Clinical Study Protocol

Study Title:	A multicenter, open-label, safety and proof-of-concept study to assess safety, tolerability and efficacy of AR-1105 in subjects with macular edema due to retinal vein occlusion (RVO)
Study Number:	AR-1105-CS201
Study Phase:	Phase 2a
Product Name:	AR-1105 (dexamethasone) implant for intravitreal administration
Indication:	Macular edema following retinal vein occlusion
Investigators:	Multicenter
Sponsor: **Sponsor Contact:**	[redacted]
Medical Monitors:	[redacted]
NCT Number:	03739593

	Date
Original Protocol (Rev 0):	29 November 2018
Amendment 1 (Rev 01):	22 January 2019

Confidentiality Statement

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A multicenter, open-label, safety and proof-of-concept study to assess safety, tolerability and efficacy of AR-1105 in subjects with macular edema due to retinal vein occlusion (RVO)

Study No: AR-1105-CS201

Original Protocol Date: 29 November 2018

Protocol Version No: Rev 01

Protocol Version Date: 22 January 2019

Role	Contact information
Clinical Operations	[redacted] Signature Date
Clinical Research	[redacted] Email: mh

Aerie Management and Sponsor Safety Officer

[redacted]

ature

Medical Monitors

[redacted]

Clinical Laboratory

[redacted]

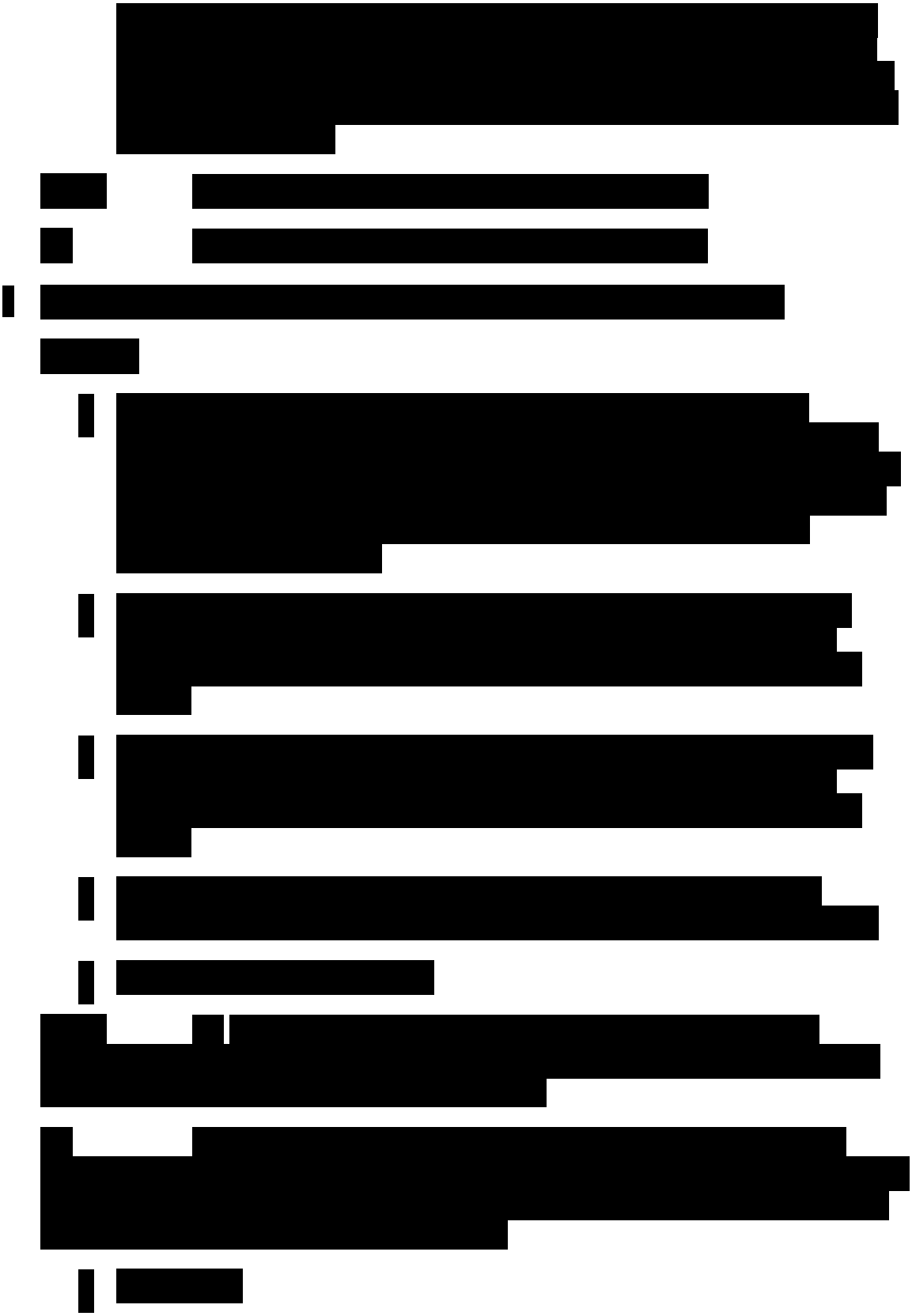
Biostatistics and Data Management

[redacted]

Reading Center [redacted]

[redacted]

sites within the United States, comprising a total of



[redacted]

- [redacted]
- [redacted]
- [redacted]

SYNOPSIS

Sponsor: Aerie Pharmaceuticals, Inc.

Name of Finished Product: AR-1105 (dexamethasone) implant for intravitreal administration

Name of Active Ingredients: Dexamethasone

Study Title:
A multicenter, open-label, safety and proof-of-concept study to assess safety, tolerability and efficacy of AR-1105 in subjects with macular edema due to retinal vein occlusion (RVO)

Study Number: AR-1105-CS201

Study Phase: Phase 2a

Primary Objective:

- To evaluate the safety and tolerability of 2 formulations of AR-1105 in subjects with macular edema due to branch RVO (BRVO) or central RVO (CRVO)

Secondary Objectives:

- To evaluate the effect of AR-1105 on Best Corrected Visual Acuity (BCVA) by ETDRS methodology
- To evaluate the effect of AR-1105 on central retinal/foveal thickness (CRT/CFT) and subretinal fluid by spectral-domain ocular coherence tomography (SD-OCT)

Study Design:
This will be a 6-month (with follow-up, if necessary, to monitor residual implant), open-label, multicenter, adaptive study evaluating the safety, tolerability, and efficacy of 2 formulations of dexamethasone intravitreal implant, AR-1105, in a single eye of up-to 45 subjects between 18 and 80 years of age with macular edema (ME) secondary to retinal vein occlusion (RVO). Since this study represents the first-in-human experience with AR-1105, the study will begin with an initial phase, during which time, up to a maximum of 5 subjects will be treated with AR-1105 clinical formulation 1 (AR-1105-CF1) and followed during weekly visits for up to 2 weeks post-treatment to assess tolerability and safety. Providing none of the subjects experience any clinically-meaningful ocular adverse reactions (possibly) related to treatment with AR-1105 during the initial phase, the study will continue into the randomized phase. During the randomized phase of the study, subjects will be assigned in a 1:1 ratio to either AR-1105-CF1 or AR-1105 clinical formulation 2 (AR-1105-CF2). Data collected from the subjects enrolled into the randomized phase of the study will be primarily summarized separately from subjects enrolled during the initial phase.

Treatment will consist of a single intravitreal administration with AR-1105-CF1 or -CF2, each of which has a target dose of 340 μg dexamethasone (2 implants, single injection). During the randomized phase, each treatment group will enroll approximately 20 subjects (i.e. in addition to the enrolled subjects who will participate in the initial phase on AR-1105-CF1). An interim analysis of the first 20 subjects randomized to CF1 or CF2 may be conducted when they have completed 6 months post-treatment to assist in planning future studies. When all subjects in each treatment group have completed their Month 6 visit, the primary safety and efficacy analyses will be conducted. Data collected through Month 6 on the safety and tolerability of each formulation, as well as efficacy signals for each subject randomized, will be used to determine which formulation will be selected for further clinical development. Any subject who presents at Month 6 with visible residual implant will be followed until they require retreatment (following the criteria provided for rescue therapy), or until 1 month after the implant is no longer visible or to Month 9, whichever occurs first.

Rescue therapy in the form of standard of care, will be offered to any subject who, in the opinion of the investigator, requires additional therapy for their RVO due to lack of efficacy after Month 3/Week 12. Minimum guideline criteria for considering rescue are an increase in CRT of 50 μm and decrease in BCVA of ≥7 letters at any time compared to baseline.

In the case of elevated intraocular pressure (IOP) or cataract, investigators should treat the subject according to standard practice. In the case of a cataract, removal should be performed as soon as possible since BCVA could be impacted by the cataract.

Inclusion criteria:
Subjects MUST meet all of the following criteria at the screening and baseline visits to enter into the study:

1. At least 18 years of age
2. Vision loss due to clinically detectable ME associated with either CRVO or BRVO. Subjects may be treatment-naïve, or if previously-treated with a steroid, must have demonstrated response to treatment
3. Duration of ME (defined as the time since initial diagnosis of ME) ≥9 months in subjects with CRVO and ≥12 months in subjects with BRVO. If both eyes are eligible, the study eye will be the eye with worse VA
4. Best-corrected visual acuity (BCVA) as measured by the early treatment of diabetic retinopathy study (ETDRS) methodology of between 25 and 70 letters, (+1.2 and +0.3 logarithm of the minimum angle of resolution (logMAR) units or 20/320 and 20/40 Snellen equivalent) in the study eye
5. Retinal thickness in the central subfield (as measured by SD-OCT) of >290 µm (females) and >305 µm (males) if using a Cirrus (Zeiss) instrument, or if a Spectralis (Heidelberg) instrument is used, thickness should be >305 µm (females) or >320 µm (males) in the study eye
6. Be able to understand and willing to provide written informed consent
7. Be willing and able to adhere to the instructions set forth in the study protocol

Exclusion criteria:

Subjects meeting any of the following criteria during the screening or baseline evaluations will be excluded from entry into the study:

Ophthalmic:

