1 TITLE PAGE

CLINICAL STUDY PROTOCOL

A Phase I/II trial of TLC399 (ProDex) in Patients with Macular Edema due to Retinal Vein Occlusion (RVO): An Open-label, Sequential Dose Escalation Phase I Part to Determine Dose Limiting Toxicities (DLTs) Followed by an Open-label, Single-arm Part to Evaluate Efficacy and Tolerability

Sponsor:	Taiwan Liposome Company, Ltd. (TLC) 11F-1, No. 3, Yuanqu St., Nangang District, Taipei, Taiwan 115
Protocol Number:	TLC399.1
Development Phase:	I/II
Protocol Version & Date:	V9.0, 28 Mar 2019

Signature Page of Approvers:

Protocol No. TLC399.1

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The study will be conducted in compliance with the clinical study protocol, international Good Clinical Practice (GCP) principles (International Conference on Harmonization [ICH] - GCP), and regulatory authority requirements.

Approved by the following:

Carl Brown	Carl Brown	28 MAR 2019
Director Medical Science Department Product Development Division Taiwan Liposome Company, Ltd.	Signature	Date

Wing Chuang	Wing Chuang	28 Mar 2019
Senior Medical Science Specialist, Medical Science Department Product Development Division Taiwan Liposome Company, Ltd.	Signature	Date

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Ling Yeung		2019 / 03 / 28
Medical Monitor, Taiwan Liposome Company, Ltd.	Signature	Date

Signature Page for Principal Investigator:

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I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with the accepted version of the Declaration of Helsinki.

Principal Investigator Name: Title: Institution: Address:	Signature	Date

2 SYNOPSIS

TITLE OF STUDY: A Phase I/II trial of TLC399 (ProDex) in Patients with Macular Edema due to Retinal Vein Occlusion (RVO): An Open-label, Sequential Dose Escalation Phase I Part to Determine Dose Limiting Toxicities (DLTs) Followed by an Open-label, Single-arm Part to Evaluate Efficacy and Tolerability

SPONSOR: Taiwan Liposome Company, Ltd. (TLC)
11F-1, No. 3, Yuanqu St., Nangang District,
Taipei, Taiwan 115

DEVELOPMENT PHASE: I/II

STUDY OBJECTIVES:

Primary:

Part 1:

- To characterize the dose-limiting toxicity(ies) (DLT[s]) of TLC399 (ProDex) in patients with macular edema due to retinal vein occlusion (RVO)

Part 2

- To evaluate the safety, tolerability, and efficacy of the selected TLC399 (ProDex) strength administered as a single dose in patients with macular edema due to RVO for up to 1 year

Secondary:

Part 1:

- To evaluate the safety and tolerability of up to 4 different strengths of TLC399 (ProDex) administered as a single dose in patients with macular edema due to RVO for up to 1 year

Part 2:

- To evaluate the gain in best corrected visual acuity (BCVA) with different doses of TLC399 (ProDex) from baseline up to 1 year
- To evaluate the change in BCVA from baseline up to 1 year
- To evaluate the mean changes in intraocular pressure (IOP) in patients receiving TLC399 (ProDex) treatment from baseline up to 1 year
- To evaluate the change in central retinal thickness in patients receiving TLC399 (ProDex) treatment from baseline up to 1 year

STUDY DESIGN: This study will consist of 2 parts: Part 1 is an open-label, sequential dose escalation part to determine the DLT of TLC399 (ProDex) in patients with macular edema due to central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO). Part 2 is an open-label, single-arm design to investigate the use of TLC399 (ProDex) in patients with macular edema due to CRVO or BRVO in one dose level selected from Part 1. In Part 2, the enrollment of subjects for analysis will include approximately 20 patients in total, inclusive of Part 1 and Part 2 for the selected dose group.

Part 1

About 6 to 24 patients will be enrolled after fulfilling the inclusion and exclusion criteria to enter this part of the study. The screening period will last for up to 14 days.

