CLINICAL TRIAL PROTOCOL: TLC399A2002

Protocol Title:	A Phase IIa Trial of TLC399 (ProDex) in Subjects with Macular Edema due to Retinal Vein Occlusion (RVO)
Protocol Number:	TLC399A2002
FDA IND Number:	109804
Study Phase:	IIa
Product Name:	TLC399 (ProDex)
Indication:	Macular edema due to central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO)
Study Centers:	Multicenter
Sponsor:	Taiwan Liposome Company, Ltd. (TLC) 11F-1, No. 3, Yuanqu St., Nangang District, Taipei, Taiwan 115
Contract Research Organization:	Ora, Inc. 300 Brickstone Square Andover, MA 01810

	Date and Version
Original Protocol:	15 November 2016 Version 1.0
Amendment 1	24 May 2017 Version 2.0
Amendment 2	20 December 2017 Version 3.0
Amendment 3	21 September 2018 Version 4.0
Amendment 4	12 October 2018 Version 5.0

Statement of Compliance with Good Clinical Practice

This study will be performed in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP).

Confidentiality Statement

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SYNOPSIS

Protocol Title:	A Phase IIa Trial of TLC399 (ProDex) in Subjects with Macular Edema due to Retinal Vein Occlusion (RVO)
Protocol Number:	TLC399A2002
Investigational Product:	TLC399 (ProDex)
Study Phase:	IIa
Primary Objective:	To evaluate the efficacy of different strengths of TLC399 (ProDex) administered as a single intravitreal (IVT) injection in the improvement of visual acuity in subjects with macular edema due to RVO
Secondary Objectives:	• To evaluate the safety and tolerability of different strengths of TLC399 (ProDex) in subjects with macular edema due to RVO • To evaluate the efficacy of different strengths of TLC399 (ProDex) for reducing retinal thickness in subjects with macular edema due to RVO
Overall Study Design:	
Structure:	Part 1: Multi-center, randomized, double-masked Part 2: Multi-center, randomized, double-masked
Duration:	Subjects will be evaluated for safety and efficacy for 12 months after the single IVT injection of TLC399 (ProDex). Treatment Period: Single day (Day 1) Follow-up Period: Up to 12 months
Controls:	Not applicable
Dosage/Dose Regimen/ Instillation/Application/ Use:	TLC399 (ProDex): • Group 1: 0.36 mg dexamethasone sodium phosphate (DSP) with 100 mM phospholipid (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) • Group 4: 0.84 mg DSP with 50 mM PL (70 µL) In Part 1, subjects will be assigned to Group 1, 2, or 3 (randomized 1:1:1). In Part 2, subjects will be assigned to Group 3 or 4 (randomized 1:1).

Summary of Visit Schedule:	**Visit 1** (Day -14 to Day -1): Screening **Visit 2** (Day 1): Eligibility Confirmation and Randomization/Treatment **Visits 3-5** (Days 2 [+2 days], 14 [±2 days], 30 [±3 days]) and **Visits 6-11** (Day 60 to Day 270 [±7 days]): Follow-up Period **Visit 12** (Day 360 [±7]): Exit Visit
Measures Taken to Reduce Bias:	Stratified randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are evenly balanced across treatment groups, to reduce the possible influence of covariates on the drug evaluation, and to enhance the validity of statistical comparisons across treatment groups. Masked treatment will be used to reduce the potential of bias during data collection and evaluation of clinical endpoints. The subject, the masked Evaluating Investigator (Principal investigator or his/her designees), the best-corrected visual acuity (BCVA) technician, the photographer, and any other site staff involved in performing visit assessments are masked to the study treatment.

Study Population Characteristics:

Number of Subjects:	Part 1: 31 subjects Part 2: Up to 30 subjects
Condition/Disease:	Macular edema due to central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO)
Inclusion Criteria:	1. Male or female, at least 18 years of age. 2. Subjects with macular edema due to CRVO or BRVO diagnosed within 18 months prior to the Screening Visit with: • Visual acuity decreases attributable to the edema in the study eye; and • Non-ischemic type by fluorescein angiography (FA) in the study eye. 3. BCVA score of 20/40 (73 letters) to 20/400 (19 letters) by Early Treatment of Diabetic Retinopathy Study (ETDRS) chart in the study eye at the Screening Visit and on Day 1. 4. Mean central subfield thickness (CST) ≥350 μm on spectral domain optical coherence tomography

(SD-OCT) measurements in the study eye at the Screening Visit as determined by the site's OCT machine.
5. Willing and able to comply with the study procedure and sign a written informed consent.
6. Must agree to use a medically acceptable form of birth control throughout the study duration unless the subject or his/her partner(s) is sterile*.
*Sterile is defined as a woman who has experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or has undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy); or a man who has undergone successful orchiectomy.