1. Presence of a clinically significant epiretinal membrane, active retinal or optic disc neovascularization, active or history of choroidal neovascularization, presence of rubeosis iridis
2. History or presence of herpetic infection, toxoplasmosis, chorioretinopathy
3. Subjects with moderate non-proliferative diabetic retinopathy (as defined by the International Clinical Diabetic Retinopathy Disease Severity Scale, (2002) in AAO PPP 2017) or worse in either eye are excluded from participation
4. Any active infection
5. Aphakia, significant posterior capsule tear or iris trauma in the study eye
6. Anterior-chamber intraocular lens
7. Clinically significant media opacity
8. History of glaucoma or changes in the optic nerve head indicative of glaucomatous damage or visual field loss
9. Ocular hypertension in the study eye at qualification which is >23 mmHg without treatment or >21 mmHg if currently taking 1 IOP-lowering medication. Use of ≥2 IOP-lowering medications (fixed-dose combination therapies count as 2 medications) will exclude the subject
10. History of corticosteroid-induced IOP increase in either eye (defined as a documented increase of >10 mmHg following any previous initiation of steroid therapy, Pleyer 2013)
11. Ocular condition in the study eye that, in the opinion of the investigator, would prevent a 15-letter improvement in visual acuity (e.g. severe macular ischemia).
12. Received an intraocular steroid injection or implant (e.g. via subconjunctival or intravitreal routes of administration) within 6 months or any anti-VEGF treatment within 2 months prior to screening. Prior treatment with fluocinolone acetonide implant (e.g. RETISERT® or ILUVIEN®) or pan-retinal photocoagulation (PRP) would exclude the subject.
13. Intraocular surgery (including intraocular laser surgery), corneal refractive surgery or eyelid surgery within 3 months prior to Visit 1 or anticipated need for ocular surgery or ophthalmic laser treatment in the study eye during the study treatment period
14. Currently using topical corticosteroids in the vicinity of the eyes within the 1 month prior to Visit 1
15. Periocular depot of steroids placed within 6 months prior to Visit 2
16. Ocular medications that are specifically disallowed in this protocol for any condition during the study or within the specified timeframe prior to Visit 2
17. Have progressive optic nerve disease or retinal disease (e.g., epiretinal membrane or vitreomacular traction confirmed by SD-OCT) other than retinopathy due to RVO that affects BCVA

Systemic:

18. Currently using or anticipating the use of systemic corticosteroids during the study (with the exception of inhaled, intranasal or topical corticosteroids, providing the dose has remained stable for the 1-month prior to Visit 1, and it is not anticipated to change during the course of the study)
19. Any clinically significant or uncontrolled serious or severe medical or psychiatric condition
20. Participation in any other clinical study within 30 days prior to Visit 1
21. History of hypersensitivity or poor tolerance to any components of the preparations to be used in this study such as dexamethasone or biodegradable polymer (poly D, L-lactic co-gycolic acid, PLGA) excipients or fluorescein
22. Systemic condition that may confound the study outcome per the investigator's opinion (e.g. uncontrolled diabetes [i.e. glycosylated hemoglobin (HbA1c) level >12], uncontrolled hypertension [e.g. ≥160/100 mmHg], treatment for a serious systemic infection, history of cerebral vascular accident or myocardial infarction within 6 months prior to screening, renal failure requiring dialysis or renal transplant, cancer or other conditions)
23. Women of childbearing potential, or male subjects with a female partner of child-bearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or 3 months post-surgical sterilization. Male subjects with a female partner of child-bearing potential must have had a prior vasectomy or agree to use an effective method of birth control during the treatment period and for three months after the subject has completed the study. All females of childbearing potential must have a negative urine pregnancy test result at the screening examination and must not intend to become pregnant during the study.

Study Population:

A total of approximately 45 subjects will be enrolled into the study at approximately 20 investigational sites within the United States, comprising a total of approximately 25 subjects treated with AR-1105-CF1 (up-to 5 in the initial phase and 20 in the randomized phase), and 20 subjects treated with AR-1105-CF2 (randomized phase only). Subjects will be at least 18 years of age with a diagnosis of ME secondary to RVO, each of whom meets all the inclusion criteria and none of the exclusion criteria.

Investigational Product, Dose, and Mode of Administration:

- AR-1105-CF1, 340 µg (target dose) administered intravitreally (2 implants, single injection)
- AR-1105-CF2, 340 µg (target dose) administered intravitreally (2 implants, single injection)

Study Duration:

Overall duration of the study is approximately up-to 18 months. This includes up to a 1-month screening period, followed by an enrollment period of up-to 6 months. Each subject in both Cohorts will complete a 6-month primary evaluation period. Residual implant assessment will be performed at Day 8 and at Months 1, 2, 3, 4, 5, and 6, and if necessary at monthly visits thereafter until they require retreatment, following the criteria provided for escape to rescue therapy, or until 1 month after the implant is no longer visible, or to Month 9, whichever comes first.

Safety Assessments (see Table 1):

Assessed by evaluating changes from baseline in the following (see statistical analysis plan [SAP] and Manual of Procedures [MoP] for details):

- Intraocular pressure (IOP) by Goldmann applanation tonometry
- BCVA by ETDRS method
- 3 field Fundus Photography (FP)
- Gonioscopy
- Slit-lamp biomicroscopy
- Dilated fundus examination
- Retinal thickness by SD-OCT (Cirrus (Zeiss), or Spectralis (Heidelberg) instrument)
- Fluorescein Angiography (FA)
- Vital signs (heart rate and blood pressure)
- Non- fasting clinical laboratory tests (clinical chemistry and hematology)

- Serum or urine pregnancy tests for females of childbearing potential
- Adverse Events

Efficacy Assessments (see Table 1):

Assessed by evaluating the following (see SAP and MoP for details):

- BCVA by ETDRS method
- Central Retinal/Foveal Thickness (CRT/CFT) as assessed by SD-OCT
- Fluorescein Angiography and Fundus exam
- Percentage of subjects requiring rescue therapy overall and by visit

Other secondary efficacy analyses may be carried out as described in the study SAP.

Statistical Methods:

[redacted]

Sample Size

This study is not powered to detect a pre-stated efficacy signal, but rather will be used to inform the design and power for future studies. With a sample size of 20 evaluable subjects per treatment group, the study will have 95% confidence of ruling out adverse events with true incidence rates of 13.9% or higher within each treatment group. That is, with 20 subjects in a treatment group, if an adverse event of a specific type is not observed, then with 95% confidence, the true incidence rate of that adverse event is less than 13.9%.

Safety Analysis:

The primary safety analysis will summarize ocular and non-ocular treatment-emergent adverse events (TEAEs) using discrete summaries at the subject level by system organ class and preferred term for each treatment group. Ocular TEAEs will be summarized separately for all study and fellow eyes. A TEAE will be defined as occurring after the first dose of study medication. Serious adverse events and treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity.

Slit lamp biomicroscopy and dilated indirect ophthalmoscopy measures will be summarized at each visit using discrete summary statistics.

Intraocular pressure (IOP) will be summarized at each visit, using continuous and discrete summary statistics, including change from baseline and the proportion of study eyes with an increase from baseline in IOP of 10 mmHg or more and the proportion of study eyes with IOP of 30 mmHg or more.

Vital signs and safety laboratory data will be summarized at each visit, using continuous summary statistics, including change from baseline.

[redacted]

Additionally, a subset of the safety analyses may also be performed combining the initial phase subjects with the randomization phase subjects.

Efficacy Analyses

The percentage of study eyes gaining at least 15 letters in BCVA from baseline will be summarized using discrete summary statistics, including exact 90% and 95% confidence intervals (CIs) by treatment group. Treatment group comparisons will be completed using Fisher's exact statistic and exact 90% and 95% confidence intervals (CIs) using the Farrington-Manning score statistic. Additionally, exact logistic regression will be utilized to determine treatment effect on the percentage of study eyes gaining at least 15 letters in BCVA from baseline after adjusting for baseline BCVA. These analyses will be used to

determine differences in formulations and to assess whether there are differences in outcomes between subjects' data pre- and post-interim, to determine whether the data may be pooled.

The efficacy summaries will be performed on the intent-to-treat (ITT) population using last observation carried forward (LOCF), imputing missing as failure, and using observed data only. Subjects who receive rescue medication prior to the summarized visit will be imputed as failure for the summarized visits. No additional imputation methodologies will be performed in this early phase study, unless otherwise specified in the statistical analysis plan (SAP).

The percentage of subjects gaining or losing at least 15 letters at other study visits and the percentage of subjects gaining or losing at least 10 letters at each study visit will be analyzed similarly.

Change from baseline in BCVA letters to each on treatment visit will be summarized using continuous summary statistics, including 90% and 95% CIs by treatment group.

A linear model with change from baseline BCVA letters as the response, baseline BCVA letters as a covariate, and treatment group as a main effect factor will be fit to determine treatment group effect with separate models completed for each on treatment visit. These analyses will be used to determine differences in formulations and may be used to assess whether there are differences in outcomes between subjects' data pre- and post-interim to determine whether the data may be pooled. Subjects who receive rescue medication prior to the summarized visit will have their measure replaced with their last observation prior to receiving rescue medication. The least squares mean, standard error, and CI for each treatment group, and the difference between treatment groups, will be presented. Additionally, analyses will be completed using individual two-sample t-tests and 90% and 95% CIs around the difference between treatment groups in mean BCVA and mean change from baseline BCVA.

Median time to achieve a treatment response of ≥ 15 letters improvement from baseline in BCVA and median time to rescue therapy will be estimated using Kaplan-Meier methods with 90% and 95% CI calculated using the method of Brookmeyer and Crowley (1982). The logrank statistic will be used to determine differences in time to achieve response between the two treatment groups to determine differences in formulations and may be used to assess whether there are differences in outcomes between subjects' data pre- and post-interim to determine whether the data may be pooled. Subjects receiving rescue medication will be considered censored on the day of rescue medication receipt. Additionally, the number and proportion of subjects who achieve a treatment response at each visit will be summarized.

In all analyses, data from subject visits after receipt of rescue medication will be imputed using last observation prior to receiving rescue medication for continuous endpoints and will be imputed as failures for success/failure variables.

