KalVista Pharmaceuticals

# PROTOCOL

**A randomized sham-controlled double-masked Phase 2a study of the efficacy, safety and tolerability of the intravitreal plasma kallikrein inhibitor, KVD001, in subjects with center-involving diabetic macular edema (ciDME) who have had prior anti-vascular endothelial growth factor (VEGF) treatment**

**NCT03466099**

**9 April 2018**

**PROTOCOL TITLE**

A randomized sham-controlled double-masked Phase 2a study of the efficacy, safety and tolerability of the intravitreal plasma kallikrein inhibitor, KVD001, in subjects with center-involving diabetic macular edema (ciDME) who have had prior anti-vascular endothelial growth factor (VEGF) treatment

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| **Sponsor:** | KalVista Pharmaceuticals, Ltd.<br>Tetricus Science Park<br>Building 227<br>Porton Down SP4 0JQ<br>United Kingdom |
| **Clinical Research Organization:** | Ora, Inc.<br>300 Brickstone Square<br>Andover, MA 01810<br>USA |
| **Sponsor Protocol No.:** | KVD001-201 |
| **IND No.:** | [redacted] |
| **Study Drug Name:** | KVD001 Injection |
| **Development Phase:** | 2a |
| **Date of Protocol:** | 09APR2018 |
| **Date of Previous Protocol:** | 31OCT2017 |

*The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements.*

## SIGNATURE PAGE

**Title:** A randomized sham-controlled double-masked Phase 2a study of the efficacy, safety and tolerability of the intravitreal plasma kallikrein inhibitor, KVD001, in subjects with center-involving diabetic macular edema (ciDME) who have had prior anti-vascular endothelial growth factor (VEGF) treatment

*This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki (1989), and the guidelines on Good Clinical Practice.*

[redacted]

4/10/2018

Date

[redacted]

4/10/2018

Date

[redacted]

4/9/2018

Date

**Declaration of the Investigator**

**Title:** A randomized sham-controlled double-masked Phase 2a study of the efficacy, safety and tolerability of the intravitreal plasma kallikrein inhibitor, KVD001, in subjects with center-involving diabetic macular edema (ciDME) who have had prior anti-vascular endothelial growth factor (VEGF) treatment.

*All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure (IB), electronic case report form (eCRF), and other scientific data.*

*The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB and/or IEC, except where necessary to eliminate an immediate hazard to the patients.*

*I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.*

*I agree and understand that as the Principal Investigator, it is my responsibility to train my staff on all updates to the clinical protocol, and to ensure that such training is acknowledged in the appropriate study documentation.*

**Responsible Investigator of the local study center**

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

## PROTOCOL SYNOPSIS

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| **Title** | A randomized sham-controlled double-masked Phase 2a study of the efficacy, safety and tolerability of the intravitreal plasma kallikrein inhibitor, KVD001, in subjects with center-involving diabetic macular edema (ciDME) who have had prior anti-vascular endothelial growth factor (VEGF) treatment |
| **Sponsor Study No.** | KVD001-201 |
| **Phase** | 2a |
| **Sponsor** | KalVista Pharmaceuticals, Ltd. |
| **Study Center(s)** | Ophthalmology clinics in the United States (US) with experience in the conduct of diabetic macular edema (DME) clinical studies |
| **Objective(s)** | Primary Objective:<br>• To evaluate the efficacy of monthly dosing of intravitreal (IVT) injection of KVD001 in subjects with ciDME who have had prior anti-VEGF treatment<br>Secondary Objective:<br>• To evaluate the local and systemic safety and tolerability of monthly dosing of KVD001 Injection in subjects with ciDME who have had prior anti-VEGF treatment |
| **Design** | This is a phase 2a, randomized, double-masked, sham-controlled, 3-arm study to evaluate the efficacy, safety, and tolerability of KVD001 Injection as monotherapy in adult subjects with ciDME who have had prior anti-VEGF treatment. Approximately 123 eligible subjects will be randomized into the study.<br>The maximum duration of the study for each randomized subject will be up to 28 weeks (including up to 4 weeks for screening, 12 weeks treatment period, and 12 weeks follow-up).<br>The study will be conducted on an out-patient basis.<br>The study schedule of events will be as follows:<br>***Screening Phase:*** The screening period will be up to 4 weeks. All subjects will sign an Informed Consent Form (ICF) prior to any study related procedures being performed. Subjects will be 18 years of age or older, at the time of screening, and will have a diagnosis of ciDME with prior anti-VEGF treatment.<br>***Treatment Phase:*** On the day of first study drug administration (Day 1), the subject's eligibility will be reconfirmed and baseline assessments will be performed. Eligible subjects will be randomized 1:1:1 to receive KVD001 Injection (6 µg or 3 µg KVD001) or a sham procedure during a 12-week, double-masked treatment period (a total of 4 doses given at approximately monthly intervals).<br>Subjects will visit the study clinic on Day 1 and Weeks 4, 8, and 12 during the Treatment Phase for study drug administration or sham procedure, safety, and ophthalmic assessments (see |

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| | Table 2). The subject will remain in the clinic after study drug administration or sham procedure until all post-dose procedures and observations have been completed and the Investigator confirms that the subject may be discharged. Investigators should schedule visits at Week 4, 8, and 12 to provide 28 days between visits. The visit window for these visits is -3 days to +7 days. |
| | Approximately twenty-four (24) hours after each study drug administration or sham procedure on Day 1 and Weeks 4, 8, and 12, subjects will be contacted by telephone to evaluate any reported adverse events (AEs) and changes in concomitant medications. In the event of any reported ocular or systemic AEs that are considered by the Investigator to be a possible cause for concern, the subjects will return to the clinic for assessment as soon as possible.<br>***Follow up Phase:*** All subjects will visit the clinic at Weeks 16, 20, and 24 after the last study drug administration or sham procedure for safety and ophthalmic assessments (see Table 2). The visit window for Weeks 16, 20, and 24 is ±7 days.<br>***Early Discontinuation:*** If any subject discontinues the trial early, every effort should be made to complete the Week 24/early discontinuation (ED) evaluations as soon as possible and, whenever possible, prior to starting any new medication or treatment. All attempts will be made to not discontinue the subject unless necessary.<br>***Rescue Treatment:*** Rescue intervention (e.g., anti-VEGF, focal/grid macular laser photocoagulation, (IVT) steroids ) may be administered due to worsening DME (i.e., attributable to worsening DME and not another cause;) if either of the following occurs and, where possible, after consultation with the Medical Monitor:<br>• During Treatment Phase<br>  ○ Best corrected visual acuity (BCVA) deteriorates 3 lines (15 letters) or more from baseline<br>  ○ Central Subfield Thickness (CST) worsening of >100 µm from baseline<br>• During Follow up Phase (i.e., after week 16)<br>  ○ BCVA deteriorates 3 lines (15 letters) or more from highest BCVA during treatment phase or baseline<br>  ○ CST worsening of >100 µm from lowest CST during treatment phase or baseline.<br><br>Subjects who receive a rescue intervention in the study eye will be discontinued from further study participation. |
| **Investigational Product** | KVD001 Injection consists of KVD001 (as hydrochloride [HCl] salt), trehalose dihydrate, histidine, and water for injection.<br>KVD001.HCl will be supplied in 2 mL glass vials at the |