Part 1 is 3+3 design. At first, 3 evaluable patients will be enrolled in Group 1 and administered a single intravitreal injection of TLC399 (ProDex), i.e., 0.36 mg dexamethasone sodium phosphate (DSP) with 100 mM phospholipid (PL) (30 μL) on Day 0. During the trial conduct, a lower dose Group R1 was included based on Safety Monitoring Committee's recommendation. The study dose levels for escalation are shown below:

- Group R1: 0.24 mg DSP with 100 mM PL (20 μL)
- Group 1: 0.36 mg DSP with 100 mM PL (30 μL)
- Group 2: 0.6 mg DSP with 100 mM PL (50 μL)
- Group 3: 0.6 mg DSP with 50 mM PL (50 μL)

After the intravitreal injection, each patient will be observed for 4 weeks for DLTs. If none of the first 3

evaluable patients experiences a DLT, then dose escalation will proceed to the next dose cohort. If 1 of 3 evaluable patients develops DLT(s), the cohort will be expanded to a maximum of 6 evaluable patients (another 3 patients added subsequently), or amend study design according to SMC's recommendation. If exactly 1 of the 6 evaluable patients experiences DLT(s), then escalation to the next dose level will occur. If ≥ 2/3 or 2/6 patients develops DLT(s), the dose will not keep escalating and have to de- escalate to previous cohort to reach the maximum of 6 patients (unless previous cohort has reached 6 patients). The safety results should be evaluated by Safety Monitor Committee (SMC) regularly every 6 months and after last patient of each cohort completes DLT observation period. The SMC would advise or give permission for further dose escalation, de-escalation, or any study design adjustment.

Patient enrollment in other groups will follow in a similar manner as Group 1. If ≥ 2/3 or 2/6 patients develop DLT in the R1 group during the conduct of Part 1, the study will be terminated. The MTD must be confirmed with 6 patients.

After the study drug administration, these patients will continue to be evaluated for efficacy and safety outcomes up to a period of 12 months unless the patient is withdrawn or discontinues the study.

In the concurrent Phase IIa (NCT03093701) trial conducted in the United States, the dose levels tested represent the dose Group 1~3 of this Phase I/II trial, and the subjects randomized outnumbered the patients to be enrolled in the current study without DLT observed. Based on the safety data of the five evaluable subjects assigned in the dose Group R1 and 1, the Safety Monitoring Committee approved the sponsor's proposal to further evaluate the dose Group R1 with expansion in Part 2, without MTD determination. Pending implementation of this amendment, further subjects will be recruited into Group R1; these subjects will be included in the Part 2 of the study for analysis.

Part 2

In Part 2, the dose level of Group R1 is selected for safety/efficacy evaluation with further recruitment up to a total of 20 subjects for analysis, inclusive of the patients of Group R1 in Part 1 and 2. The safety and efficacy outcomes will be assessed for up to 12 months (Table 2).

Parts 1 and 2

The Investigator will select 1 eye per patient to be the study eye. If both eyes are eligible for the study, the eligible eye with the shorter disease duration (macular edema) will be selected as the study eye.

During the study period, other treatment modalities for RVO treatment including laser photocoagulation, intravitreal or periocular steroid injection, or intravitreal anti-vascular endothelial growth factor [VEGF] are prohibited except condition is compatible with rescue therapy or obtained approval from sponsor. Any patient experiencing a worsening of disease (ie, worsening of macular edema secondary to RVO) in the study eye beginning 12 weeks post-injection as judged by the Investigator, defined by a:

- (1) BCVA loss of ≥ 10 letters compared with the previous best post-baseline measurement in conjunction with ≥50 um increase of CST (relative to CST at best BCVA); or,
- (2) ≥ 100 μm increase of CST compared with the previous best post-baseline measurement by SD-OCT measurement (as measured by the site); or,
- (3) BCVA loss of ≥ 15 letters compared with the previous best post-baseline measurement persisting for ≥ 7 days,

the patient may be treated with any rescue treatment (excluding steroid) that the Investigator deems appropriate to ensure subject safety.

At 12 weeks post injection, any subject that has not achieved a decrease of CST from baseline ≥ 25% is allowed to use rescue medication per the Investigator's judgement.

In principle, the sponsor will reimburse the use of a single administration of rescue medication.

The patient receiving rescue treatments per protocol definition or prohibit treatment would stay in the study for safety follow-up and is not required to be discontinued from the study. Their efficacy and safety outcomes before receiving prohibited treatment/ rescue therapy will be included in the efficacy and safety analyses, respectively. The data after receiving prohibited or rescue treatment/medications will be separately presented.