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

Exclusion Criteria:

1. History of diabetic retinopathy in the study eye.
2. Presence of a brisk afferent pupillary defect (ie, obvious and unequivocal) in the study eye.
3. Stroke or myocardial infarction within 3 months prior to the Screening Visit.
4. Poorly controlled hypertension (defined as systolic blood pressure [BP] >160 mm Hg and/or diastolic BP >90 mm Hg) at the Screening Visit or at Day 1.
5. Poorly controlled diabetes (defined as hemoglobin A1c level > 9.5%) at the Screening Visit.
6. Uncontrolled systemic disease.
7. Any ocular condition that in the opinion of the masked Evaluating Investigator would prevent a 15-letter gain in visual acuity in the study eye (eg, severe macular ischemia).
8. Presence of an epiretinal membrane in the study eye which, in the opinion of masked Evaluating Investigator, is the primary cause of macular edema, or is severe enough to prevent gain in visual acuity despite reduction in macular edema.
9. History of clinically significant (CS) intraocular pressure (IOP) elevation (ie, a rise of $\geq$10 mm Hg or an absolute IOP $\geq$ 25 mm Hg which required treatment) in response to topical or systemic steroid treatment in either eye.

10. History of ocular hypertension, glaucoma, or optic nerve head change consistent with glaucomatous damage in the study eye.
11. Active ocular hypertension (with or without treatment) ≥ 22 mm Hg in the study eye at the Screening or Day 1 visit.
12. Aphakia or presence of anterior chamber intraocular lens in the study eye.
13. Active retinal neovascularization in the study eye.
14. Active or history of choroidal neovascularization in the study eye.
15. History of central serous chorioretinopathy in either eye.
16. Presence of rubeosis iridis in the study eye.
17. Any active ocular infection (ie, bacterial, viral, parasitic, or fungal) in either eye at the Screening Visit or on Day 1.
18. History of herpetic ocular infection in the study eye or adnexa.
19. Presence of active or inactive toxoplasmosis in either eye at the Screening Visit or on Day 1.
20. Presence of visible significant scleral thinning or ectasia in the study eye that would preclude safe IVT injection.
21. Media opacity in the study eye that precludes clinical and photographic evaluation (including but not limited to preretinal or vitreous hemorrhage, lens opacity).
22. Cataract surgery in the study eye within 3 months, or other intraocular surgery in the study eye within 6 months prior to the Screening Visit; or these surgeries are planned during the course of the study.
23. Anticipated need for ocular surgery in the study eye during the 12-month study period.
24. History of pars plana vitrectomy, radial optic neurotomy, or sheathotomy in the study eye.
25. Use of hemodilution for the treatment of RVO within 3 months prior to the Screening Visit.
26. Use of IVT ranibizumab or bevacizumab in the study eye within 6 weeks prior to the Screening Visit; or IVT aflibercept in the study eye within 8 weeks prior to the Screening Visit.
27. Use of laser of any type in the study eye within 3 months prior to the Screening Visit.
28. Previous use of non-depot IVT steroids in the

study eye within 3 months prior to the Screening Visit.
29. IVT Ozurdex in the study eye within 6 months prior to the Screening Visit.
30. Any prior use of Retisert or Iluvien in the study eye.
31. Use of systemic steroids or heparin within 1 month prior to the Screening Visit; or anticipated use at any time during the study.
32. 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.
33. BCVA score < 34 letters (approximately 20/200 Snellen equivalent) in the non-study eye using the ETDRS chart method at the Screening Visit or at Day 1.
34. Known allergy or hypersensitivity to the study medication or its components.
35. Known allergy or contraindication to the use of fluorescein or povidone iodine or contraindication to pupil dilation in either eye.
36. Female subjects who are pregnant, nursing, or planning a pregnancy.
37. Treatment with an investigational drug within 90 days or 5 half-lives of the investigational product ([IP]; whichever is longer) prior to the Day 1 visit.
38. Any participation in a clinical trial within 30 days of the Screening Visit.
39. Subject has a condition or is in a situation which, in the masked Evaluating Investigator's opinion, will interfere with the subject's ability to comply with the dosing and visit schedules and the protocol evaluations or may not be suitable for this study.

