mg (40 mL) **OR** N = 12: TLC590; 475 mg (25 mL); if the TLC590 570 mg (30 mL) dose is not tolerated	N = 4: Naropin®; 150 mg (30 mL)

Dose escalation of a single postsurgical administration of TLC590 will be performed using sequential dose levels starting at 190 mg up to 760 mg, as compared with Naropin® 150 mg (5 mg/mL) via infiltrative local administration in adult subjects following unilateral Lichtenstein inguinal hernia repair surgery. Dose escalation

will be determined by review of treatment-related adverse events and all serious AEs (SAEs) by a safety monitoring committee (SMC); PK data will also be reviewed only by the SMC at the end of each cohort to assess systemic exposure to total and free (unbound) ropivacaine.

Number of Subjects:

Approximately 64 evaluable subjects in up to 4 cohorts of approximately 16 subjects per cohort will be enrolled in this study.

Treatment:

At the end of the surgery, prior to wound closure, a single infiltrative local dose of blinded study medication will be administered.

Study Duration:

The study duration will be approximately 60 days. Each subject will be screened within 28 days before blinded study medication administration. At the end of the surgery, prior to wound closure, a single infiltrative local dose of blinded study medication will be administered. The subject will remain in the clinic at least 48 hours after administration of blinded study medication, and each subject will be followed for 30 days.

Study Population:

Inclusion Criteria:

To be eligible for study entry, subjects must satisfy all of the following criteria:

1. Able and willing to provide a written informed consent, indicating that he/she is aware of the investigational nature of this study involved and willing to comply with the requirements of this study protocol.
2. Male or female between 18 and 65 years of age, inclusive.
3. Scheduled to undergo a primary, unilateral Lichtenstein inguinal hernia repair with mesh, and be able to use the anesthesia regimen.
4. Have an American Society of Anesthesiology (ASA) Physical Status Classification of 1 or 2.
5. Female subjects are eligible only if all of the following apply:
    - Not pregnant (female subjects of childbearing potential must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline before randomization);
    - Not lactating;
    - Not planning to become pregnant during the study;
    - Commits to the use of an acceptable form of birth control or be surgically sterile; or be at least 2 years post-menopausal; or is practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA for greater than 2 months prior to Screening visits and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days from completion of the study.
6. Male subjects must be sterile (biologically or surgically) or commit to the use of a reliable method of birth control (e.g., must agree to use double-barrier contraception in the event of sexual activity) for the duration of the study until at least 1 week after the administration of blinded study medication.
7. Have a body mass index ≤ 35 kg/m^2.

Statistical Analysis:

No formal sample size calculation will be performed, but rather, the number of subjects per cohort is based on previous experience with other drugs for first-in-human trials and is generally considered adequate for determination of tolerability and PK characterization.

NPRS scores following rescue analgesics will be imputed by the windowed worst observation carried forward. The worst NPRS score prior to each rescue analgesic will be carried forward within the following 4-hour window. If the pain intensity score for the windowed observation is higher than the worst observed score, it will not be replaced. Missing NPRS scores will be imputed via the last observation carried forward (LOCF) using the last observed scores. Sensitivity analyses on NPRS related endpoints will be performed by imputing data following rescue analgesics using LOCF. The NPRS scores just prior to the rescue analgesics will be carried forward for all subsequent scheduled assessments.

Analysis of variance (ANOVA) or a Kruskal-Wallis test (if the normality assumption is not met) will be used to assess the overall difference among treatments for NPRS at rest and with movement, AUC of NPRS at rest and with movement, the total postoperative consumption of rescue analgesics, and the average daily rescue analgesic consumption.

The Kaplan-Meier method will be used to analyze time to the first postoperative use of rescue analgesic, and time to the first postoperative use of rescue opioid. Comparison of the survival curves among treatments will be assessed by a log-rank test.

Chi-square test or Fisher's exact test will be used to assess the overall differences among treatments for the proportions of subject who are opioid free, subjects who used no rescue analgesics, and subjects who used no postoperative antiemetic therapy, and PGA.

All the exploratory endpoints will be summarized descriptively.

Blood concentrations of ropivacaine (unbound and total) will be descriptively summarized at each scheduled time of PK sampling by treatment. PK parameters will be derived by non-compartmental analysis.

The dose-exposure relationship of TLC590 will be evaluated by the tabulation of AUC and C_{max} parameters obtained from each dose level and displayed graphically. The power model will be used to investigate the dose proportionality for subjects who received the TLC590 treatment. The relative systemic bioavailability (including relative AUC and C_{max}) compared to Naropin® will be analyzed by using a general linear model (GLM). Exposure-response relationship between PK parameters and NPRS scores will be displayed graphically and will be evaluated accordingly

Safety analysis will be based on all safety information collected including physical examination, surgical site assessment, vital signs assessments, clinical laboratory data, 12-lead electrocardiogram (ECG), AEs, and SAEs.