STUDY POPULATION: Patients who have macular edema due to RVO will be enrolled at multiple sites in Taiwan. About 6 to 24 patients are planned to be enrolled for the sequential dose escalation Part 1 of the study. Patients will be further enrolled in Part 2 of the study, to include a total of 20 subjects in the dose group R1 from both Parts 1 and 2.

DIAGNOSIS AND MAIN CRITERIA FOR ENROLLMENT:

Inclusion Criteria:

1. Male or female, at least 20 years of age.
2. Patients with macular edema due to CRVO or BRVO diagnosed within 36 months prior to Screening visit with:
   - Visual acuity decreases attributable to the edema
   - In the Investigator's opinion, unlikely to be adversely affected if not treated for 6 months
   - Non-ischemic type by fluorescein angiography (FA)
3. BCVA score of 20/40 to 20/400 by chart Early Treatment of Diabetic Retinopathy Study (ETDRS) in the study eye at Screening visit and Baseline visit.
4. Mean central subfield thickness ≥350 μM on Spectral/Fourier domain by optical coherence tomography (OCT) measurements in the study eye at Screening visit.
5. Willing and able to comply with the study procedure and sign a written informed consent.

Note: If both eyes are eligible for the study, the eligible eye with the shorter duration of disease will be used as the study eye.

Exclusion Criteria:

1. Macular edema due to diabetic retinopathy or other etiologies at Screening visit.
2. Brisk afferent pupillary defect (i.e., obvious and unequivocal) at Screening visit.
3. Stroke or myocardial infarction within 3 months prior to the Screening visit.
4. Uncontrolled systemic disease, or poorly controlled hypertension (defined as systolic blood pressure [BP] >160 mm Hg and/or diastolic BP >90 mm Hg), or poorly controlled diabetes (defined as hemoglobin A1c level > 9.5%) at Screening visit.
5. Any ocular condition that in the opinion of the Investigator would prevent a 15-letter gain in visual acuity (e.g., severe macular ischemia).
6. Presence of an epiretinal membrane in the study eye which, in the opinion of the Investigator, is the primary cause of macular edema, or is severe enough to prevent gain in visual acuity despite reduction in macular edema.
7. History of clinically significant IOP elevation in response to steroid treatment.
8. History of glaucoma or optic nerve head change consistent with glaucoma damage, and/or typical glaucomatous visual field loss in both eyes.
9. Active ocular hypertension ≥ 21 mm Hg or history of treated ocular hypertension in the study eye.
10. Aphakia or presence of anterior chamber intraocular lens in the study eye.
11. Active retinal neovascularization in the study eye at the Screening visit.
12. Active or history of choroidal neovascularization in the study eye.
13. History of central serous chorioretinopathy in either eye.
14. Presence of rubeosis iridis in the study eye at the Screening visit.
15. Any active ocular infection (i.e., bacterial, viral, parasitic, or fungal) in either eye at the Screening visit.
16. History of herpetic ocular infection in the study eye or adnexa.
17. Presence of active or inactive toxoplasmosis in either eye at the Screening visit.
18. Presence of visible scleral thinning or ectasia in the study eye at the Screening visit.
19. Media opacity in the study eye at the Screening visit that precludes clinical and photographic evaluation (including but not limited to preretinal or vitreous hemorrhage, lens opacity).

20. Intraocular surgery, including cataract surgery, in the study eye within 6 months prior to the Screening visit.
21. History of pars plana vitrectomy, radial optic neurotomy, or sheathotomy in the study eye.
22. Anticipated need for ocular surgery in the study eye during the 12-month study period.
23. Use of hemodilution for the treatment of RVO within 3 months prior to the Screening visit.
24. Use of any intraocular anti-VEGF therapy in the study eye, including aflibercept within 56 days, ranibizumab within 28 days and bevacizumab within 28 days, and has satisfied improvement prior to the Screening visit.
25. Use of laser of any type in the study eye within 3 months prior to the Screening visit.
26. Previous use of intravitreal steroids in the study eye within 6 months prior to the Screening visit. Prior use of Iluvien® is not allowed.
27. Periocular depot of steroids to the study eye within 1 month prior to the Screening visit.
28. Use of systemic steroids, or warfarin/heparin within 1 month prior to the Screening visit or anticipated use at any time during the study.