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| | concentration of 60 µg/mL and 30 µg/mL KVD001.<br>KVD001 Injection is 6 µg or 3 µg KVD001 administered as a 100 µL volume IVT injection. |
| **Number of Subjects** | Approximately 123 eligible subjects will be randomized into this study. |
| **Population** | The study population will include male and female subjects 18 years of age or older with ciDME who have received prior anti-VEGF treatment.<br>Except as otherwise defined, subjects must fulfill all of the following criteria both at Screening and on Day 1 to be eligible for inclusion in the study. For applicable conditions, subjects who do not meet the inclusion criteria at Visit 1 or 2 may be rescreened with permission from the Sponsor or Ora.<br>The study eye will be defined as the eye that meets all of the inclusion and none of the exclusion criteria. If both eyes qualify, the eye with the worse BCVA ETDRS at Day 1 will be used as the study eye. If both eyes have the same BCVA ETDRS at Day 1, the eye with the highest CST on spectral-domain optical coherence tomography (SD-OCT) on Day 1, as assessed by the Investigator, will be used as the study eye. If both eyes qualify and neither is preferred based on the inclusion/exclusion criteria and have the same BCVA ETDRS and CST on Day 1, either eye may be chosen as the study eye. In this instance, the Investigator should select the eye that, in their opinion, is most likely to respond to treatment as the study eye.<br>**Inclusion Criteria:**<br>1. Male or female adult subjects 18 years of age and older.<br>2. Confirmed diagnosis of Type I or Type II diabetes mellitus (DM). Any of the following are sufficient:<br>o Current regular use of insulin for the treatment of diabetes<br>o Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes<br>o Documented diabetes by American Diabetes Association and/or World Health Organization (WHO) criteria<br>3. BCVA, using Standard Early Treatment Diabetic Retinopathy Study (ETDRS) chart, of ≥19 letters (~20/400) and ≤73 letters (~20/40) in the study eye and ≥34 letters (~20/200 or better) in the fellow eye at Screening and Day 1.<br>4. Presence of ciDME in the study eye defined as Heidelberg Spectralis Optical Coherence Tomography (SD-OCT) CST ≥305 µm in women and ≥320 µm in men in the study eye (as assessed at Screening by the Investigator and Central Image Reading Center (CIRC) and on Day 1 by the Investigator).<br>5. Subjects' first anti-VEGF injection in the study eye occurred ≤36 months prior to Day 1.<br>6. Subjects have received at least 3 anti-VEGF injections in the study eye within a 6-month period within the 36 months prior |

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| | to Day 1.<br>7. The last anti-VEGF injection in the study eye is ≥ 8 weeks prior to Day 1.<br>8. Subjects, who in the view of the Investigator, are able to defer treatment in the study eye for at least 6 months following Day 1. Note, rescue treatment is available (see Section 5.8).<br>9. Values for blood and urine safety labs at the Screening visit showing no clinically significant deviation as determined by the Investigator.<br>10. Women who are post menopausal for at least 1 year, surgically sterile for at least 3 months prior to Day 1, or who are agreeable to using highly effective contraception (adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for two or more menstrual cycles prior to screening; intrauterine device (IUD); bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly or diaphragm plus contraceptive sponge, foam, or jelly), or abstinence.<br>11. Sexually active men who are not vasectomized and have sexual partners of childbearing potential should be agreable to using highly effective contraception.<br>12. Provide signed informed consent and are willing and capable of complying with clinic visits and study procedures. |
| | **Exclusion Criteria:**<br>1. Females who are pregnant or lactating, or expecting to become pregnant during the course of the study.<br>2. Evidence of ocular pathology (e.g. visually significant cataract) that impacts subject's vision in the study eye from any cause other than DME, in the opinion of the Investigator.<br>3. Evidence/presence of amblyopia, vitreomacular traction, epiretinal membrane, foveal atrophy, or foveal ischemia, or any other condition in the macula that is thought to impair the subject's vision (other than DME) in the opinion of Investigator.<br>4. Prior treatment with panretinal photocoagulation or focal grid macular photocoagulation in the study eye within the previous 3 months prior to Day 1.<br>5. Prior treatment with IVT steroid in the study eye (in the 3 months prior to Day 1 for triamcinolone, 6 months prior to Day 1 for Ozurdex and at any time for Iluvien).<br>6. Prior treatment with topical NSAIDs or topical steroids in the study eye within 1 month prior to Day 1.<br>7. Prior treatment with Jetrea® (ocriplasmin) injection in the study eye within the previous 3 months prior to Day 1. |

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| | 8. Prior treatment with systemic corticosteroids or systemic anti-VEGF therapy within 3 months prior to Day 1.<br>9. Prior vitrectomy in the study eye.<br>10. Prior intraocular surgery in the study eye except for cataract surgery. Cataract surgery within the previous 6 months of Day 1 in the study eye is excluded.<br>11. Intraocular pressure (IOP) at Screening or Day 1 of >22 mmHg in the study eye or use of >2 antiglaucoma agents (combination agents count as 2 agents) in the study eye.<br>12. Evidence of infectious dacrocystitis, significant blepharitis, active conjunctivitis, infectious keratitis, or scleritis in either eye, or any other condition that might affect the safety of the IVT injection in the opinion of Investigator.<br>13. Evidence of active intraocular inflammation in the study eye.<br>14. Current active proliferative diabetic retinopathy (PDR), active anterior segment neovascularization (ASNV), active retinal neovascularization, or the presence of vitreous hemorrhage in the study eye. (Note, quiescent PDR is not exclusionary).<br>15. Any concurrent ocular condition in the study eye which, in the opinion of the Investigator, could interfere with the evaluation of efficacy or safety.<br>16. Poorly controlled DM defined as glycosylated hemoglobin [HgA1c] ≥12.0% or having initiated intensive insulin treatment (a pump or multiple daily injections) within prior 4 months or planning to do so in the next 2 months, or two (2) or more episodes of diabetic ketoacidosis requiring hospitalization within the preceding 6 months.<br>17. Uncontrolled hypertension at Screening or Day 1 defined as systolic ≥180 mmHg or diastolic ≥110 mmHg.<br>18. Significant co-existing disease such as marked hepatic impairment, end stage renal disease (defined as a current or imminent requirement for dialysis), symptomatic cardiac failure, or significant pulmonary dysfunction that may place the subject at higher risk for treatment complications, failure of follow-up, and/or may impact the outcome of the data interpretation of the study, in the opinion of the Investigator.<br>19. History of other disease (e.g., unstable psychiatric illness), metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational product, might affect interpretation of the results of the study, or renders the subject at high risk for treatment complications or lack of follow-up, in the opinion of Investigator.<br>20. History of alcohol and/or drug abuse in the last 2 years.<br>21. Participation in an interventional investigational clinical study |

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| | within 3 months or within 5 half-lives of the last dosing of investigational drug (whichever is longer) prior to Screening.<br>22. Inadequate media clarity or pupillary dilation that does not allow acquisition of an adequate quality OCT and/or fundus image. |
| **Criteria for Evaluation of Efficacy** | **Primary Efficacy Endpoints:**<br>• Change from baseline in BCVA letter count as measured by ETDRS at Week 16<br>**Secondary Efficacy Endpoints**<br>• Change from baseline in CST as measured by Spectral Domain OCT (SD-OCT)<br>• Proportion of eyes with a ≥2 step improvement from baseline in Diabetic Retinopathy Severity Scale (DRSS) score<br>• Change from baseline in BCVA letter count as measured by ETDRS at Weeks 4, 8, 12, 20 and 24<br>• Proportion of study eyes with ≥5, ≥10, and ≥15 BCVA letter change from baseline (gain and loss) |
| **Efficacy Variables** | • BCVA in letters as measured by ETDRS<br>• CST in µm as measured by Spectral Domain (SD)-OCT<br>• Retinopathy severity as measured by the DRSS and graded from fundus photography |
| **Safety Variables** | • AEs<br>• Ophthalmic and physical exam findings<br>• Laboratory test results (clinical chemistry, hematology, and urinalysis)<br>• Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate (PR), and respiratory rate) |
| **General Statistical Methods and Types of Analyses** | Analysis Populations:<br>• Full Analysis Set (FAS) – All randomized subjects following the principle of intention-to-treat (ITT). Subjects will be included in the analysis according to the treatment to which they were randomized.<br>• Per Protocol Set (PPS) – All randomized subjects who are compliant with the study protocol, i.e., who do not experience any major protocol deviations. Subjects will be included in the analysis according to the treatment received.<br>• Safety Set (SAF) – All randomized subjects who receive at least one dose of study treatment. Subjects will be included in the analysis according to the treatment received.<br>Sample Size:<br>The proposed sample size (41 per treatment group) will provide |