[redacted]

Date of Original Protocol (Rev 0): 29 November 2018
Date of Original Protocol Amendment (Rev 01): 22 January 2019

Table 1 Schedule of Visits and Procedures

Procedure	Screening[1]	Baseline/ Treatment	Initial Phase		Follow-Up Period[1] (Randomized Phase)						Implant Observation Period[2] (if required)		
	V1 [redacted] to -1	V2	V3[3] [redacted] (± 2 days)	[redacted] (± 2 days)	V4 [redacted] (± 3 days)	V5 [redacted] (± 3 days)	V6 [redacted] (± 3 days)	V7 [redacted] (± 3 days)	V8 [redacted] (± 3 days)	V9 [redacted] (± 3 days)	V10 [redacted] (± 3 days)	V11 [redacted] (± 3 days)	V12 [redacted] (± 3 days)
Informed consent review	X												
Demographics/ medical & ocular history[5]	X												
Concomitant medication query	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events query		X	X	X	X	X	X	X	X	X	X	X	X
BCVA – (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit-lamp biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy*	X	X					X*			X*			
IOP check	X	X	X	X	X	X	X	X	X	X	X	X	X
Posterior segment OCT*	X	X			X*	X*	X*	X*	X*	X*	X*	X*	X*
Fluorescein Angiography	X	X					X			X			
3-Field fundus photography*	X	X					X*			X*	X*	X*	X*
Dilated fundus exam*	X	X	X	X	X	X	X*	X	X	X*	X*	X*	X*
Vitreous implant residual assessment*			X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Screening[1]	Baseline/ Treatment	Initial Phase		Follow-Up Period[1] (Randomized Phase)						Implant Observation Period[2] (if required)		
Laboratory tests	X				X	X				X			
Pregnancy test	X									X			
Treatment[6]		X											

1. Screening and post-implant treatment schedule applies to both Cohorts.
2. Implant observation period should continue for any individual subject as long as residual implant is visible, or to Month 9, whichever comes first.
3. [redacted]
4. An interim database lock may be conducted when the first 20 subjects have completed their [redacted] visit.
5. [redacted]
6. [redacted]

* Assessments performed in study eye only at these visits

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AR-1105	Aerie's dexamethasone intravitreal implant drug delivery system
BCVA	Best-corrected visual acuity
BRVO	Branch retinal vein occlusion
CFT	Central Foveal Thickness
CI	Confidence Interval
CRF	Case Report Form
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
DR	Diabetic retinopathy
EDC	Electronic data capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	Fluorescein Angiography
FDA	Food and Drug Administration
FP	Fundus Photography
GCP	Good Clinical Practice
GR	Glucocorticoid receptors
HRVO	Hemi-central vein occlusion
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IRB	Institutional Review Board

ITT	Intent to treat
IVT	Intravitreal
LOCF	Last observation carried forward
LogMAR	Logarithm of the minimum angle of resolution
ME	Macular edema
mmHg	Millimeters Mercury
µm	Micrometer
MoP	Manual of Procedures
OTC	Over-the-counter
OU	Both eyes
PLA	Poly (D, L-lactic acid)
PLGA	Poly (D, L-lactic-co-glycolic acid)
PK	Pharmacokinetic
PP	Per Protocol
PRP	Pan-retinal photocoagulation
RVO	Retinal vein occlusion
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD-OCT	Spectral-domain optical coherence tomography
TEAE	Treatment-emergent adverse event
US	United States
VA	Visual acuity
VEGF	Vascular endothelial growth factor

1. INTRODUCTION

Retinal vein occlusion (RVO) is the second-most common sight-threatening vascular disorder of the retina after diabetic retinopathy (DR) (RCO 2015, Klein 2000). Current estimates put global prevalence at approximately 16 million people affected with the disease in one or both eyes and around 520 new cases per million are reported each year (Rogers 2010, Klein 2000).

RVO is the result of thrombus formation in the central (CRVO), hemi-central (HRVO) or branch (BRVO) retinal vein, often due to compression by adjacent atherosclerotic retinal arteries or vasculitis (RCO 2015). The two main complications resulting from RVO are macular edema (ME) and retinal ischemia leading to retinal or iris neovascularization. ME is a non-specific response of the retina to a variety of insults and involves the breakdown of the blood-retina barrier at the capillary endothelium, which results in increased vascular permeability and subsequent leakage of fluids into the adjacent retinal tissues and significant visual disturbances. This reduction in vision may be reversible in the short-term, but chronic ME causes irreversible damage to the retina and permanent vision loss.

Within the last 10 years, intravitreal pharmacotherapy has revolutionized the therapeutic options for ME-associated retinal vascular diseases, and particularly for RVO. Current options for treating ME depend upon the cause and severity of the condition. In the case of RVO, the goal is to reduce the amount of fluid leakage and decrease the edema, thus leading to improved visual acuity (VA). Argon laser photocoagulation was used for many years to treat ME associated with BRVO, but was less effective in the treatment of CRVO, and was not successful in all patients (Fekrat 1997). Currently, two classes of medication are approved to treat ME following RVO – corticosteroids (such as OZURDEX® dexamethasone intravitreal implant), and more recently, anti-vascular endothelial growth factor (VEGF) therapies such as ranibizumab (LUCENTIS®) and aflibercept (EYLEA®). The anti-VEGFs, while effective at modulating vascular permeability, do not address the inflammatory component of RVO however. Corticosteroids have the advantage of targeting the three components of the pathophysiology of RVO; reducing ME through inhibition of multiple inflammatory mediators, stabilizing the blood brain barrier and decreasing vascular permeability (Zas 2017, OZURDEX PI). Corticosteroids such as dexamethasone (OZURDEX) and triamcinolone (KENALOG®) have demonstrated ME reduction and improvement in VA when dosed intravitreally (Cekic 2005, Ip 2003, OZURDEX PI). OZURDEX (0.7 mg dexamethasone) intravitreal implant has been evaluated in RVO and demonstrated efficacy up to 6 months (Haller 2010), although the peak efficacy is generally achieved by Month 3 (Joshi 2013, Bandello 2015).

While both classes of medication have demonstrated efficacy in RVO patients, the treatment burden is high, with the anti-VEGFs typically requiring monthly (LUCENTIS PI, EYLEA PI) intravitreal injections, and the dexamethasone intravitreal implant typically requiring re-injection every 3 months (Bezatis 2013, Augustin 2014). A corticosteroid implant that offered a longer duration of effect would provide the benefit of reducing the

treatment burden on patients while treating the inflammatory components of ME that are not addressed by inhibition of VEGF.

AR-1105 (dexamethasone intravitreal implant) is being developed at Aerie Pharmaceuticals for the treatment of ME following RVO. AR-1105 has been designed to provide a longer duration of efficacy than the currently available dexamethasone intravitreal implant with a lower dosage of dexamethasone. The proposed initial clinical trial would evaluate these AR-1105 formulations for safety, tolerability, durability, and also collect data on efficacy signals including best-corrected visual acuity (BCVA), and anatomical markers of ME such as subretinal fluid and central retinal thickness (CRT) in order to select the optimal implant to continue in clinical development. The objective of developing a longer-duration (>3months) lower-dose steroid implant, is based on the hypothesis that such a product may afford some safety benefits (e.g. potential reduction in the incidence of steroid-related adverse events and a lower treatment burden with respect to the number and frequency of intravitreal injections required) without compromising efficacy.

The potential risks to subjects receiving AR-1105 are: 1) the risks associated with the use of dexamethasone in general; 2) the risks associated with the intravitreal injection procedure; 3) the risk associated with the use of a solid, biodegradable implant in the vitreous; and 4) the risks associated with the use of the biodegradable polymers used for the sustained-release delivery system.

Risks to human subjects participating in this study are based on the findings from pre-clinical studies, and on extensive safety, tolerability and efficacy data extrapolated from published studies and the FDA approval of OZURDEX. Currently, there has been no exposure to AR-1105 in humans.

Any intravitreal injection can be associated with the risk of endophthalmitis, ocular inflammation, increased intraocular pressure (IOP) and retinal detachments. While investigators and study staff will be instructed that aseptic technique must be used at all times when handling the implant and applicator components, when loading the applicator, and when dosing the subject, there is an inherent risk of infection including endophthalmitis. Similarly, as with other ocular surgeries, there is a risk of cataract development. Increased IOP is a risk due to both the addition of an implant into the vitreous cavity, and because the implant contains dexamethasone. Corticosteroids, including dexamethasone, have been associated with increased IOP and the development of posterior subcapsular cataracts.

AR-1105 is formulated as a solid, biodegradable, rectangular prism-shaped implant of dimensions of approximately [redacted] The implant is designed to undergo slow erosion of the biodegradable matrix of different poly D, L- lactic-co-glycolic acid (PLGA) polymers to provide delivery of dexamethasone. Dexamethasone, like other corticosteroids, is a potent anti-inflammatory agent that works by suppressing multiple genes which encode pro-inflammatory cytokines, chemokines, adhesion molecules and enzymes and other proteins that are activated during the inflammatory process (Barnes 2006, OZURDEX PI). Steroid molecules readily diffuse across cell membranes and bind to glucocorticoid receptors (GR) in the cytoplasm. Thus activated, steroids control

inflammation both directly, by suppressing transcription of pro-inflammatory genes thereby reducing the expression of inflammatory proteins, or indirectly (i.e. a non-genomic mechanism) by inhibiting the effects of other transcription factors that regulate expression of genes which encode proinflammatory proteins.

In pre-clinical studies, Aerie has evaluated multiple formulations containing various [redacted]

The duration of dexamethasone exposure in ocular tissues following intravitreal (IVT) injection in rabbits was evaluated for 2 different clinical formulations of AR-1105 implants and for OZURDEX implants. Both AR-1105 implant formulations, AR-1105-CF1 and AR-1105-CF2, were well-tolerated and there were no mortalities or significant adverse clinical observations in the study.

Isolated findings, including retinal damage from implant contact during IVT injection, were noted in both AR-1105-treated and OZURDEX-treated animals. [redacted] This study demonstrated that the AR-1105-CF1 and AR-1105-CF2 implants were well-tolerated in the pigmented rabbit and provided a longer duration of sustained release of dexamethasone compared to OZURDEX.

The 2 clinical formulations of AR-1105 were also evaluated in Sinclair™ miniature-pigs to determine the ocular and systemic distribution and duration of dexamethasone tissue exposure following IVT injection. Half-length (350 µg) OZURDEX was used as a positive control. The dexamethasone IVT implants AR-1105-CF1 and AR-1105-CF2 were well-tolerated. Isolated ocular observations were noted from the IVT injection procedure, including incidences of subconjunctival bleeding, blood on the end of an implant, and the presence of blood in the vitreous chamber after the dosing procedure. The ocular observations were attributed to the IVT injection procedure and did not appear to be test article related, or pose any risk affecting the pharmacokinetic (PK) or ocular distribution results. Compared to the OZURDEX implant, the AR-1105 implants degraded at a slower rate and provided a longer duration of dexamethasone exposure in ocular tissues. Fundus imaging showed that both AR-1105-CF1 and AR-1105-CF2 implants were visible and partially-degraded at Week 10. In contrast, the OZURDEX implant was either not visible or highly degraded by Week 6.

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

To evaluate the safety and tolerability of 2 formulations of AR-1105 in subjects with macular edema due to BRVO or CRVO

2.2 Secondary Objective(s)

- To evaluate the effect of AR-1105 on BCVA by early treatment of diabetic retinopathy study (ETDRS) methodology
- To evaluate the effect of AR-1105 on CRT/CFT and subretinal fluid by spectral-domain ocular coherence tomography (SD-OCT)

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This will be a 6-month (with follow-up, if necessary, to monitor residual implant), open-label, multicenter study evaluating the safety, tolerability, and efficacy of 2 formulations of dexamethasone intravitreal implant, AR-1105, in a single eye of up-to 45 subjects between 18 and 80 years of age with ME secondary to RVO. [redacted]

Data collected through Month 6 on the safety and tolerability of each formulation, as well as efficacy signals for each subject randomized, will be used to determine which formulation will be selected for further clinical development. Any subject who presents at Month 6 with

visible residual implant will be followed until they require retreatment (following the criteria provided for rescue therapy), or until 1 month after the implant is no longer visible or to Month 9, whichever occurs first.