Exclusion Criteria (cont'd):

29. Use of immunosuppressants, immunomodulators, antimetabolites, and/or alkylating agents within 6 months prior to the Screening visit or anticipated use at any time during the study.
30. BCVA score < 34 letters (approximately 20/200 Snellen equivalent) in the non-study eye using the chart ETDRS method at the Screening visit.
31. Known allergy or hypersensitivity to the study medication or its components.
32. Known allergy or contraindication to the use of fluorescein or povidone iodine or contraindication to pupil dilation in either eye.
33. Female patients who are pregnant, nursing, or planning a pregnancy, or who are of childbearing potential and not using a reliable means of contraception.
34. Current enrollment in an investigational drug or device study or participation in such a study within 90 days prior to the Screening visit.
35. Patient has a condition or is in a situation which, in the Investigator's opinion, will interfere with the patient's ability to comply with the dosing and visit schedules and the protocol evaluations or may not suitable for this study.

INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION:

Test Product: TLC399 (ProDex) designed as a 2-vial system; 1 with DSP and 1 with PL containing lipid excipients.

Study dose levels:

Part 1: 4 planned dose levels for sequential dose escalation:

Group R1: 0.24 mg DSP with 100 mM PL (20 μL),

Group 1 (start dose level): 0.36 mg DSP with 100 mM PL (30 μL)

Group 2: 0.6 mg DSP with 100 mM PL (50 μL)

Group 3: 0.6 mg DSP with 50 mM PL (50 μL)

Part 2:

Group R1: 0.24 mg DSP with 100 mM PL (20 μL)

Route of test drug administration: Intravitreal injection to the study eye to be administered by the Investigators.

REFERENCE THERAPY, DOSE, AND METHOD OF ADMINISTRATION: None.

ENDPOINTS:

Primary:

Part 1**:**

- To determine DLT of TLC399 (ProDex) in patients with macular edema due to CRVO or BRVO; DLT will be determined by definition

Part 2**:**

- Safety assessment, including AEs, physical examination, vital signs (including BP), clinical chemistry and hematology for up to 1 year

Secondary:

Part 1**:**

- Safety assessment, including AEs, physical examination, vital signs (including BP), clinical chemistry and hematology for up to 1 year

Part 2:

- Mean change from baseline in IOP in the study eye at the scheduled visits
- Mean change from baseline in number of letters read correctly (using BCVA) in the study eye at the scheduled visits
- Mean change from baseline of retinal thickness in the study eye (by using OCT) at the scheduled visits
- Proportion of patients with BCVA gain of 15 or more letters from baseline BCVA in the study eye at the scheduled visits
- Time to achieve a treatment response of gain of 15 or more letters from baseline BCVA in the study eye up to 12 months (using survival analysis methods)

EVALUATION CRITERIA:

Determination of Maximum Tolerated Dose and Dose Limiting Toxicities

Maximum Tolerated Dose: The MTD will be defined either as the dose that was one level below the dose cohort which elicited a DLT in at least 2 patients or as the highest dose cohort with ≤ 1/6 DLTs. During the dose escalation period, only the subjects receiving the correct dose administration are considered evaluable and will be include in DLT analysis. The MTD must be confirmed with 6 patients.

Dose Limiting Toxicities: The DLT determination will be made by the following criteria:

Ophthalmic DLTs: Ocular AEs by standard clinical ophthalmic examination, visual acuity changes from BCVA (chart ETDRS) at baseline, slit-lamp biomicroscopy (SLB), indirect ophthalmoscopy/fundus photography, FA, and OCT central macular thickness. The acute ophthalmologic toxicities which constitute a DLT are any occurrence of the following at the study eye and is considered related to the study drug within 4 weeks post injection:

- Clinically significant examination that is severe (obscuring visualization of the retinal vasculature) and vision threatening
- Other ocular abnormalities not usually seen in patients with RVO, such as (but not limited to) acute retinal detachment or endophthalmitis
- BCVA: Significant acute reduction in visual acuity – loss of ≥ 3 ETDRS lines (15-letter) within the first 7 days that persist until Day 14, with the exception that in the opinion of the Investigator the reduction in visual acuity is due to the dispersion of the drug in the vitreous cavity.
- Tonometry: Increase from baseline IOP by 25 mm Hg on 2 consecutive separate examinations at least 1 day apart or sustained pressure of 30 mm Hg for more than a week, despite pharmacologic intervention; Goldmann tonometer will be used for all IOP measurements

Systemic DLTs:

These include Grade 3 (severe) events, such as hospitalization of the patient or an event that results in significant or persistent deficiency or inability, or Grade 4 (life-threatening) toxicities or any significant severe toxicity deemed related to the study drug by the Investigator

Efficacy:

BCVA: BCVA will be used to assess primary as well as secondary endpoints. BCVA will be assessed in Parts 1 and 2 of the study.