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| | approximately 80% power to detect a difference in change from baseline of 5 letters between either of the KVD001 treatment groups and sham based on a two-sided, two-sample t-test with significance level 0.05 and assuming a pooled standard deviation (SD) of 7.5 letters.<br>Multiplicity Considerations:<br>No multiplicity adjustments are planned in this exploratory Phase 2a study.<br>Primary Efficacy Analyses:<br>The primary efficacy endpoint is the change from baseline in BCVA letter count in the study eye at Week 16. Change from baseline in BCVA letter count will be calculated as Week 16 BCVA letter count minus Day 1 BCVA letter count such that a negative difference indicates a worsening in vision. In addition, treatment comparisons between each dose of the KVD001 Injection and the sham procedure will be calculated as KVD001 Injection minus sham, such that a positive result indicates more letters gained in the KVD001 Injection treatment group.<br>The study eye ETDRS letter scores including changes from baseline will be summarized using continuous descriptive statistics. An analysis of covariance (ANCOVA) model will be used to compare the change from Day 1 in BCVA letter count at Week 16 between each dose of the KVD001 Injection and the sham. The ANCOVA model will include treatment as a main effect and baseline BCVA letter count as a covariate. Least-squares means (LSMeans) for each treatment group, the LSMeans difference between each dose of the KVD001 Injection group and the sham procedure group, the corresponding confidence intervals (CIs) and the p-values will be presented. The primary analysis [redacted] in the FAS population at the Week 16 visit, as described in Section 8.2.<br>As a sensitivity analysis, treatment group differences for changes from baseline in BCVA letter count will be evaluated using a mixed model repeated measures (MMRM) ANCOVA fitted with treatment group, visit and the treatment by visit interaction as categorical variable terms with baseline BCVA letter score and baseline CST as covariates with contrasts included for each visit. LSMeans and 95% confidence intervals for each treatment group, the LSMeans difference between each dose of the KVD001 Injection and the sham, the corresponding confidence intervals, and the p-values will be presented for each visit.<br>Secondary Efficacy Analyses:<br>Change from baseline in BCVA letter count in the study eye at Week 24 and change from baseline in CST in the study eye as measured by SD-OCT at Week 16 and Week 24 will be analyzed, separately, using the same method described for the primary efficacy analysis. |

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| | The proportion of study eyes with improvement of 2 or more steps from baseline on the ETDRS DRSS score between the sham procedure group and each of the KVD001 Injection groups will be summarized by visit using discrete summary statistics, including 95% asymptotic normal CIs for each treatment group. The difference in proportions between each of the KVD001 Injection groups and the sham procedure group will be analyzed at Week 16 and Week 24 using a Pearson's chi-squared test. The 95% asymptotic normal CIs for the differences in proportions will also be calculated. Fisher's exact tests and exact CIs will be employed in cases of expected counts <5.<br>The proportion of study eyes with ≥5, ≥10 and ≥15 BCVA letter change from baseline (gain and loss) at Weeks 16 and 24 will be analyzed using the same method described for the proportion of study eyes with improvement of 2 or more steps from baseline on the ETDRS DRSS score.<br>Safety Variables:<br>AEs will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of randomized study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class (SOC) and preferred term (PT); by SOC, PT and maximal severity; by SOC, PT and strongest relationship; by SOC and PT for SAEs; and by SOC, PT and day of onset. Separate analyses will be performed for ocular specific and all AEs (including systemic).<br>Other safety endpoints including manifest refraction/BCVA, slit lamp biomicroscopy, dilated ophthalmoscopy, IOP, SD-OCT, ETDRS DRSS, physical exam findings, laboratory test results, and vital signs will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately. |

## LIST OF STUDY PERSONNEL

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**Adverse Event Reporting**

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**Central Laboratory**

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**Reading Center**

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[redacted]

[redacted]

**Biomarker Lab**

[redacted]

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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| AE | adverse event |
| ANCOVA | analysis of covariance |
| ASNV | anterior segment neovascularization |
| ATC | anatomical therapeutic chemical |
| BCVA | best corrected visual acuity |
| BMI | body mass index |
| BP | blood pressure |
| C1-INH | C1-esterase Inhibitor |
| ciDME | center-involving diabetic macular edema |
| CIRC | Central Image Reading Center |
| CST | central subfield thickness |
| DBP | diastolic blood pressure |
| DRSS | Diabetic Retinopathy Severity Scale |
| DM | diabetes mellitus |
| DME | diabetic macular edema |
| DRL | Drug Reference List |
| eCRF | electronic case report form |
| ED | early discontinuation |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| FAS | full analysis set |
| FE | fellow eye |
| GCP | Good Clinical Practice |
| HgA1c | glycosylated hemoglobin |
| HMWK | high-molecular-weight kininogen |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| IEC | Independent Ethics Committee |
| IOP | intraocular pressure |
| IRB | institutional review board |
| IRT | interactive response technology |
| ITT | intention-to-treat |
| IVT | intravitreal |
| [redacted] | [redacted] |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NOAEL | no-observed adverse effect level |
| NSAID | nonsteroidal anti-inflammatory drug |
| OCT | optical coherence tomography |
| PDR | proliferative diabetic retinopathy |
| PKal | plasma kallikrein |
| PPS | per protocol set |
| PR | pulse rate |
| RVP | retinal vascular permeability |
| SAE | serious adverse event |
| SAF | safety set |
| SAP | statistical analysis plan |
| SBP | systolic blood pressure |
| SD-OCT | spectral-domain optical coherence tomography |

| | |
|---|---|
| SD | standard deviation |
| SE | study eye |
| SUSAR | serious unexpected suspected adverse reaction |
| TEAE | treatment-emergent adverse event |
| US | United States |
| VA | visual acuity |
| VEGF | vascular endothelial growth factor |
| WHO | World Health Organization |

# 1 INTRODUCTION AND BACKGROUND

Diabetic macular edema (DME) is a common complication of diabetes mellitus (GS, N et al. 2017). It leads to vision loss, if untreated, and becomes increasingly prevalent with progressing diabetes. In 2015, over 30 million Americans were estimated to be affected by diabetes and almost 10 million by diabetic retinopathy; 1.5M were estimated to have vision-threatening diabetic retinopathy and 908,000 of these would have DME (Lee, Wong et al. 2015). DME is the leading cause of moderate vision loss among working age adults in most developed countries (Diabetes, Complications Trial/Epidemiology of Diabetes et al. 2009).

The clinical signs of diabetic retinopathy begin with retinal hemorrhages and micro-aneurysms, usually associated with areas of retinal pericyte loss and loss of the endothelial cell barrier function (GS, N et al. 2017). The resulting leakage can lead to macular edema, consisting of an accumulation of fluid and lipoproteins in the retina. Visual acuity declines dramatically when the central macula is affected.

Therapies directed against the vascular endothelial growth factor (anti-VEGF therapies) have made a significant difference in the treatment of DME (Campochiaro, Aiello et al. 2016). The treatments currently in use, aflibercept, bevacizumab and ranibizumab, were shown in clinical trials to be more effective than laser therapy after one year. While laser therapy is expected to improve vision by 3 or more lines in one in 10 people with DME, about three in 10 people are expected to gain vision with anti-VEGF treatment: risk ratio (RR) versus laser 3.66 (95% CI: 2.79 to 4.79) for aflibercept; 2.47 (95% CI 1.81 to 3.37) for bevacizumab; 2.76 (95% CI 2.12 to 3.59) for ranibizumab (Virgili, Parravano et al. 2017). However, a significant proportion (up to 50%) of patients with DME does not achieve vision gain under anti-VEGF therapy (Nguyen, Brown et al. 2012).