Rescue therapy in the form of standard of care will be offered to any subject who, in the opinion of the investigator, requires additional therapy for their RVO due to lack of efficacy after Month 3/Week 12. Minimum guideline criteria for consideration of rescue are an increase in CRT of 50 μm and decrease in BCVA of ≥7 letters at any time compared to baseline.

In the case of elevated IOP or cataract, investigators should treat the subject according to standard practice. In the case of a cataract, removal should be performed as soon as possible since BCVA could be impacted by the cataract.

3.2 Rationale for Study Design and Control Group

While current treatment options for RVO are effective for many patients, the treatment burden is high. This study is designed to enable selection of the optimal AR-1105 formulation to continue with further clinical development. The optimal formulation will provide strong efficacy and a long duration of effect. The hypothesis is that a longer (>3 months) sustained release should necessitate less frequent intravitreal injections, and a lower steroid dose would potentially result in fewer, or less-frequent steroid-associated AEs without compromising effectiveness. Taken together these attributes would reduce the burden of treatment. The study is designed to inform decisions on further development of AR-1105 as safely and efficiently as possible. [redacted]

3.3 Study Duration and Dates

Overall duration of the study is approximately 18 months. This includes up to a 1-month screening period, followed by an enrollment period of up-to 6 months. Each subject in both treatment groups will complete a 6-month primary evaluation period. Residual implant assessment will be performed on Day 8 and at Months 1, 2, 3, 4, 5, and 6, and if necessary at monthly visits thereafter until the subject requires retreatment, or to 1 month after the implant is no longer visible, or to Month 9, whichever comes first.

4. STUDY POPULATION SELECTION

4.1 Study Population

[redacted]

[redacted]

4.2 Inclusion Criteria

Subjects MUST meet all of the following criteria at the screening and baseline visits to enter into the study:

1. At least 18 years of age

2. Vision-loss attributed to clinically detectable ME associated with either CRVO or BRVO. Subjects may be treatment-naïve, or if previously-treated with a steroid, must have demonstrated response to treatment.

3. Duration of ME (defined as the time since initial diagnosis of ME) ≥9 months in subjects with CRVO and ≥12 months in subjects with BRVO. If both eyes are eligible, the study eye will be the eye with worse VA

4. Best-corrected visual acuity (BCVA) as measured by the ETDRS methodology of between 25 and 70 letters (+1.2 and +0.3 logMAR units or 20/320 and 20/40 Snellen equivalent) in the study eye

5. Retinal thickness in the central subfield (as measured by SD-OCT) of >290 μm (females) and >305 μm (males) if using a Cirrus (Zeiss) instrument, or if a Spectralis (Heidelberg) instrument is used, thickness should be >305 μm (females) or >320 μm (males) in the study eye

6. Be able to understand and willing to provide written informed consent

7. Be willing and able to adhere to the instructions set forth in the study protocol

4.3 Exclusion Criteria

Subjects meeting any of the following criteria during the screening or baseline evaluations will be excluded from entry into the study:

Ophthalmic:

1. Presence of a clinically significant epiretinal membrane, active retinal or optic disc neovascularization, active or history of choroidal neovascularization, presence of rubeosis iridis

2. History or presence of herpetic infection, toxoplasmosis, chorioretinopathy

3. Subjects with moderate non-proliferative diabetic retinopathy (as defined by the International Clinical Diabetic Retinopathy Disease Severity Scale, 2002, in AAO PPP 2017) or worse in either eye are excluded from participation

4. Any active infection

5. Aphakia, significant posterior capsule tear or iris trauma in the study eye

6. Anterior-chamber intraocular lens

7. Clinically significant media opacity

8. History of glaucoma or changes in the optic nerve head indicative of glaucomatous damage or visual field loss

9. Ocular hypertension in the study eye at qualification which is >23 mmHg without treatment or >21 mmHg if currently taking one IOP- lowering medication. Use of ≥2 IOP-lowering medications (fixed-dose combination therapies count as 2 medications) will exclude the subject

10. History of corticosteroid-induced IOP increase in either eye (defined as a documented increase of >10 mmHg following any previous initiation of steroid therapy, Pleyer 2013)

11. Ocular condition in the study eye that, in the opinion of the investigator, would prevent a 15-letter improvement in visual acuity (e.g. severe macular ischemia).

12. Received an intraocular steroid injection or implant (e.g. via subconjunctival, or intravitreal routes of administration) within 6 months or any anti-VEGF treatment within 2 months prior to screening; Prior treatment with fluocinolone acetonide implant (e.g. RETISERT® or ILUVIEN®) or pan-retinal photocoagulation (PRP) would exclude the subject.

13. Intraocular surgery (including intraocular laser surgery), corneal refractive surgery or eyelid surgery within 3 months prior to Visit 1 or anticipated need for ocular surgery or ophthalmic laser treatment in the study eye during the study treatment period

14. Currently using topical corticosteroids in the vicinity of the eyes within the 1 month prior to Visit 1

15. Periocular depot of steroids placed within 6 months prior to Visit 2

16. Ocular medications that are specifically disallowed in this protocol for any condition during the study or within the specified timeframe prior to Visit 2

17. Have progressive optic nerve disease or retinal disease (e.g., epiretinal membrane or vitreomacular traction confirmed by SD-OCT) other than retinopathy due to RVO that affects BCVA

Systemic:

18. Currently using or anticipating the use of systemic corticosteroids during the study (with the exception of inhaled, intranasal or topical corticosteroids, providing the dose has remained stable for the 1-month prior to Visit 1, and it is not anticipated to change during the course of the study)

19. Any clinically significant or uncontrolled serious or severe medical or psychiatric condition

20. Participation in any other clinical study within 30 days prior to Visit 1

21. History of hypersensitivity or poor tolerance to any components of the preparations to be used in this study such as dexamethasone or biodegradable polymer (PLGA) excipients or fluorescein

22. Systemic condition that may confound the study outcome per the investigator's opinion (e.g. uncontrolled diabetes [i.e. glycosylated hemoglobin (HbA1c) level >12], uncontrolled hypertension [e.g. ≥160/100 mmHg], treatment for a serious systemic infection, history of cerebral vascular accident or myocardial infarction within 6 months prior to screening, renal failure requiring dialysis or renal transplant, cancer or other conditions)

23. Women of childbearing potential, or male subjects with a female partner of child-bearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or 3 months post-surgical sterilization. Male subjects with a female partner of child-bearing potential must have had a prior vasectomy or agree to use an effective method of birth control during the treatment period and for three months after the subject has completed the study. All females of childbearing potential must have a negative urine pregnancy test result at the screening examination and must not intend to become pregnant during the study.

5. STUDY TREATMENTS

- AR-1105-CF1, administered intravitreally
- AR-1105-CF2, administered intravitreally

5.1 Description of Treatments

5.1.1 Study Drug

AR-1105 dexamethasone intravitreal implant. Two different formulations will be evaluated in this study, AR-1105-CF1 and AR-1105-CF2. [redacted]

[redacted] Prior to dosing, the applicator, consisting of a handle and a 25-gauge needle hub, will be assembled and both implants will be loaded into the lumen of the needle under aseptic conditions. The applicator will then be used to deliver the 2 implants by a single intravitreal injection. The procedure for assembling the applicator and loading the implants is described in the separate Manual of Procedures (MoP).

5.1.2 Placebo or Control Drug

[redacted]

5.2 Treatments Administered

Two implants each containing a target dose of 170 µg dexamethasone (for a total target dose of 340 µg) will be injected intravitreally into the study eye.

5.3 Selection and Timing of Dose for Each Patient

A single intravitreal injection (with 2 implants) will be given on Day 1.

5.3.1 Instructions for Administration of AR-1105

[redacted] Following loading of the applicator with the 2 AR-1105 implants, the procedure for administration of the implants is similar to that used for other intravitreal injections and should follow the guidelines on technique provided online by the American Academy of Ophthalmology (AAO, www.aao.org).

Precautions to minimize the risk of infection should be taken, and these include using appropriate barrier methods (sterile fields, drapes, gloves etc) and aseptic technique. Preparation of the applicator is described in a separate Manual of Procedures. Figure 1 is an image of the fully-assembled applicator (comprising 25-gauge needle, needle-hub assembly and handle assembly) as it appears prior to dosing.

Figure 1 AR-1105 (dexamethasone intravitreal implant) Applicator and Needle Hub Assembly

5.4 Method of Assigning Patients to Treatment Groups

Subjects will be assigned to treatment groups through the use of an interactive response technology (IRT) system.

5.5 Masking

Open-label.

5.6 Permissible Concomitant Therapy

Other than medications specified as prohibited in this Protocol (Section 5.7.1 and Exclusion Criteria, [Section 4.3]), medications that are considered necessary to the welfare of the subject should be given at the discretion of the Investigator. If there is any question whether a specific medication is allowed during the study, please contact Aerie.

If required, the contralateral eye may be treated with standard of care to maintain vision.

5.7 Restrictions

5.7.1 Prior and Concomitant Therapies

The subject will not be eligible to enroll in the study if they have received an ocular steroid injection or implant or any other peri-ocular steroid depot within 6 months prior to Screening. Prior treatment with fluocinolone acetonide (e.g. ILUVIEN®) or pan-retinal photocoagulation (PRP) will exclude the subject. Additionally, if a subject has a history of corticosteroid-induced glaucoma (or increased IOP associated with steroid therapy of >10 mmHg) they will be ineligible to enroll in this study. Subjects who have had an anti-VEGF injection within 2 months prior to Screening will be ineligible.

Topical steroid eye drops and the use of topical steroid creams on the face are prohibited during the study. Systemic steroid treatment (except via inhalation, intranasal or topical transdermal administration, providing the dose has remained stable for the 1 month prior to

Visit 1 and is anticipated to remain stable through the duration of the study) is prohibited during the treatment period.

Use of diuretic treatments for control of blood pressure must have been stable in dose for 30 days prior to Visit 1 and be anticipated to remain stable through the duration of the study.

Medications for treatment of diabetes of any type should have been stable in dose for 30 days prior to the Visit 1 and be anticipated to remain stable in dose for the duration of the study.

5.7.2 Subject Activity Restrictions

In-line with standard practice for intravitreal injections, or other ocular procedures, the subject should be allowed to remain seated for approximately 30 minutes following the injection, and then monitored for elevation of IOP and perfusion of the optic nerve head. Subjects should be advised that they may experience temporary visual blurring after receiving an intravitreal injection and they should not drive or use machines until it has resolved.

If the subject experiences pain or vison blurring in the days following the intravitreal procedure, they should return to the investigator immediately for evaluation.

5.8 Treatment Compliance

Not applicable.

5.9 Packaging and Labeling

Two different formulations, AR-1105-CF1 and AR-1105-CF2 (dexamethasone intravitreal implants) will be packaged in sterilized vials.