Study Formulations and Mode of Administration:

TLC399 (ProDex) is designed as a 2-vial system; 1 with DSP and 1 with PL containing lipid excipients. On Day 1, subjects will be administered a single dose IVT injection according to the randomized group. Mode of Administration: IVT injection to the study eye to be administered by the unmasked Injecting Physician.

Evaluation Criteria:

Efficacy Measures:

Primary:

- Proportion of subjects with BCVA gain of 15 or

more letters from baseline in the study eye at 6 months

Secondary:

- Change from baseline of retinal CST (using SD-OCT) in the study eye at scheduled visits
- Proportion of subjects with retinal CST (using SD-OCT) <300 μm in the study eye at scheduled visits
- Change from baseline in number of letters read correctly (using BCVA) in the study eye at scheduled visits
- Proportion of subjects with BCVA gain of 15 or more letters from baseline in the study eye at scheduled visits
- Proportion of subjects with BCVA letter score >73 (20/40 Snellen equivalent) in the study eye at scheduled visits
- Time to achieve a treatment response of gain of 15 or more letters from baseline BCVA in the study eye

Safety Measures:

- Adverse Events (AEs)
- IOP
- Slit lamp biomicroscopy (SLB)
- Indirect ophthalmoscopy (dilated)
- Fundus photography (FP)
- FA
- Physical examination
- Vital signs (BP, pulse)
- Clinical laboratory evaluations (routine hematology, chemistry, and urinalysis)

General Statistical Methods and Types of Analyses

Sample Size Calculation

This is an exploratory study and there is no formal sample size evaluation. For Part 1, approximately 20 subjects are expected to be enrolled in each study group completing the 12-month follow-up period after study drug administration. Given a drop-out rate of 10%, approximately 22 subjects in each group will be enrolled. A total of approximately 66 subjects will be randomly assigned to 1 of 3 different strengths of TLC399 (ProDex).

Based on the SMC recommendation, following review of data for 31 subjects from Part 1 (10, 10, and 11 in Groups 1, 2, and 3, respectively), up to 30 additional subjects will be randomly assigned in Part 2 to one of 2 different strengths of TLC399 (ProDex).

General Statistical Considerations

All efficacy and safety variables will be summarized using descriptive statistics and presented by treatment groups. Continuous variables will be presented as number of

observations, mean, standard deviation, median, minimum, and maximum, as well as number of missing data (if relevant); while categorical variables will be presented as number of observations, count, percentage, and number of missing data (if relevant) in a frequency table. In general, missing values will remain as missing. Specific rules for handling missing efficacy data are described in Efficacy Analysis.

Analysis Population

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

Safety population: All randomized subjects who receive any dose of study drug administration.

Modified intent-to-treat (mITT) population: A subset of the safety population comprised of subjects who have at least 1 post-treatment efficacy evaluation.

Per protocol (PP) population: A subset of the mITT population comprised of subjects who complete the study without any major protocol violations.

Efficacy Analysis

The efficacy data will be descriptively summarized with the mITT and PP analysis populations and presented by study part and treatment group. Data for the Group 3 dose in both study parts will be pooled and summarized as well.

The mITT analysis will be considered primary and the PP supportive.

For all analyses of BCVA data, missing data will be imputed using multiple imputation methods. Patients who receive rescue medication/procedures within 6 months after the study treatment is initiated will be considered failure to achieve a gain of at least 15 BCVA letters. For continuous measures, all data points after a subject starts rescue medication will be replaced with the last observation prior to rescue medication administration.

Sensitivity analyses on the primary endpoint will be performed as follows:

1) On observed data only, with subjects requiring rescue medications prior to Month 6 included as treatment failures (mITT and PP populations)
2) Imputing missing data using the last observation carried forward, with subjects requiring rescue medications prior to Month 6 included as treatment failures (mITT population)
3) On observed data only, with subjects who require rescue medications prior to Month 6 using their Month 6 data (mITT population)

The same approach to missing data as described for BCVA data will apply to CST data.

The time to achieve a treatment response of gain of 15 or more letters from baseline BCVA will be analyzed using the Kaplan-Meier method. Survival plots will be created and the survival time will be presented as mean, median, 95% confidence intervals (CIs) for the median, and the range.