Researchers associated with Kalvista have shown that retinal vascular permeability can also be induced by contact system activation, which would be a complementary pathobiologic explanation for the macular edema observed in patients with DME (Gao, Clermont et al. 2007). Observations on human vitreous samples confirmed activation of carbonic anhydrase I, possibly through hemolysis, to be a physiologic trigger of the plasma kallikrein (PKal) – kinin system cascade. Release of the vasoactive peptide bradykinin upon cleavage of high molecular weight kininogen by plasma kallikrein would be the final mediator of vascular permeability and edema generation. Animal experiments confirmed that it is possible to abrogate the vascular permeability induced by bradykinin (Gao, Clermont et al. 2007).

Further experiments in diabetic rats confirmed the presence of bradykinin mediated edema in the eye subsequent to induced diabetes (Clermont, Chilcote et al. 2011). Inhibition of plasma kallikrein activation either via a small-molecule plasma kallikrein inhibitor or physiologic C1-esterase inhibitor significantly reduced edema generation and confirmed PKal inhibition as a potential treatment target for DME.

Plasma kallikrein and its cleavage products were also highly elevated in samples of vitreous from human subjects with diabetes (Kita, Clermont et al. 2015). Moreover, many human samples with clear signs of PKal activation were low in VEGF stimulation, and vice versa, confirming PKal inhibition as a therapeutically independent target in patients with DME.

[redacted]

The proposed study is a phase 2a, randomized, double-masked, sham-controlled, 3-arm study to evaluate the efficacy, safety, and tolerability of KVD001 Injection as monotherapy in adult subjects with center-involving DME (ciDME) who have had prior anti-VEGF treatment.

## 1.1 Rationale for the Study

Strong pathobiologic data support activation of the PKal – kinin cascade as a VEGF-independent explanation for DME. This mechanism is amenable to intervention with PKal, both intravitreally and systemically in animal models, and intravitreally in humans. Relevant investigations were performed with KVD001.HCl in animals and humans to justify proceeding with a phase 2a dose-finding study. The aim of this study is to confirm the therapeutic rationale through multiple injections and over a longer time horizon.

## 1.2 Benefit Risk Assessment

Patients with DME who have been treated with anti-VEGF therapy and continue to experience impaired vision can potentially benefit from a therapy that targets a different pathobiologic mechanism. [redacted]

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

To evaluate the efficacy of monthly dosing of IVT injection of KVD001 in subjects with ciDME who have had prior anti–VEGF treatment.

## 2.2 Secondary Objective(s)

To evaluate the local and systemic safety and tolerability of monthly dosing of KVD001 Injection in subjects with ciDME who have had prior anti–VEGF treatment.

# 3 OVERALL DESIGN AND PLAN OF THE STUDY

## 3.1 Overview

This is a phase 2a, randomized, double-masked, sham-controlled, 3-arm study to evaluate the efficacy, safety, and tolerability of KVD001 Injection as monotherapy in adult subjects with ciDME who have had prior anti-VEGF treatment. Approximately 123 eligible subjects will be randomized into the study.

The maximum duration of the study for each randomized subject will be up to 28 weeks (including up to 4 weeks for screening, 12 weeks treatment period, and 12 weeks follow-up).

The study will be conducted on an out-patient basis.

The study schedule of events will be as follows:

***Screening Phase:*** The screening period will be up to 4 weeks prior to study Day 1. All subjects will sign an Informed Consent Form (ICF) prior to any study related procedures being performed. Subjects will be 18 years of age or older, at the time of screening, and will have a diagnosis of ciDME with prior anti-VEGF treatment.

***Treatment Phase:*** On the day of first study drug administration (Day 1), the subject's eligibility will be reconfirmed and baseline assessments will be performed. Eligible subjects will be randomized 1:1:1 to receive KVD001 Injection (6 µg or 3 µg KVD001) or a sham procedure during a 12-week, double-masked treatment period (a total of 4 doses given at approximately monthly intervals).

Subjects will visit the study clinic on Day 1 and Weeks 4, 8, and 12 during the Treatment Phase for study drug administration or sham procedure, safety, and ophthalmic assessments (see Table 2). The subject will remain in the clinic after study drug administration or sham procedure until all post-dose procedures and observations have been completed and the Investigator confirms that the subject may be discharged. Investigators should schedule visits at Week 4, 8, and 12 to provide 28 days between visits. The visit window for these visits is -3 days to +7 days.

Approximately twenty-four (24) hours after each study drug administration or sham procedure on Day 1 and Weeks 4, 8, and 12, subjects will be contacted by telephone to evaluate any reported AEs and changes in concomitant medications. In the event of any reported ocular or systemic AEs that are considered by the Investigator to be a possible cause for concern, the subjects will return to the clinic for assessment as soon as possible.

***Follow up Phase:*** All subjects will visit the clinic at Weeks 16, 20, and 24 after the last study drug administration or sham procedure for safety and ophthalmic assessments (see Table 2). The visit window for Weeks 16, 20, and 24 is ±7 days.

***Early Discontinuation:*** If any subject discontinues the trial early, every effort should be made to complete the Week 24/early discontinuation (ED) evaluations as soon as possible and, whenever possible, prior to starting any new medication or treatment. All attempts will be made to not discontinue the subject unless necessary.

***Rescue Treatment:*** Rescue intervention (e.g., anti-VEGF, focal/grid macular laser photocoagulation, IVT steroids) may be administered due to worsening DME (i.e., attributable to worsening DME and not another cause) if either of the following occurs and, where possible, after consultation with the Medical Monitor:

- During Treatment Phase

  - Best corrected visual acuity (BCVA) deteriorates 3 lines (15 letters) or more from baseline
  - Central Subfield Thickness (CST) worsening of >100 µm from baseline
- During Follow up Phase (i.e., after week 16)
  - BCVA deteriorates 3 lines (15 letters) or more from highest BCVA during treatment phase or baseline
  - CST worsening of >100 µm from lowest CST during treatment phase or baseline.

If a study subject meets the criteria for rescue intervention and receives a rescue treatment in the study eye, the study subject will be discontinued from further participation in the study.