Ancillary supplies also provided to each investigative site may include forceps (requiring sterilization at the site), a sterile pouch containing the applicator handle and, packaged separately, and a sterile needle hub.

5.10 Storage and Accountability

The study medication will be stored in a secure area under the appropriate physical conditions for the product according to the conditions specified in the label and in the MoPs.

Only subjects enrolled in the study may receive study treatment, in accordance with all the applicable regulatory requirements. Only authorized staff will have access to the study medication.

Under normal conditions of handling and administration, the study medication is not expected to pose a significant safety risk to site staff. Adequate precautions must be taken to avoid direct contact with the study treatment.

The study treatments should be stored refrigerated (2°C to 8°C/ 36°F to 46°F). Temperature of the study treatment storage location at the site is to be monitored using a calibrated monitoring device and documented.

5.11 Investigational Product Retention at Study Site

Following dosing, the entire applicator assembly should be disposed-of in a sharps container. All other components of each patient kit should be retained at the site and available for reconciliation by the Sponsor/Sponsor representatives.

6. STUDY PROCEDURES

6.1 Informed Consent

Prior to any study procedures in the treatment period the study will be discussed with each subject and subjects wishing to participate must give written informed consent. The verbal explanation of the study will cover all the elements specified in the written information provided for the subject. The Investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and, if necessary, may ask for more information. At the end of the interview, the subject should be given time to reflect. Subjects and/or legally authorized representative then will be required to sign and date the informed consent form.

The informed consent form must have received approval/favorable review by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC) prior to use. A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the Investigator's site.

The Investigator or staff is responsible for ensuring that no subject undergoes any study related examination or activity before the subject has given written informed consent. It should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, and should be notified that discontinuation from the study will not impact on their subsequent care.

6.2 Medical History

Demographic data and details of any ongoing medication use will be collected and recorded. In addition, the number of prior treatments for RVO (anti-VEGF or corticosteroid) and the frequency of historical retreatment should be recorded. Any medications the subject took but discontinued within the 30 days prior to screening also will be recorded. Significant, relevant (to the condition under investigation) medical history will be collected and any current

underlying medical conditions, including those that began within the last 30 days and which may have resolved before screening, additionally must be recorded.

6.3 Vital Signs

Subject heart rate will be measured at screening, and during each subsequent study visit attended by the subject. Heart rate will be determined only once during each study visit by the method described in the MoP.

Blood pressure will be measured once for each subject after the subject heart rate has been determined, with the subject in a sitting position. A mechanical or digital sphygmomanometer may be used, but effort should be made to use the same instrument and the same arm of the subject for each reading. Blood pressure will be determined only once during each study visit by the method described the MoP.

6.4 Clinical Laboratory Tests

6.4.1 Laboratory Parameters

Pregnancy testing will be conducted at any time prior to randomization for females of child-bearing potential. A female of child-bearing potential is defined as an adult woman unless she is 1-year post-menopausal or 3 months post-surgical sterilization. Any female who is pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control will be excluded from the study. All females of childbearing potential must have a negative pregnancy test result at the screening examination or at any time prior to Visit 2 (randomization, Day 1, baseline) and must not intend to become pregnant during the study.

Chemistry and hematology laboratory analyses will be performed according to those described in the separate Laboratory Manual.

The clinical laboratory results must be reviewed by the Investigator prior to subject enrollment, and the tests CANNOT be indicative of any clinically significant disease in the opinion of the Investigator.

6.4.2 Sample Collection, Storage and Shipping

Details for the preparation and shipment of samples and reference ranges will be provided in the Laboratory Manual.

6.5 Dispensing Investigational Product

Investigational product will be administered only by trained personnel, under aseptic conditions in an operating room, surgical suite or office using sterile technique as described briefly in Section 5.3.1, and in detail in the MoP.

6.6 Efficacy Assessments

Best Corrected Visual Acuity (BCVA) will be assessed by the ETDRS method. Subjects will have their visual acuity measured in a 4-meter lane under standard illumination by a certified examiner reading a standard ETDRS chart. Subjects will undergo manifest refraction for each BCVA evaluation at each visit. The visual acuity lane will be certified, as will the visual acuity examiner prior to study initiation. Exact specifications for the visual acuity lane, illumination, charts, light box and refraction lens are detailed in the MoP.

Efficacy will be assessed by evaluating the following (see Statistical Analysis Plan [SAP] and MoP for details):

- BCVA by ETDRS method
- Central Retinal/Foveal Thickness (CRT/CFT) as assessed by SD-OCT (Heidelberg or Zeiss instruments – see Section 4.2 and MoP)
- Fluorescein Angiography and Fundus exam
- Percentage of subjects requiring rescue therapy overall and by visit

Other secondary efficacy analyses may be carried out as described in the study SAP.

6.7 Safety Assessments

Assessed by evaluating changes from baseline in the following (for specific details on instrumentation and Imaging assessments, refer to the MoP):

- IOP by Goldmann applanation tonometry
- BCVA by ETDRS method
- 3 field Fundus Photography (FP)
- Gonioscopy
- Slit-lamp biomicroscopy
- Dilated fundus examination
- Retinal thickness by SD-OCT (Cirrus (Zeiss), or Spectralis (Heidelberg) instrument)
- Fluorescein Angiography (FA)
- Vital signs (heart rate and blood pressure)
- Non- fasting clinical laboratory tests (clinical chemistry and hematology)
- Serum or urine pregnancy tests for females of childbearing potential
- Adverse Events (AEs)

6.8 Performing Adverse Event (AE) Assessments

This includes assessment of AE severity and relationship to investigational product. AE information may be volunteered by the subject or solicited by study personnel through non-leading questions.

All AEs occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective case report form (CRF). Adverse events should be documented from the time the subject signs the informed consent until 30 days after the subject's last study visit.

If a subject has an ongoing AE at the time of study completion, the ongoing AE must be followed-up and provided appropriate medical care until the event has resolved or stabilized.

Documentation of AEs/adverse reactions includes start date and stop date, severity, action(s) taken, seriousness and outcome.

The following definitions of terms apply to this section:

- *Adverse event (AE)*. Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
- *Suspected adverse reaction (SAR)*. Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, ''reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.
- *Life-threatening AE or life-threatening SAR*. An AE or SAR is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- *Serious adverse event (SAE) or serious suspected adverse reaction (SSAR)*. An AE or SAR is considered ''serious'' if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: Death, a life-threatening AE, patient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

Note: In the present study, Investigators are asked to report any loss in BCVA of ≥3 lines as a SAE.

- *Unexpected AE or unexpected SAR*. An AE or SAR is considered ‘‘unexpected’’ if it is not listed in the Investigator’s Brochure (IB) ‘Reference Safety Information’ or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Note: If an event occurs during the washout period (prior to subject enrollment and the administration of study medication), it should be recorded as an AE.

Note: Any medical condition present prior to administration of the study medication which remains unchanged or improved should not be recorded as an AE at subsequent visits.

6.8.1 Timing

The AEs occurring during the study must be documented, regardless of the assumption of a causal relationship. AEs should be documented from the time the subject signs and dates the patient consent form until subject participation in the study has been completed. If a subject has one or more ongoing AEs at the time of study completion, the subject must be followed and provided appropriate medical care until the sign(s) and/or symptoms(s) of the AE have remitted or stabilized in the opinion of the Investigator.

When recording an AE, the following information should be provided on the study AE eCRF:

1. Action Taken with Study Drug:

- None
- Investigational Product Discontinued

2. Other Action Taken:

- None
- Non-Drug Therapy
- New OTC or Rx Drug Added
- Hospitalized less than 24 hours

- Hospitalized greater than or equal to 24 hours

3. Outcome of an adverse event is coded as:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Unknown/Lost to follow-up

6.8.2 Severity

Severity of an AE is defined as a qualitative assessment of the level of discomfort or the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of study medication relationship or seriousness of the event and should be evaluated according to the following scale:

1 = Mild: present and noticeable, but not distressing, and no disruption of normal daily activities.

2 = Moderate: bothersome, discomfort sufficient to possibly reduce or affect normal daily activity.

3 = Severe: incapacitating, with inability to work or perform normal daily activity.

A change in severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity. For example, a change in severity may go from mild to severe or from severe to moderate. In both cases, the start and stop dates should be recorded.

Please note: a severe AE is not the same as a serious AE. Seriousness of an AE (NOT severity) serves as a guide for defining regulatory reporting obligations (see Section 6.8.7.1 for further information on serious AEs [SAEs]).

6.8.3 Relationship

The study medication relationship for each AE/adverse reaction should be determined by the Investigator using these explanations:

- **Not Related:** The event is clearly related to other factors such as subject's clinical condition; therapeutic interventions, concomitant disease or therapy administered to the subject and does not follow a known response pattern to the product.

- **Unlikely Related:** The event is most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between administration and the onset of the AE is incompatible with a causal relationship. Therefore, there is not a reasonable possibility that the AE was caused by the study medication.

- **Possibly Related:** The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject.

- **Related:** The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject, and either occurs immediately following study medication administration, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

6.8.4 Expectedness

Since there is currently no human experience with AR-1105, expectedness of AEs that may be associated with AR-1105 are based on pre-clinical data with this product, and published data on OZURDEX.

Intravitreal injections have been associated with the risk of infection, inflammation, increased IOP and retinal detachment. It is required that AR-1105 will be administered using good sterile technique and that the subject will be adequately anesthetized, but there will still be inherent risk associated with the procedure, including endophthalmitis and injection-site reactions (pain, inflammation).

The most-common events noted in studies with rabbits and monkeys were conjunctival changes and vitreous hemorrhage associated with the procedure. Additionally, ocular discharge and eye discoloration were observed but were not deemed to be AEs. No post-injection changes were observed in the retina, or in IOP. Other findings during follow-up were consistent with known class-effects of corticosteroids, including decreased white blood cell counts, decreased blood concentrations of urea, creatinine and phosphorus, and adrenal cortical atrophy.

In the PI and SmPC for OZURDEX the most commonly-reported AEs during clinical trials are listed as increased IOP and conjunctival hemorrhage. Other AEs reported included eye pain, conjunctival hyperemia, ocular hypertension, cataract, vitreous detachment, visual disturbance and vitreous floaters and headache. Adverse events reported during the studies that were associated with the procedure, rather than the implant or dexamethasone treatment

included vitreous hemorrhage, vitreous opacity, eye pain, photopsia, conjunctival edema, anterior chamber cells and conjunctival hyperemia.

6.8.5 Clinical Significance

Determination of the significance of any AE for a particular subject, and in the context of the entire study, is the responsibility of the Investigator. The Sponsor additionally has overall responsibility for the safety of all subjects, and timely documentation and reporting of any safety concerns.

6.8.6 Clinical Laboratory Adverse Events

Clinical laboratory values (other than pregnancy tests results) that are noted as abnormal and clinically significant at study exit and that are changes from Screening values will be documented as AEs.