BCVA testing will be performed using the ETDRS chart – 3 ETDRS visual acuity charts each with a different letter sequence (ETDRS visual acuity charts R, 1, and 2) will be employed for standardized measurement of visual acuity at each of the participating sites. Visual acuity will be measured using letters only. Both eyes will be tested at each study visit - the right eye will always be tested with Chart 1 and the left eye with Chart 2.

OCT Scan: OCT will be used to assess 1 of the secondary endpoints, i.e., to evaluate the mean change from baseline of the central retinal thickness at the scheduled visits. Spectral/Fourier domain OCT will be used throughout the study at the participating sites. All OCT examinations at the same site should be performed by the same type of machine. OCT scans will be obtained after dilating the study eye in all enrolled patients at the time points specified in the protocol. In patient of significant IOP elevation, OCT for neural fiber layer is recommended.

Safety:

Safety will be assessed based on physical examination, vital signs (BP and pulse), clinical laboratory results (routine hematology and chemistry), and AEs. Safety parameters will also include BCVA measurements, IOP measurements, SLB, indirect ophthalmology, fundus photography, OCT scan at neural fiber layer, visual field and FA evaluations.

DURATION OF THE STUDY: The entire duration of the study will be about 12.5 months for patients enrolled in both parts of the study. Patient enrollment is expected to be 14 days prior to the single intravitreal injection of TLC399 (ProDex) on Day 0 for both parts. For patients in Part 1, after the 4-week observational period for DLTs, the patients will be followed for an 11-month evaluation period. For patients in Part 2, patients will be evaluated for safety and efficacy for a period of 12 months after the single intravitreal injection of TLC399 (ProDex). For patient have unresolved vitreous opacity or still need IOP lowering medication at D360 visit, it is suggested following-up patient safety every 3 months after D360 visit until total recovery, stable or investigator deems not necessary.

Screening Period: 14 days

Treatment Period: Single day (Day 0)

Observation Period for DLTs: 4 weeks for patients in Part 1 only.

Follow-up Period: 11 months for patients in Part 1 (after DLT observation period) and 12 months for patients in Part 2.

PLANNED STUDY DATES:

First patient first visit: August 2014

STATISTICAL ANALYSIS:

Sample size determination

The primary objective for Part 1 of the study is to determine the DLTs of TLC399 (ProDex). The conventional 3+3 design will be used; no formal sample size calculations have been performed. About 6 to 24 patients who have macular edema due to CRVO or BRVO are planned to be enrolled for the sequential dose escalation Part 1 of the study.

No formal sample size calculation will be performed for open-label, single-arm, single-dose Part 2 of the study. In Part 2, eligible subjects will be recruited in dose Group R1 only and approximately 20 patients (inclusive of the Group R1 subjects from Part 1) will be included for analysis in Part 2.

Efficacy Analysis

The efficacy analysis will be descriptively summarized with the ITT and PP analysis population. For Part 1 of the study, the efficacy analysis will be presented by treatment group. Data in Part 2 will be combined with the data at the same dose level in Part 1 for efficacy analysis. Missing data (including those due to early discontinuations) will not be imputed. Subgroup analyses will be performed for the efficacy assessment by RVO type in Part 2.

Patients receiving prohibited or rescue treatment will be included in efficacy analysis. All BCVA and CST data

after the administration of rescue therapy will be replaced with the last observation prior to the start of rescue therapy. If there is no other major protocol deviation, these patients will not be excluded from PP population due to receiving prohibited or rescue treatment.

Safety Analysis

The safety data analysis will be descriptively summarized with the safety population. For Part 1 of the study, the safety analysis will be presented by treatment group. Data in Part 2 will be combined with the data at the same dose level in Part 1 for safety analysis. Missing data (including those due to early discontinuations) will not be imputed.

Frequency distribution and individual listings of all DLTs and AEs will be generated. Safety data including physical examination, vital signs, clinical laboratory data, BCVA assessments, IOP assessments, SLB, indirect ophthalmology, and fundus photography evaluations will be descriptively summarized.