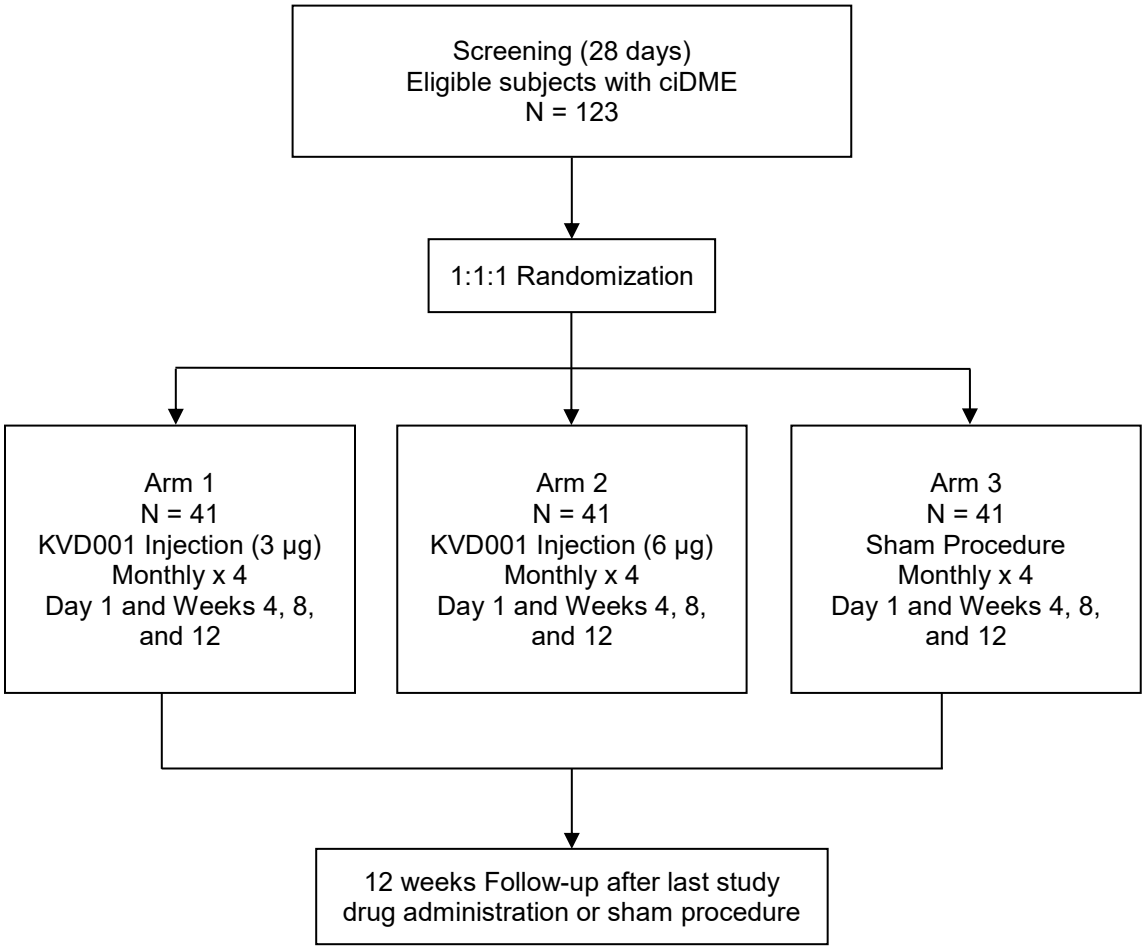



**Figure 1: Study Flow Chart**

## 3.2 Criteria for Evaluation of the Study

### *3.2.1* Efficacy Endpoints

3.2.1.1 Primary Efficacy Endpoints

- Change from baseline in BCVA letter count as measured by ETDRS at Week 16.

3.2.1.2 Secondary Efficacy Endpoints

- Change from baseline in CST as measured by Spectral Domain OCT (SD-OCT)
- Proportion of eyes with a ≥2 step improvement from baseline in Diabetic Retinopathy Severity Scale (DRSS) score
- Change from baseline in BCVA letter count as measured by ETDRS at Weeks 4, 8, 12, 20 and 24
- Proportion of study eyes with ≥5, ≥10, and ≥15 BCVA letter change from baseline (gain and loss).

### *3.2.2* Safety endpoints

- AEs;
- Ophthalmic and physical exam findings;
- Laboratory test results (clinical chemistry, hematology, and urinalysis);
- Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate (PR), and respiratory rate).

## 3.3 Justification of the Study Design

This phase 2a study is the first clinical investigation of the potential efficacy of KVD001 Injection in the treatment of DME. The randomized, double-masked design has been chosen to allow an unbiased and controlled assessment of the safety and efficacy of the drug. The control group will receive a sham injection procedure rather than placebo to avoid unnecessary breaching of the integrity of the eye and risk of endophthalmitis, retinal detachment, cataract, etc.

The study population is representative of the likely target population for the product. The sample size of 123 subjects is appropriate for this stage of development.

The dosing schedule for KVD001 Injection (4 doses at approximately monthly intervals intervals) is supported by animal toxicology data and is within the range shown in the first-in-man study to be well tolerated and to result in potentially beneficial pharmacodynamics effects.

The endpoints are commonly-measured in DME and are clinically relevant.

# 4 STUDY POPULATION

The study population will include male and female subjects 18 years of age or older with ciDME who have received prior anti-VEGF treatment.

Except as otherwise defined, subjects must fulfill all of the following criteria both at Screening and on Day 1 to be eligible for inclusion in the study. For applicable conditions, subjects who do not meet the inclusion criteria at Visit 1 or 2 may be rescreened with permission from the Sponsor or Ora.

The study eye will be defined as the eye that meets all of the inclusion and none of the exclusion criteria. If both eyes qualify, the eye with the worse BCVA ETDRS at Day 1 will be used as the study eye. If both eyes have the same BCVA ETDRS at Day 1, the eye with the highest CST on spectral-domain optical coherence tomography (SD-OCT) on Day 1, as assessed by the Investigator, will be used as the study eye. If both eyes qualify and neither is preferred based on the inclusion/exclusion criteria and have the same BCVA ETDRS and CST on Day 1, either eye may be chosen as the study eye. In this instance, the Investigator should select the eye that, in their opinion, is most likely to respond to treatment as the study eye.

## 4.1 Inclusion Criteria

Subject must fulfill all of the following criteria at Screening and on Day 1 to be eligible for inclusion in the study:

**Inclusion Criteria:**

1. Male or female adult subjects 18 years of age and older.
2. Confirmed diagnosis of Type I or Type II diabetes mellitus (DM). Any of the following are sufficient:
   - Current regular use of insulin for the treatment of diabetes
   - Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes
   - Documented diabetes by American Diabetes Association and/or World Health Organization (WHO) criteria
3. BCVA, using Standard Early Treatment Diabetic Retinopathy Study (ETDRS) chart, of ≥19 letters (~20/400) and ≤73 letters (~20/40) in the study eye and ≥34 letters (~20/200 or better) in the fellow eye at Screening and Day 1.
4. Presence of ciDME in the study eye defined as Heidelberg Spectralis Optical Coherence Tomography (SD-OCT) CST ≥305 µm in women and ≥320 µm in men in the study eye (as assessed at Screening by the Investigator and Central Image Reading Center (CIRC) and on Day 1 by the Investigator).
5. Subjects' first anti-VEGF injection in the study eye occurred ≤ 36 months prior to Day 1.
6. Subjects have received at least 3 anti-VEGF injections in the study eye within a 6-month period within the 36 months prior to Day 1.
7. The last anti-VEGF injection in the study eye is ≥ 8 weeks prior to Day 1.
8. Subjects, who in the view of the Investigator, are able to defer treatment in the study eye for at least 6 months following Day 1. Note, rescue treatment is available (see Section 5.8).
9. Values for blood and urine safety labs at the Screening visit showing no clinically significant deviation as determined by the Investigator.

10. Women who are post menopausal for at least 1 year, surgically sterile for at least 3 months prior to Day 1, or who are agreeable to using highly effective contraception (adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for two or more menstrual cycles prior to screening; IUD; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly or diaphragm plus contraceptive sponge, foam, or jelly), or abstinence.
11. Sexually active men who are not vasectomized and have sexual partners of childbearing potential should be agreable to using highly effective contraception.
12. Provide signed informed consent and are willing and capable of complying with clinic visits and study procedures.

### 4.2 Exclusion Criteria

Subjects will be excluded from the study if one or more of the following statements are applicable at Screening and on Day 1:

1. Females who are pregnant or lactating, or expecting to become pregnant during the course of the study.
2. Evidence of ocular pathology (e.g. visually significant cataract) that impacts subject's vision in the study eye from any cause other than DME, in the opinion of the Investigator.
3. Evidence/presence of amblyopia, vitreomacular traction, epiretinal membrane, foveal atrophy, or foveal ischemia, or any other condition in the macula that is thought to impair the subject's vision (other than DME) in the opinion of Investigator.
4. Prior treatment with panretinal photocoagulation or focal grid macular photocoagulation in the study eye within the previous 3 months prior to Day 1.
5. Prior treatment with IVT steroid in the study eye (in the 3 months prior to Day 1 for triamcinolone, 6 months prior to Day 1 for Ozurdex and at any time for Iluvien).
6. Prior treatment with topical NSAIDs or topical steroids in the study eye within 1 month prior to Day 1.
7. Prior treatment with Jetrea® (ocriplasmin) injection in the study eye within the previous 3 months prior to Day 1.
8. Prior treatment with systemic corticosteroids or systemic anti-VEGF therapy within 3 months prior to Day 1.
9. Prior vitrectomy in the study eye.
10. Prior intraocular surgery in the study eye except for cataract surgery. Cataract surgery within the previous 6 months of Day 1 in the study eye is excluded.
11. Intraocular pressure (IOP) at Screening or Day 1 of >22 mmHg in the study eye or use of >2 antiglaucoma agents (combination agents count as 2 agents) in the study eye.
12. Evidence of infectious dacrocystitis, significant blepharitis, active conjunctivitis, infectious keratitis, or scleritis in either eye, or any other condition that might affect the safety of the IVT injection in the opinion of Investigator.
13. Evidence of active intraocular inflammation in the study eye.
14. Current active proliferative diabetic retinopathy (PDR), active anterior segment neovascularization (ASNV), active retinal neovascularization, or the presence of vitreous hemorrhage in the study eye. (Note, quiescent PDR is not exclusionary).