6.8.7 Serious Adverse Events, Serious Suspected Adverse Events, Serious Unexpected Suspected Adverse Events

6.8.7.1 Reporting Serious Adverse Events (SAEs) or Serious Suspected Adverse Reactions (SSARs)

An Investigator must immediately report any SAE or SSAR (see Section 6.8 for definitions) to the Sponsor or Sponsor representative using the SAE report form, whether or not considered drug-related, including those listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the drug caused the event. The Investigator must report any SAE or SSAR that occurs during the course of the study or within 4 weeks of last study visit. In case of incomplete information, the Investigator must provide follow-up information as soon as possible, again using the SAE report form.

In addition, in the case of immediately life-threatening AEs or AEs with fatal outcome, or AEs that are serious, unexpected (i.e., not in the Clinical Investigator's Brochure) and judged related to the investigational product, or a loss in BCVA ≥3 lines, the Investigator must inform the Sponsor or Sponsor representative by phone within 24 hours of observation or occurrence of the SAE.

Pregnancies occurring in subjects enrolled in the study or in their partners, occurring up to 30 days after the subject's last study visit, must be reported and followed to outcome. While pregnancy itself is not considered to be an AE or SAE, pregnancy reports are tracked by the study Medical Monitors. Premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as an SAE. Other pregnancy complications should be reported as SAEs, if they meet serious criteria. Should a pregnancy result in a congenital anomaly or birth defect, a separate SAE report must be submitted for the baby. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality.

The Investigator must complete the pregnancy report form and fax or email the form to the study Medical Monitors within 1 business day of knowledge of the pregnancy. Following delivery or termination of pregnancy, the pregnancy report form is to be completed and submitted by fax or email to the Medical Monitors for the study.

SAEs must be reported to the IRB/IEC according to the IRB/IEC requirements.

The contact information of the study Medical Monitors is as follows:

6.8.7.2 Reporting Serious Unexpected Suspected Adverse Reactions (SUSARs)

The Investigator must immediately report SUSARs that occur or are observed during the course of the study or within 30 days of the subject's last study visit. In the event of a SUSAR, the site must notify the Medical Monitors for the study (contact information in Section 6.8.7.1) using the SAE report form within 24 hours of notification, observation, or occurrence of the SUSAR, whether or not complete information is available. In the case of incomplete information, the Investigator must provide follow-up information as soon as possible using the SAE report form. If the event is reported outside of regular business hours and collected by Trial Runners, their Medical Monitor will notify the Sponsor Medical Monitor within 24 hours of knowledge of the event (contact information in Section 6.7.8.1).

Reports will be evaluated by the Medical Monitor. The IRB/IEC and Investigators at other study sites will be informed as required.

6.9 Concomitant Medication Assessments

Use of any medication – prescription or over-the-counter (OTC) should be recorded at the screening visit, and captured on the appropriate CRF, and the indication noted as part of the medical history. Treatments that are permitted to continue throughout the duration of the study will be recorded as concomitant medications at all subsequent visits. Judgment of continued study participation by the subject, and inclusion of this subject's subsequent visits in the safety and efficacy analysis will be made by the Investigator.

All medications which the subject has taken within 30 days prior to screening and during the study will be recorded in the CRF. The name of the drug, dose, route of administration,

duration of treatment and indication will be recorded for each medication. For combination products (e.g., CONTAC®), the brand name is required. For non-combination products, the generic name is preferred. The use of routine ophthalmic diagnostic pharmaceutical agents (e.g., fluorescein) will be allowed, and individual documentation not required. However, medications used as part of the intravitreal injection process other than topical or subconjunctival anesthetic and povidone iodine swabs (e.g. pre-or post-injection antibiotics or IOP-lowering medications) should be recorded on the CRF. Any change in dosing parameters should also be recorded in the CRF.

6.10 Removal of Subjects from the Study or Investigational Product

Subjects may be discontinued from the study at any time for any reason. Removal of the investigational product should not be necessary, but if it is, it will be performed by vitrectomy, and the subject will be informed of this during the Consent process. Participation is entirely voluntary, and only possible if the subject has signed informed consent. Consent may be withdrawn at any time.

6.10.1 Completed Subject

A completed subject is defined as one who completes all visits planned through the completion of the Month 6 visit procedures.

6.10.2 Non-Completing Subject

A non-completing subject is defined as one who exits the study by their own volition or at the discretion of the Investigator and/or the study Medical Monitor. Any subject may decide to voluntarily withdraw from the study at any time without prejudice. In this event, Investigator will make every attempt to complete all assessments scheduled for the final (Month 6) visit.

6.11 Appropriateness of Measurements

The ophthalmic and systemic measures included in this study are consistent with standard of care.

7. STUDY ACTIVITIES

A detailed Schedule of Visits and Procedures is provided in Table 1.

7.1 Screening Visit (Visit 1, [redacted] to -1)

This visit may take place at any time of the day.

Adult subjects (18 years or older) with decreased VA as a result of clinically-detectable ME secondary to BRVO or CRVO are eligible for this study. Potential subjects will arrive at the Investigator's office and be interviewed by a member of staff regarding their eligibility for the study. Individuals will be presented with the informed consent form (ICF) and asked to

review it and discuss as needed with site staff, family or friends and return to the site to sign the form. Once informed consent has been obtained, the Screening visit can continue.

The subject's demographic and medical history will be collected, and a record made of their current and recent medication use. Vital signs will be collected and documented. Blood samples will be collected and if the subject is a female deemed to be of child-bearing potential, a urine pregnancy test will be administered. Male subjects with female partners of child-bearing potential should agree to comply with the guidelines on acceptable birth control described in Exclusion criterion # 23.

Ocular assessments will be performed on both eyes (OU) unless otherwise noted. The following ocular assessments will be performed prior to pupil dilation (mydriasis):

- BCVA using the ETDRS method and following manifest refraction
- Slit-lamp biomicroscopic examination
- Gonioscopy
- IOP measured using a Goldmann applanation tonometer.

Following mydriasis, the following procedures will be performed OU unless otherwise noted:

- SD-OCT
- Fundus examination
- 3-field fundus photography
- Fluorescein angiography

The subject will then schedule their return visit when their laboratory tests and Reading Center assessments will be available to the Investigator prior to randomization. The subject will be allowed to leave the office on condition that they have help and/or transportation to return home since they will have undergone pupil dilation.

7.2 Treatment Period

7.2.1 Visit 2 ([redacted] Procedures

This visit may take place at any time of the day.

The subject will be queried regarding any changes to their ocular or medical health status since the previous visit, and also if there have been any changes to their ongoing medications or procedures. Vital signs (heart rate and blood pressure) will be collected. The Investigator should go over the results from the Reading Center and the clinical chemistry and hematology values with the subject.

The following ocular assessments will be performed OU prior to pupil dilation:

- BCVA using the ETDRS method and following manifest refraction
- Slit-lamp biomicroscopic examination
- Gonioscopy
- IOP measured using a Goldmann applanation tonometer

Following mydriasis, the following procedures will be performed OU:

- SD-OCT
- Fundus examination
- 3-field fundus photography
- Fluorescein angiography

If the subject is deemed to be still eligible to enroll in the study in the Investigator's opinion, trained personnel will prepare the implant and applicator, and administer the implant following the directions provided in the MoP. Following administration, the subject should be monitored to ensure their retinal circulation returns to normal, their optic disc is perfused and their IOP returns to baseline (pre-administration) levels.

7.2.2 Visit 3 (± 2 days) Procedures (also applies to Visit 3b, (2 days,)

At this visit, the subject will be queried regarding any changes to their ocular or medical health status since the previous visit, and also if there have been any changes to their ongoing medications or procedures. Vital signs (heart rate and blood pressure) will be collected.

The following procedures will be performed OU:

- BCVA by ETDRS will be conducted following manifest refraction
- Slit-lamp biomicroscopy examination
- IOP measured using a Goldmann applanation tonometer

Following mydriasis, the following procedures will be performed OU, unless otherwise noted:

- Fundus examination
- The implant will be viewed to verify its status (study eye only)

7.2.3 Visits 4 and 5 (± 3 Days) and Visits 7 and 8 (± 3 Days) Procedures

At these visits, the subject will be queried regarding any changes to their ocular or medical health status since the previous visit, and also if there have been any changes to their ongoing medications or procedures. Vital signs (heart rate and blood pressure) will be collected. Blood samples will be collected (Month 1 and Month 2 visits only) for laboratory assessment of clinical chemistry and hematology.

The following assessments will be conducted OU:

- BCVA by ETDRS will be conducted following manifest refraction
- Slit-lamp biomicroscopy
- IOP measured using a Goldmann applanation tonometer

Following mydriasis, the following procedures will be performed OU, unless otherwise specified:

- SD-OCT (study eye)
- Fundus examination
- The implant will be viewed to verify its status. (study eye)

7.2.4 Visit 6 (± 3 Days) and Visit 9 (± 3 Days) Procedures

At these visits, the subject will be queried regarding any changes to their ocular or medical health status since the previous visit, and also if there have been any changes to their ongoing medications or procedures. Vital signs (heart rate and blood pressure) will be collected.

Blood samples will be collected for laboratory assessment of clinical chemistry and hematology and if the subject is a female of child-bearing potential, a urine pregnancy test should be administered (Visit 9 only).

The following procedures will be conducted OU:

- BCVA by ETDRS will be conducted following manifest refraction
- Slit-lamp biomicroscopy examination
- Gonioscopy (study eye)
- IOP measured using a Goldmann applanation tonometer

Following mydriasis, the following procedures will be performed OU unless otherwise noted:

- SD-OCT (study eye)
- Fundus examination (study eye)
- Fluorescein angiography
- 3-field fundus photography (study eye)
- The implant will be viewed to verify its status (study eye)

If residual implant is still visible in the vitreous at the Month 6 visit, the subject will be required to return to the site at Month 7 for safety follow-up. Otherwise, the Month 6 visit will be the final visit, and the subject should be thanked for their participation in the study.

7.3 [redacted] or Early Termination Procedures

Procedures that should be conducted in the event that the subject needs to exit the study prior to Month 6 (Visit 9) are provided above in Section 7.2.4.

7.4 Follow-up Visits ([redacted] ± 3 days as required for residual implant assessment)

Monthly safety visits should be scheduled if, following the assessments at Month 6 (Visit 9) are completed, it is noted that the vitreous still contains visible implant. At these visits, the subject will be queried regarding any changes to their ocular or medical health status since the previous visit, and also if there have been any changes to their ongoing medications or procedures. Vital signs (heart rate and blood pressure) will be collected.