Change from baseline in number of letters read correctly (using BCVA) and change from baseline of retinal CST (by using SD-OCT scan) in the study eye during the 12-month period will be summarized by treatment groups at scheduled visits. Additionally, 95% CIs for the treatment estimates in changes from baseline will be constructed.

Subgroup Analysis

Subgroup analyses will be performed for the primary efficacy endpoint and selected

secondary endpoints by RVO type.

Safety Analysis

All safety data analyses will be performed on the safety population and displayed in subject data listings and summarized in tables. Treatment-emergent adverse events (TEAEs) will be listed and categorized by start date, stop date, seriousness, severity, relationship to IP, action taken, and outcome. TEAEs with a missing relationship to study treatment will assume greatest relationship to study treatment. TEAEs with missing severity grades will be categorized as "missing" for tabulation of TEAEs by severity. Summary tables will display the total number of TEAEs and the number of subjects with each TEAE by treatment groups. TEAEs will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term for all TEAEs, serious adverse events (SAEs), and TEAEs leading to study withdrawal. In addition, TEAEs will be summarized by day of onset relative to the injection day of IP.

Safety data including physical examination, vital signs, clinical laboratory data, IOP assessments, SLB, indirect ophthalmology, FA, and FP evaluations will be descriptively summarized by treatment group.

Continuous safety data will be summarized by visit and include changes from baseline. Continuous data will also be converted to categorical values where possible (ie, below, within, and above normal ranges) and summarized in shift from baseline tables.

Categorical safety data collected by visit will be summarized showing the counts and percentages in each category at each visit, as well as shifts from baseline.

Interim Analysis

An interim analysis for the primary efficacy evaluation was planned to be conducted after all subjects have completed at least 6 months in the study or had been withdrawn. For this Phase 2 trial, efficacy and safety evaluation beyond Month 6 will be considered exploratory.

Safety monitoring committee (SMC) reviews will be performed throughout the study. The unmasked SMC reviewed unmasked listings for 31 subjects on 29 March 2018 (data cutoff 09 March 2018), and requested that recruitment be temporarily paused pending further data analysis. Additional descriptive efficacy summaries were provided to the SMC for a review meeting on 25 April 2018. An unmasked team from the sponsor presented further data for an unmasked SMC meeting held on 18 August 2018 (data cutoff 06 August 2018). Following this meeting, the SMC approved the sponsor's proposal to enroll additional subjects treated with the Group 3 dose and a new Group 4 dose (containing a greater volume of the same formulation of Group 3).

As of Protocol Amendment 3 (v4), data from Part 1 (31 subjects) will be unmasked. Given that, as of protocol preparation, 1) all 31 subjects randomized in Part 1 have completed at least Month 7.5 in the trial or have been withdrawn (and evaluations beyond 6 months were considered exploratory); 2) no formal statistical comparisons will be made between the groups in Part 1 or Part 2; and 3) the selection of dose to carry forward from Part 1 has already been decided, it was deemed that minimal bias will be introduced by unmasking the data. The sponsor intends to disclose key unmasked efficacy and safety data from Part 1 with the investigators and other stakeholders so that they can adequately understand the benefits and risks of the study treatment.

For Part 2, no formal interim analysis is planned.

Summary of Known and Potential Risks and Benefits to Human Subjects

ProDex is developed to provide an ideal, safe, long-acting, DSP delivery system for the treatment of macular edema.

Subjects receiving ProDex IVT injection may be at risk for transient vitreous opacity, which might result in transient visual acuity decrease but would be expected to resolve within 2-6 weeks after study drug dosing. IVT injections have been associated with endophthalmitis, eye inflammation, increased IOP, vitreous hemorrhage, and retinal detachments. Subjects should be monitored following the injection. Use of corticosteroids may produce posterior subcapsular cataracts, increased IOP, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

From the experience of preclinical and preliminary clinical data, the expected adverse reactions of ProDex IVT injection on subject with macular edema following CRVO and BRVO include vitreous opacity, increased IOP, visual acuity decrease, conjunctival hemorrhage, eye pain, dry eye, foreign body sensation, conjunctival hyperemia, cataract, floaters, and hypertension. Previous human experience from Ozurdex shows that potential adverse reactions include vitreous detachment, optic nerve damage, visual acuity and field defects, posterior subscapular cataract formation, secondary ocular infection, and perforation of the globe where there is thinning of the cornea or sclera. The expected systemic adverse reactions such as hypertension, hyperglycemia, vasovagal reaction, and facial flushing are also rare, but will be monitored carefully.