15. Any concurrent ocular condition in the study eye which, in the opinion of the Investigator, could interfere with the evaluation of efficacy or safety.
16. Poorly controlled DM defined as glycosylated hemoglobin [HgA1c] ≥12.0% or having initiated intensive insulin treatment (a pump or multiple daily injections) within prior 4 months or planning to do so in the next 2 months, or two (2) or more episodes of diabetic ketoacidosis requiring hospitalization within the preceding 6 months.
17. Uncontrolled hypertension at Screening or Day 1 defined as systolic ≥180 mmHg or diastolic ≥ 110 mmHg.
18. Significant co-existing disease such as marked hepatic impairment, end stage renal disease (defined as a current or imminent requirement for dialysis), symptomatic cardiac failure, or significant pulmonary dysfunction that may place the subject at higher risk for treatment complications, failure of follow-up, and/or may impact the outcome of the data interpretation of the study, in the opinion of the Investigator.
19. History of other disease (e.g., unstable psychiatric illness), metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational product, might affect interpretation of the results of the study, or renders the subject at high risk for treatment complications or lack of follow-up, in the opinion of Investigator.
20. History of alcohol and/or drug abuse in the last 2 years.
21. Participation in an interventional investigational clinical study within 3 months or within 5 half-lives of the last dosing of investigational drug (whichever is longer) prior to Screening.
22. Inadequate media clarity or pupillary dilation that does not allow acquisition of an adequate quality OCT and/or fundus image.

### 4.3 Subject Withdrawal

Subjects are free to withdraw from participation in the study at any time, for any reason (or without providing reasons) and without prejudice to further treatment or they may be discontinued by the investigator, if deemed in their best medical interests.

The Investigator may also discontinue a subject from further study drug dosing or withdraw a subject from the study at any time for the following reasons:

- Positive pregnancy test;
- AEs, serious adverse events (SAEs),
- Use of prohibited medication (see section 5.7) or rescue medication (see section 5.8);
- Administrative reasons (e.g., lack of subject compliance to study visits / procedures, lost to follow-up).

#### *4.3.1* Withdrawal from Participation

Subjects who withdraw or are withdrawn from the study will complete the ED visit as soon as possible. The reason for discontinuation / withdrawal will be documented in the electronic case report form (eCRF) and the Medical Monitor must be informed immediately. If the reason for withdrawal is the occurrence of an AE, the subject will be followed up until the AE has resolved or is considered chronic and stable or the AE has been clearly shown to be unrelated to the investigational product.

Subjects will also be withdrawn if the entire study is terminated prematurely as described in Section 9.10.

Subjects who are randomized and subsequently withdraw from study participation will not be replaced.

#### 4.3.2 Lost to Follow–up

If a subject does not return for a scheduled visit, every effort should be made at least once every month to contact the subject to reschedule the visit, including mandatory telephone contact and written letter. All efforts should be documented in the subject's medical source record. A subject is considered lost to follow–up if subject cannot be reached after 3 months from the scheduled visit. However, if the subject re–initiates contact beyond 3 months, the available data may still be collected on the eCRF, provided that subject consent has not been withdrawn.

If a subject discontinues study medication or is withdrawn from the study for any reason, the study site must immediately notify the medical monitor.

The Sponsor has the right to terminate the study at any time and for any reason. In the event, the Investigators will be informed of the reason for study termination by written notification.

### 4.4 Planned Sample Size

Ophthalmology clinics in the United States (US) will randomize approximately 123 eligible subjects into the study. Only study sites with experience in the conduct of DME clinical studies will be selected. See Section 8.8 for a discussion of sample size.

### 4.5 Subject Identification and Randomization

#### *4.5.1* Subject Identification

Each subject will receive a unique screening ID number. Subjects who are screen failures and are not randomized will retain their screening ID number.

#### *4.5.2* Randomization Scheme

Subjects will be randomized on a 1:1:1 basis to KVD001 Injection 60 µg/mL or 30 µg/mL (6 µg/eye or 3 µg/eye in a 100 µL dose volume) or a sham procedure. Randomization will be centralized with stratification by visual acuity and CST at Day 1.

#### *4.5.3* Allocation/Randomization of Subjects to Treatment

Subjects must not be randomized unless all eligibility criteria have been met.

Subjects who satisfy all the entry criteria will be centrally assigned to study medication by the Interactive Response Technology (IRT), according to the randomization scheme generated by Ora. Each randomized subject will receive a unique randomization

number. Subjects will be randomized in a 1:1 ratio to 60 µg/mL or 30 µg/mL KVD001 Injection or sham procedure.

The actual treatment given to subjects will be determined by the randomization scheme in IRT. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers. One randomization list will be produced containing sufficient random numbers for both randomization strata.

The dose and regimen of randomized therapy to be administered is as follows:

- KVD001 6 µg by IVT injection;
- KVD001 3 µg by IVT injection;
- Sham procedure.

Subjects will be identified using subject initials, randomization number, and date of birth. Subjects will be randomized sequentially within their stratification category, as subjects are eligible for randomization. The IRT will inform the Investigator of the kit identification (ID) number to be allocated to the subject at each dispensing visit.

First dose of study drug administration or sham procedure will be administered on Day 1, after completion of all pre–dose assessments.

Randomized subjects who are discontinued from further study drug administration or are terminated from the study for any reason, regardless of whether study drug was taken or not, will not have their screening/randomization code be reused.

# 5 STUDY DRUG

## 5.1 Identity

For clinical trial use, KVD001.HCl has been formulated as KVD001 Injection. [redacted]

Further information about KVD001 Injection can be found in the current IB (Gardner and Antonetti 2007).

## 5.2 Administration

KVD001 Injection or sham procedure will be administered to the study eye on Day 1 and Weeks 4, 8, and 12 during the Treatment Phase. At each scheduled visit, the date and time of study medication administration will be recorded in the eCRF.

The injecting physician cannot be the Investigator as they should remain masked throughout the study. In order to avoid breaking the mask, real and sham injections will be performed by study personnel who are not masked and not otherwise involved in the study (note that post-injection IOP evaluations must be performed by study personnel who are unmasked). For sham injections, the subjects will be prepared exactly as for a real injection (i.e., including but not limited to: insertion of lid speculum, application of povidone-iodine and subconjunctival injection of an anesthetic) following which an empty syringe with no needle will be pressed against the eye to mimic the pressure of an injection.

Please refer to the Pharmacy Manual for detailed instructions on administration.

## 5.3 Packaging, Labelling and Storage

The study packaging and labelling of drug product will be performed by Ora. The storage and distribution supply of drug product will be performed by Ora. All packaging and labelling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements. [redacted] All boxes will remain closed except while being accessed by the nominated unmasked personnel administering the real and sham injections.

The Investigator will ensure that the drug product is stored in appropriate conditions [redacted] Upon completion of dosing, the used drug product may be destroyed with routine medical waste at the clinical site. The Investigator (or designee) will dispense the drug product only to the identified subjects of this study following the procedures described in this study protocol and documented in the subject dispensing log.

Drug Product inventory/dispensing will be documented in the source documentation and the eCRF for each subject. The Investigator is responsible for all drug products. Written

documentation is mandatory. After completion of the study, all unused drug product will be returned to the location designated by Ora for accountability and destruction.

## 5.4 Masking and Breaking the Masking

The study will be performed in a double–masked manner. The study is masked by sham procedure and sham packaging. The sham procedure will be identical to injecting study drug, except as described previously, thereby enabling double-masked conditions.

The study mask should not be broken except in a medical emergency (where knowledge of the study drug received would affect the treatment of the emergency) or regulatory requirement (e.g., for SAEs or death). The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unmasked.