The following procedures will be conducted OU:

- BCVA by ETDRS following manifest refraction
- Slit-lamp biomicroscopy examination
- IOP measured using a Goldmann applanation tonometer

Following mydriasis, the following procedures will be performed in the study eye:

- SD-OCT
- Fundus examination
- 3-field fundus photography
- The implant will be viewed to verify its status

If necessary, a second follow-up visit will be scheduled. The format of this follow-up visit should continue until either the subject requires re-treatment (i.e. standard of care rescue treatment), or until 1 month after no residual implant is observed, or to Month 9, whichever comes first, at which point the subject will exit the study.

8. QUALITY CONTROL AND ASSURANCE

The progress of the study will be monitored by on-site, written, and telephone communications between personnel at the Investigator's site and the Study Monitor. The Investigator will allow the Sponsor or designee to inspect all CRFs; subject records (source documents); signed consent forms; records of study medication receipt, storage, preparation, and disposition; and regulatory files related to this study.

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

All continuous study assessments will be summarized by treatment [and phase (initial vs. randomized) for CF1] and visit (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by treatment and visit (as applicable) using frequency counts and percentages.

All study data will be listed by treatment [and phase (initial vs randomized) for CF1], patient and visit (as applicable).

The unit of analysis for efficacy will be the study eye.

Statistical methods will be more fully described in separate document(s) (i.e., the Statistical Analysis Plan).

9.2 Determination of Sample Size

This study is not powered to detect a pre-stated efficacy signal, but rather will be used to inform the design and power for future studies. With a sample size of 20 evaluable subjects per treatment group, the study will have 95% confidence of ruling out AEs with true incidence rates of 13.9% or higher within each treatment group. That is, with 20 subjects in a treatment group, if an AE of a specific type is not observed, then with 95% confidence, the true incidence rate of that adverse event is less than 13.9%.

9.3 Analysis Populations

9.3.1 Safety Population

The safety population will include all subjects who received study medication. This population will be used to summarize safety variables and will summarize subjects as treated.

9.3.2 Intent-to-Treat (ITT) Population

The ITT population will include all subjects who received study medication. This population will be the primary population for efficacy analyses and will be used to summarize all efficacy variables and will summarize subjects as treated.

9.3.3 Per Protocol (PP) Population

The PP population is a subset of the ITT population, which will include those subjects who do not have major protocol violations likely to seriously affect the efficacy outcomes of the study. This population will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables. If the PP and ITT populations are exactly the same, then additional efficacy analyses on the PP population will not be performed. The PP population will summarize subjects as treated.

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics such as age, gender, race, and ethnicity will be summarized and listed. Medical history, history of ocular surgery and procedures, and RVO history will also be summarized and listed.

9.5 Primary Safety Assessments and Analyses

The primary safety analysis will summarize ocular and non-ocular treatment-emergent adverse events (TEAEs) using discrete summaries at the subject level by system organ class and preferred term for each treatment group. Ocular TEAEs will be summarized separately for all study and fellow eyes. A TEAE will be defined as occurring after the first dose of study medication. Serious adverse events and treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity.

Slit lamp biomicroscopy and dilated indirect ophthalmoscopy measures will be summarized at each visit using discrete summary statistics.

Intraocular pressure will be summarized at each visit, using continuous and discrete summary statistics, including change from baseline and the proportion of study eyes with an increase from baseline in IOP of 10 mmHg or more and the proportion of study eyes with IOP of 30 mmHg or more.

Vital signs and safety laboratory data will be summarized at each visit, using continuous summary statistics, including change from baseline.

[redacted]

9.6 Efficacy

9.6.1 Efficacy Endpoint(s)

- Percentage of subjects with ≥15-letter improvement (ETDRS) compared to baseline BCVA at Month 6.

Additional efficacy evaluations will include:

- Change from baseline in Central Retinal/Foveal Thickness (CRT/CFT) as assessed by SD-OCT at Months 1, 2, 3, 4, 5, and 6
- Change from baseline BCVA in ETDRS letter score at Months 1, 2, 3, 4, 5, and 6,
- Percentage of subjects with a >10 letter improvement (ETDRS) compared to baseline BCVA at Months 1, 2, 3, 4, 5, and 6
- Percentage of subjects with a >10 letter worsening (ETDRS) compared to baseline BCVA at Months 1, 2, 3, 4, 5, and 6
- Percentage of subjects with a >15 letter improvement (ETDRS) compared to baseline BCVA at Months 1, 2, 3, 4, and 5
- Percentage of subjects with a >15 letter worsening (ETDRS) compared to Baseline BCVA at Months 1, 2, 3, 4, 5 and 6
- Percentage of subjects requiring rescue therapy overall and by visit

9.6.2 Efficacy Analyses

The percentage of study eyes gaining at least 15 letters in BCVA from baseline will be summarized using discrete summary statistics, including exact 90% and 95% confidence intervals (CIs) by treatment group. Treatment group comparisons will be completed using Fisher's exact statistic and exact 90% and 95% CIs using the Farrington-Manning score statistic. Additionally, exact logistic regression will be utilized to determine treatment effect on the percentage of study eyes gaining at least 15 letters in BCVA from baseline after adjusting for baseline BCVA. These analyses will be used to determine differences in formulations and to assess whether there are differences in outcomes between subjects' data pre- and post-interim to determine whether the data may be pooled.

The efficacy summaries will be performed on the ITT population using last observation carried forward (LOCF), imputing missing as failure, and using observed data only. Subjects who receive rescue medication prior to the summarized visit will be imputed as failure for the summarized visits. No additional imputation methodologies will be performed in this early phase study, unless otherwise specified in the SAP.

The percentage of subjects gaining or losing at least 15 letters at other study visits and the percentage of subjects gaining or losing at least 10 letters at each study visit will be analyzed similarly.

The percentage of subjects requiring rescue therapy overall as well as at each study visit will be summarized using discrete summary statistics, including exact 90% and 95% CIs by treatment group. Treatment group comparisons will be completed using Fisher's exact statistic and exact 90% and 95% CIs using the Farrington-Manning score statistic.

Change from baseline in BCVA letters to each on treatment visit will be summarized using continuous summary statistics, including 90% and 95% CIs by treatment group.

A linear model with change from baseline BCVA letters as the response, baseline BCVA letters as a covariate, and treatment group as a main effect factor will be fit to determine treatment group effect with separate models completed for each on treatment visit. [redacted]. Subjects who receive rescue medication prior to the summarized visit will have their measure replaced with their last observation prior to receiving rescue medication. The least squares mean, standard error, and CI for each treatment group, and the difference between treatment groups, will be presented. Additionally, analyses will be completed using individual two-sample t-tests and 90% and 95% CIs around the difference between treatment groups in mean BCVA and mean change from baseline BCVA.

Median time to achieve a treatment response of ≥15 letters improvement from baseline in BCVA and median time to rescue therapy will be estimated using Kaplan-Meier methods with 90% and 95% CI calculated using the method of Brookmeyer and Crowley (1982). The logrank statistic will be used to determine differences in time to achieve response between the two treatment groups to determine differences in formulations and may be used to assess whether there are differences in outcomes between subjects' data pre- and post-interim to determine whether the data may be pooled. Subjects receiving rescue medication will be considered censored on the day of rescue medication receipt. Additionally, the number and proportion of subjects who achieve a treatment response at each visit will be summarized. Cox proportional hazards may also be used to analyze time to response, including baseline BCVA as a covariate.

In all analyses, data from subject visits after receipt of rescue medication will be imputed using last observation prior to receiving rescue medication for continuous endpoints and will be imputed as failures for success/failure variables.

[redacted]

Additionally, a subset of the efficacy analyses may also be performed combining the initial phase subjects with the randomization phase subjects.

9.7 Interim Analysis

An interim analysis may be conducted when the first 20 subjects enrolled in the randomized phase complete their Month 6 visit or discontinued the study. Safety, tolerability and efficacy data will be reviewed during this interim analysis to assist in planning of future studies. A final analysis will be performed when all randomized subjects in each treatment group have completed the Month 6 visit.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Good Clinical Practice (GCP) Compliance

The proposed study is subject to all applicable governmental rules and regulations concerning the conduct of clinical trials on human subjects. This includes, but is not limited to:

- Approval of properly constituted IRB/IEC
- Declaration of Helsinki (See Manual of Procedures)
- US FDA Law
- International Conference on Harmonization (ICH) GCP guidelines
- Obtaining prospective informed consent
- Monitoring of the conduct of the study
- Completeness of the CRFs by the Sponsor or its designee(s)
- Appropriate record retention by the Investigator

Protocol change or amendment procedures, applicable IRB/IEC requirements, Investigator/Sponsor obligations, and study monitoring procedures are detailed in Section 10.2 through Section 10.8 of this protocol.

10.2 Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The IRB/IEC must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The Investigator must not implement any deviation from or change to the protocol, without discussion with, and agreement by Aerie and prior review and documented approval/favorable opinion of the amendment from the relevant ethics committee, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor[s], change of telephone number[s]).

Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

10.3 Investigators and Study Administrative Structure

The Principal Investigator is responsible for all site medical-related decisions. The qualified Sponsor Medical Monitors are responsible for the safe conduct of this study. The contact information of the Sponsor Medical Monitors is as follows:

10.4 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

This protocol, materials used to recruit subjects, and materials used to document consent must be approved by the IRB/IEC prior to initiation of the study. The name and address of each reviewing IRB/ IEC will be documented in the Trial Master File. Written IRB/IEC approval must adequately identify the protocol and informed consent. In addition to approving the protocol, the IRB/IEC must also approve the Subject Information and Consent Form, as well as any advertising tools that will be used for the study.

Written approval also must indicate whether approval was granted based on full committee review or expedited review. Copies of all approved materials, all correspondence with the IRB/IEC and written approval from the IRB/IEC must be made available to the Sponsor, prior to the start of subject enrollment into the study. The investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study to the IRB/IEC as required. On completion of the study the IRB/IEC will be notified that the study has ended.

10.5 Ethical Conduct of the Study

The proposed study is subject to all applicable governmental rules and regulations concerning the conduct of clinical trials on human subjects. This includes, but is not necessarily limited to: the approval of IRB/IECs, the Helsinki Declaration, US FDA Law, ICH E6 (GCP) R2 guidelines, obtaining prospective informed consent, monitoring of the conduct of the study and the completeness of the CRFs by the Sponsor or its designee(s); and appropriate record retention by the Investigator. Applicable IRB/IEC, Investigator/Sponsor obligations, study monitoring and protocol change procedures are detailed in Sections 10.2 to 10.8.

10.6 Subject Information and Consent

Written informed consent will be obtained from each subject before any subject specific procedures are initiated. A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the Investigator's site.

The investigator is responsible for ensuring that no subject is subject to any study-related examination or activity before that subject has given informed consent. The subject must give written consent after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the subject.

It should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact on their subsequent care.

The investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview, the subject may be given time to reflect if this is required, or if the subject requests more time. Subjects and/or legal guardian will be required to sign and date the informed consent form.

Signed informed consent must be attained prior to the conductance of any study procedures.