Before breaking the mask of an individual subject's treatment, the Investigator should determine that the unmasked information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the study drug, the problem may be properly managed by assuming that the subject is receiving active product. The decision to unmask treatment assignment should be discussed with the Sponsor and Medical Monitor. The Investigator should only call in for emergency unmasking AFTER the decision to discontinue the subject has been made.

If the mask is broken, the date, time, and reason must be recorded in the subject's eCRF system and any associated AE report.

Once approval for unmasking is obtained, the Investigator can unmask study drug assigned to a subject through the IRT system.

If an Investigator, site personnel performing assessments, or subject is unmasked, the subject must be listed as major protocol deviation.

Serious unexpected suspected adverse reactions (SUSARs), which are subject to expedited reporting, should be unmasked before submission to the Regulatory Authorities.

The overall randomization code will be broken only for reporting purposes. This will occur once all final clinical data have been entered onto the database and all data queries have been resolved, and the assignment of subject to the analysis sets has been completed.

## 5.5 Drug Accountability

The Investigator is responsible for maintaining accurate study drug accountability records throughout the study.

Each dispensing of study drug will be documented in the eCRF.

The Investigator is responsible for returning all unused study drug to Ora at the completion of the study. Ora will ensure no remaining supplies are in the Investigator's possession and agree with the Sponsor the fate of returned study drug.

## 5.6 Compliance

Study drug shall be administered by qualified unmasked staff at the clinical site; the procedure must be recorded in the eCRF.

## 5.7 Concomitant Medications/Therapy

The concomitant use of the following medications will not be allowed in the study:

- Anti–VEGF administered systemically;
- Any treatment in the study eye or given intravitreally in the study eye for DME other than the study medication. Note, the fellow (non-study) eye may be treated for DME at the Investigator's discretion;
- Steroid administered systemically, intravitreally in the study eye, or topically in the study eye;
- NSAIDs administered topically in the study eye;
- Any Jetrea® (ocriplasmin) intravitreal injection in the study eye.
- Any ophthalmic medication that in the opinion of the Investigator may influence the interpretation of the safety and/or efficacy parameters in this study.

Details of all medications (other than those intended to treat the study subjects' DME), therapies and supplements administered within 3 months prior to Screening Visit until the end of the study will be recorded in the eCRF. See section 6.3.2.1 for details regarding requirements for data collection relative to DME history and previous treatments and medications. With the exception of ocular medications intended to treat DME, prior medications are defined as those medications taken within 3 months prior to Screening Visit; concomitant medications are defined as those medications ongoing at or started after Day 1.

See section 5.8 regarding the collection of rescue treatment medications as concomitant medication.

## 5.8 Rescue Treatment

Rescue intervention (e.g., anti-VEGF, focal/grid macular laser photocoagulation, IVT steroids) may be administered due to worsening DME (i.e., attributable to worsening DME and not another cause) if either of the following occurs and, where possible, after consultation with the Medical Monitor:

- During Treatment Phase
  - Best corrected visual acuity (BCVA) deteriorates 3 lines (15 letters) or more from baseline
  - Central Subfield Thickness (CST) worsening of >100 µm from baseline
- During Follow up Phase (i.e., after Week 16)
  - BCVA deteriorates 3 lines (15 letters) or more from highest BCVA during treatment phase or baseline
  - CST worsening of >100 µm from lowest CST during treatment phase or baseline.

Subjects who receive a rescue intervention in the study eye will be discontinued from further study participation. The Week 24/ED evaluations should be collected prior to study discontinuation and prior to administration of the rescue medication. Details regarding the medications used as rescue treatment must be entered as concomitant medications for the respective study subject.

# 6 VARIABLES AND METHODS OF ASSESSMENT

## 6.1 Efficacy Variables

Efficacy variables of interest in this study are:

- BCVA in letters as measured by ETDRS;
- CST in µm as measured by Spectral Domain OCT;
- Retinopathy severity as measured by the DRSS and graded from fundus photography.

## 6.2 Safety Variables

Safety variables of interest in this study are:

- AEs;
- Ophthalmic and physical findings;
- Laboratory test results (clinical chemistry, hematology, and urinalysis);
- Vital signs (SBP, DBP, PR, and respiratory rate).

### *6.2.1* Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of an investigational product (IP) in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, without any judgment about causality. An AE can arise from any use of the investigational product (e.g. off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the CRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to investigational product, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

#### 6.2.1.1 Severity

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

- *Mild*: Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.

- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.

- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

#### 6.2.1.2 Relationship to Investigational Product

The relationship of each AE to the investigational product should be determined by the investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the investigational product caused the AE.

- *Not Suspected*: A reasonable possibility does not exist that the investigational product caused the AE.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the investigational product caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE. Types of evidence that would suggest a causal relationship between the investigational product and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with investigational product exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with investigational product exposure, but is otherwise uncommon in the population exposed to the investigational product (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the investigational product-treatment group than in a concurrent or historical control group.

#### 6.2.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the investigational product using these explanations:

- *Unexpected*: an AE that is not listed in the Investigator's Brochure (IB)(IB 2017) or is not listed at the specificity or severity that has been observed.

- *Expected*: an AE that is listed in the IB at the specificity and severity that has been observed.

- *Not applicable:* an AE unrelated to the investigational product.

AEs that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/ mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

#### 6.2.1.4 Serious Adverse Events

An AE 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;
  - Note: An AE is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization;
  - Note: The term “inpatient hospitalization” refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.
  - Note: The term “prolongation of existing hospitalization” refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
  - Note: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject’s eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).
- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

#### 6.2.1.5 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora, the study sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate CRF.

#### 6.2.1.6 Reporting a Suspected Unexpected Adverse Reaction

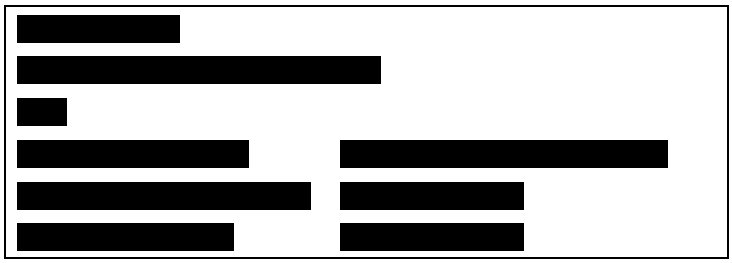
All AEs that are ‘suspected’ and ‘unexpected’ are to be reported to Ora within 24 hours. Ora and the Sponsor will immediately conduct an evaluation of the reported event. The results of the evaluation will be reported to the IRB within 10 days of Ora and/or the Sponsor becoming aware of the event. Events must be reported to the study sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

#### 6.2.1.7 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the investigational product, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate case report forms. The investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to that information reported on the case report form. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify Ora and the sponsor within 24 hours; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Ora and the study sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the investigational product; and inform the IRB of the SAE within their guidelines for reporting SAEs.

Contact information (SAEs):



#### 6.2.1.8 Type and Duration of the Follow-up of Subjects after Adverse Events

All AEs irrespective of the suspected causality will be monitored until the AE has resolved or until the end of the study (Week 24), unless the subject is lost to follow–up or withdraws consent or the subject died prior to the end of the study. All SAEs, irrespective of the suspected causality, will be monitored until the SAE has resolved or until the subject is lost to follow-up or the subject has died.

#### 6.2.1.9 Pregnancy

The Sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the study drug.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

All pregnancies must be reported by the Investigator to Ora/Sponsor on the initial pregnancy report form within 30 days after becoming aware of the pregnancy. The Investigator must follow-up and document the course and the outcome of all pregnancies even if the patient was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the Investigator to Ora on the pregnancy outcome report form within 30 days of becoming aware of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy (including SAEs occurring after last administration of study drug) must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

If a female partner of a male study patient who has been exposed to the study drug becomes pregnant, the pregnancy and outcome of pregnancy should be monitored according to the same guidelines as for female subjects who become pregnant during the study.