10.7 Subject Confidentiality

The Investigator and his/her staff will maintain all personal subject data collected and processed for the purposes of this study using adequate precautions to ensure confidentiality, in accordance with local, state and federal laws and regulations.

Monitors, auditors and other authorized representatives of the Sponsor, the IRB/IEC approving this study, and government regulatory authorities (e.g., FDA) may be granted

direct access to the study subject's original medical and study records for verification of the data or clinical study procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

A report of this study's results may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but subject identities will not be disclosed in these documents.

10.8 Study Monitoring

Clinical research associates hired or contracted by the Sponsor will be responsible for monitoring the study sites and study activities. Clinical research associates will contact and visit the Investigator regularly. The actual frequency of monitoring visits depends on subject enrollment and on study site performance. Among others, the following items will be reviewed:

- Study progress
- Compliance with the protocol
- Completion of CRFs
- Dispensing, storage, and accountability of investigational product
- Source data verification
- AE and SAE reporting
- Essential documents contained within the Investigator's site file

For source data verification (i.e., comparison of CRF entries with subject records), data will be 100% source verified and will include as a minimum:

- Subject identification
- Informed consent (procedure, signature, and date)
- Selection criteria
- Primary efficacy and safety parameters (i.e., AEs)

Member(s) of the Sponsor or their designee will meet with the Investigator prior to the initiation of the study in order to assess the adequacy of the Investigator's subject population, facilities, and equipment, and to familiarize the Investigator with the protocol.

A member of the Sponsor or their designee in the role of Study Monitor will subsequently meet with the Investigator after several of the subjects have initiated the study in order to

ensure that the subjects are being properly selected, that adequate supplies for the study have been provided and that the assignment of medication is properly recorded. In addition, the Study Monitor will verify that the Investigator follows the approved protocol and all approved amendments, if any, by reviewing the Investigator's regulatory documents, source documents, ICFs, and CRFs of study subjects.

The Study Monitor will meet with the Investigator when all subjects have completed the Final Visit of the study, in order to collect unused study medications and unused supplies and materials.

Interim monitoring visits and telephone consultations will be done by the Study Monitor as necessary, to ensure the proper progression and documentation of the study.

10.9 Case Report Forms and Study Records

The initial point of entry of study data should be the subject source documentation. The location and nature of the source documentation for all data collected in the study will be identified in the study files at the investigator's site. In cases where no source documents will be used (i.e., data will be recorded directly onto the CRF without first being recorded on another document, such as a flowsheet, laboratory report, or other typical form of data reporting for later transcription to the CRF), the original data will be included in the CRF.

Source document information should be legible. Recorded data should only be corrected by drawing a single line through the incorrect entry and writing the revision next to the corrected data. The person who has made the correction should place his or her initials as well as the date of the correction next to the correction. Data may not be obliterated by erasure, redaction, or with correction fluid.

Study data will be transcribed and recorded via an electronic data capture (EDC) system as electronic CRFs (eCRFs). Security and authorization procedures consistent with the EDC system must be used. At each subject visit, the appropriate eCRFs must be completed. Whenever an eCRF is used, be sure to provide all information requested including subject identification number and initials, name or number of Investigator, date(s), etc. All applicable questions should be answered, and all data requested should be provided. Those areas that require a response but are not filled in correctly are considered incomplete or erroneous entries and will have to be corrected.

Each authorized study staff member will receive a unique access account in order to use the EDC system. Access accounts will not be shared among study staff. Authorized users will make entries and/or changes to eCRFs via a secure internet access. Each completed set of eCRFs will be reviewed by the Investigator who will then electronically sign and date the eCRF confirming that data for the subjects are complete and accurate.

The study records must include a copy of each Investigator's CV and medical license, and statement of Investigator qualifications. The name of each sub-investigator working under the supervision of the investigator is also required to be filed in the study records. In addition,

each eCRF, subject charts/source documents, Investigator's Brochure, protocol, protocol amendments, correspondence with the Sponsor/designee and the IRB/IEC, investigational product storage, receipts, returns and dispensing records, Delegation of Responsibilities Log, site training records, records of site monitoring, any unmasking documentation, AE and SAE reporting, IRB/IEC approvals, advertisements, written information provided to subjects, and subject completed ICFs will be included in the study records.

If the Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person (e.g., Sponsor, other Investigator) who will accept the responsibility. Notice of this transfer, including written acceptance, must be made to and agreed upon by the Sponsor.

10.10 Protocol Deviations

Per ICH E6 (GCP) R2 Section 4.5.1 the investigator/institution should conduct the trial in compliance with the protocol agreed with the sponsor and, if required, by the Regulatory Authority and which was given approval/favorable opinion by IRB/IEC

Protocol waivers or deviations from the protocol inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The site will contact the Sponsor for clarification of inclusion /exclusion criteria as needed prior to enrollment of the study subject. The Sponsor will document clarification requests and responses or their representative. If a subject does not meet all the inclusion and exclusion criteria during screening, that subject may not be enrolled into the study.

If a protocol deviation is identified by the investigator or through site monitoring activities an immediate submission to the IRB/IEC may be required e.g. 24 or 48 hours. The Sponsor will assess any protocol deviation and decide whether any of these non-compliances should be reported to the relevant competent authority as a serious breach of GCP and the protocol. If per the relevant competent authorities' requirements, the protocol deviation is not required to be reported immediately but is still required to be notified to the IRB/IEC, the specific protocol deviation will be added to the annual progress report.

The Sponsor will review, designate, and/or approve all protocol deviations prior to the database lock.

10.11 Access to Source Documentation

The Investigator will permit study-related monitoring visits, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data and documents.

The monitor and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time of their staff to monitor to discuss findings and any issues.

Sponsor/designee will monitor the study to ensure:

- Data are authentic, accurate and complete.
- Safety and rights of the subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP and all applicable regulatory requirements.

10.12 Data Generation and Analysis

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and the Sponsor for resolution. The study database will be updated by the clinical investigator or their staff, in accordance with the resolved query reports. All changes to the study database will be documented.

10.13 Retention of Data

The Investigator's site and clinical laboratory will retain all records related to the study in compliance with ICH Good Clinical Practices Guidelines E6 (R2) section 4.9.4.

Archived versions of the database will be saved by the Sponsor consistent with ICH Good Clinical Practices Guidelines E6 (R2) section 5.5.11, complying with whichever of the requirements is longer. The Sponsor will notify the investigator when study records should be destroyed.

10.14 Financial Disclosure

The Principal Investigator and Sub-Investigators (as listed on Form FDA 1572) will provide financial disclosure information prior to participation in the study. The Principal Investigator and any Sub-Investigators will notify the Sponsor promptly of any required revision to their financial disclosure status during the term of this study, annually, or at the end of the study (if applicable) and 1-year post-study completion. The Principal Investigator and Sub-Investigators will provide updated financial disclosure information upon the Sponsor's written request following completion of the study.

10.15 Publication and Disclosure Policy

Study information for this protocol will be posted on publicly available clinical trial registers before enrollment of Subjects begins. Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The

investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review the complete study results at a mutually agreeable location. Aerie will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted no later than 8 months after the final primary completion date, the date the final subject examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit when manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register for not publishing.

11. REFERENCES

1. American Academy of Ophthalmology (AAO) Diabetic Retinopathy Preferred Practice Guidelines, Updated 2017 (www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp-updated-2017)

2. American Academy of Ophthalmology Guidelines and Technique; Intravitreal Injections. 2015 (www.aao.org/clinical-statement/intravitreal-injections-statement)

3. Augustin AJ, Holz FG, Haritoglou C, et al. Retrospective, observational study in patients receiving a dexamethasone intravitreal implant 0.7 mg for macular oedema secondary to retinal vein occlusion. Ophthalmologica 2014; 233: 18–26

4. Bandello F, Parravano M, Cavallero E, et al. Prospective evaluation of morphological and functional changes after repeated intravitreal dexamethasone implant (OZURDEX®) for retinal vein occlusion. Ophthalmic Res. 2015; 53: 207–16

5. Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. Br. J. Pharmacol. 2006; 148:245-254

6. Bezatis A, Spital G, Höhn F, et al. Functional and anatomical results after a single Intravitreal ozurdex injection in retinal vein occlusion: a 6-month follow-up- the SOLO study. Acta Opthalmol. 2013; 91(5): e340–7

7. Brookmeyer, R. and Crowley, J. (1982) A confidence interval for the median survival time. Biometrics 1982; 38: 29-41.

8. Cekic O, Chang S, Tseng JJ et al. Intravitreal Triamcinolone Injection for Treatment of Macular Edema Secondary to Branch Retinal Vein Occlusion. Retina 2005; 25: 851-855

9. EYLEA [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.;2017.

10. Fekrat S & Finkelstein D. Current Concepts in the Management of Central Retinal Vein Occlusion. Curr. Opin. Ophthalmol. 1997; 8(3): 50-54

11. Haller JA, Bandello F, Belfort R et al. Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Macular Edema due to Retinal Vein Occlusion. Ophthalmol. 2010; 117: 1134-1146

12. ILUVIEN® [package insert]. Alpharetta, GA: Alimera Sciences, Inc.; 2016

13. Ip MS, Scott MM, Altaweel BA et al. Treatment of Central Retinal Vein Occlusion with Intravitreal Triamcinolone Acetonide (Abstract). IOVS 2003; 44: 3217

14. Joshi L, Yaganti S, Gemenetzi M, et al. Dexamethasone implants in retinal vein occlusion: 12-month clinical effectiveness using repeat injections as-needed. Br. J. Ophthalmol. 2013; 97(8): 1040–4

15. Klein R, Klein BEK, Moss SE and Meuer S. The Epidemiology of Retinal Vein Occlusion: The Beaver Dam Eye Study. Tr. Am. Ophth. Soc. 2000; 98: 133-143

16. LUCENTIS® [package insert]. San Francisco, CA: Genentech, Inc.;2017.

17. OZURDEX® [package insert]. Madison, NJ: Allergan USA, Inc.;2018.

18. OZURDEX 700 micrograms intravitreal implant in applicator [Summary of Product Characteristics] Westport, Co. Mayo: Allergan Pharmaceuticals Ireland; 2015.

19. Pleyer U, Ursell PG and Rama P. Intraocular Pressure Effects of Common Topical Steroids for Post-Cataract Inflammation: Are they all the same? Ophthalmol Ther. 2013; 2: 55-72

20. Rogers S, McIntosh RL, Cheung N et al. The Prevalence of Retinal Vein Occlusion: Pooled Data from Population Studies from the United States, Europe, Asia and Australia. Ophthalmol. 2010; 117(2): 313-319

21. Royal College of Ophthalmologists Clinical Guidelines: Retinal Vein Occlusion Guidelines; 2015

22. Zas M. When to use Steroids for Retinal Vein Occlusion; Early, Late or Never? Retina Today. 2017; May/June: 46-50