### *6.2.2* Laboratory Variables

Laboratory assessments will be performed by a central laboratory, as identified in the List of Study Personnel. Before starting the study, the central lab will supply a list of the normal ranges and units of measurement.

Blood samples should be taken using standard venipuncture techniques. A lab manual will be provided by the central laboratory; this will contain very detailed instructions for collection, storage, and shipment of samples (e.g., what kind of tubes, what kind of sample preparation, mailing addresses, etc.).

The following laboratory variables will be determined in accordance with the Schedule of Procedures (Table 2):

**Table 1: Laboratory Assessments**

| | | | |
|---|---|---|---|
| Hematology: | Erythrocytes<br>MCV<br>MCH<br>Neutrophils<br>Eosinophils<br>Basophils<br>Lymphocytes<br>Monocytes<br>Platelets<br>Leukocytes<br>Hemoglobin<br>Hematocrit | Urinalysis: | pH<br>Protein<br>Glucose<br>Ketone<br>Bilirubin<br>Blood<br>Nitrite<br>Microalbuminemia<br>Proteinuria |
| Clinical chemistry: | HgA1c<br>Creatinine<br>Glucose<br>Triglycerides<br>Urea<br>Uric acid<br>Bilirubin<br>Cholesterol | Liver enzymes: | Alkaline phosphatase<br>AST<br>ALT<br>GGT |
| Electrolytes: | Sodium<br>Potassium | | |
| Urine pregnancy test: | In women with childbearing potential | | |

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma glutamyl transferase; HgA1c = Glycosylated hemoglobin; HMWK = high molecular weight kininogen; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume: pH = potential hydrogen; PKal = plasma kallikrein.

The Investigator must review screening laboratory results for subject eligibility prior to enrolling.

Laboratory tests can be repeated earlier than the next scheduled consecutive study visit at the Investigator's discretion and any associated safety issue should be followed up as per the Investigator's clinical judgement until resolution/stabilization.

Laboratory data will be electronically transferred to the clinical database at specified time points during the study.

## 6.3 Methods of Assessment

The following assessments will be conducted and recorded in the eCRF. The Schedule of Procedures and Procedures by Visit can be found in Sections 7.1 and 7.2, respectively.

### *6.3.1* Subject Demography

Subject demography will be performed at the Screening visit and consists of:

- Date of birth;
- Height;
- Weight;
- Race and ethnicity;
- Gender
- Iris color

### *6.3.2* Medical and Ocular History

For the documentation of the medical history, any relevant previous and concurrent diseases will be documented.

The medical history will be obtained by interviewing the subject or by inspecting relevant medical records.

For coding of medical history, see Section 9.4.

#### 6.3.2.1 DME Disease History

DME disease history will be recorded at the Screening visit. For disease history the following will be documented:

- Date of first diagnosis of DME in the study eye
- Date and details of the first anti-VEGF injection
- Dates and details of the last three anti-VEGF injections
    - BCVA score or Snellen equivalent of each VA assessment in the study eye beginning with the VA assessment immediately prior to the last three anti-VEGF injections
    - CST from each OCT assessment in the study eye beginning with the OCT assessment immediately prior to the last three anti-VEGF injections
- Estimate or actual total number of anti-VEGF injections
- Date of last IVT steroid injection (if any)
- Estimate or actual total number of IVT steroid injections (if any)

The Investigator's assessment of the subject's response to anti-VEGF treatment after the last 3 IVT injections compared to baseline will be recorded using the following scales (baseline is defined as the status of edema and vision immediately prior to the first of the 3 injections):

***Edema:***

- Satisfactory response – Absence of intraretinal/subretinal fluid;
- Partial response 1 – Significant reduction of intraretinal/subretinal fluid;
- Partial response 2 - Little or some reduction (~20%) of intraretinal/subretinal fluid;
- No response – No reduction or worsening of intraretinal/subretinal fluid.

***Vision:***

- No change in or worsening of BCVA
- Gain of 1-4 letters
- Gain of 5 to 9 letters
- Gain 10 to 14 letters
- Gain of ≥15 letters

#### *6.3.3* Previous and Concomitant Medications

Previous and concomitant medication will be documented as described in Section 5.7.

#### *6.3.4* Vital Signs

The following vital signs will be assessed at rest (5 minutes in a supine position) in accordance with the Schedule of Procedures (Table 2). The same equipment for each vital sign evaluation should be used on given patient for all study visits. Vital signs should be conducted prior to study drug administration and approximately 30 minutes post-study drug administration on applicable visits.

- Blood pressure (SBP and DBP; mmHg);
- Pulse rate (beats per minute);
- Body temperature (°C);
- Respiration rate (breaths per minute).

#### *6.3.5* Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Procedures (Table 2). The physical examination should be symptom directed and include the following body systems: general appearance, skin, lymphatic, head and neck, ears, nose and throat, chest and lungs, cardiovascular, abdomen, extremities, musculoskeletal and neuromuscular.

#### *6.3.6* Safety Laboratory Assessments

Laboratory assessments will be conducted in accordance with Section 6.2.2. The central laboratory will provide a lab manual with detailed procedures. Safety labs should be collected prior to study drug administration on applicable visits.

#### *6.3.7* Ophthalmic Assessments

Ophthalmic findings will be performed in accordance with the Schedule of Procedures (Table 2). All ophthalmic assessments will be conducted on both eyes except fundus photography which will be taken in both eyes at the Screening visit and only in the study eye at subsequent visits.

**Best Corrected Visual Acuity Early Treatment Diabetic Retinopathy Study (BCVA ETDRS):**

BCVA of both eyes will be assessed using the ETDRS protocol. Detailed instructions for performing manifest refraction and BCVA will be provided in the study-specific BCVA manual. BCVA should be performed prior to all other ophthalmic assessments at all visits.

**Slit Lamp Biomicroscopy:**
The eyelids, cornea, conjunctiva, anterior chamber, iris/pupil and lens should be evaluated. Findings will be graded as normal, abnormal non-clinically significant, or abnormal clinically significant. Slit lamp biomicroscopy will be performed on both eyes and should be conducted prior to study drug administration on applicable visits.

**Intraocular Pressure (IOP):**
IOP will be assessed in both eyes at all study visits. IOP will be assessed with either applanation tonometry or tonopen; the method should be consistent throughout the study. IOP will be assessed at both pre- and post- injection at visits with study drug administrations. Pre-injection IOP must be performed prior to dilation. Post-injection IOP should be assessed within 60 minutes after study drug or sham administration and should be assessed by someone who is unmasked.

**Dilated Indirect Ophthalmoscopy:**
The vitreous, macula, choroid, optic nerve, and retina of both eyes will be assessed. Findings will be graded as normal, abnormal non-clinically significant, or abnormal clinically significant. The dilated indirect ophthalmoscopy will be performed on both eyes and should be conducted prior to study drug administration on applicable visits.

**Fundus Photography:**
Color fundus photographs will be taken in both eyes at Screening and in the study eye at subsequent visits to evaluate retinal anatomy and grade DRSS. Photographs will be transferred to the CIRC for independent analysis. Detailed instructions for imaging and data transfers will be provided in the study-specific Image Acquisition and Submission Protocol. Fundus photography should be conducted prior to study drug administration on applicable visits.

**Spectral Domain Optical Coherence Tomography (SD-OCT):**
SD-OCT will be utilized to assess retinal thickness. All sites will be required to use a Heidelberg Spectralis SD-OCT. OCT imaging data will be transmitted to a Central CIRC for independent analysis. Detailed instructions for imaging and data transfers will be provided in the study-specific Image Acquisition and Submission Protocol. SD-OCT should be conducted prior to study drug administration on applicable visits.

[redacted]

# 7 STUDY CONDUCT

## 7.1 Schedule of Procedures

A list of procedures to be conducted, by visit, is described in Table 2.

Visits should occur on:

- Day 1 and Weeks 4, 8, and 12 during the Treatment Phase;
- Weeks 16, 20, and 24 during Follow–up Phase.

Changes to the dosing schedule outside of the specified windows must be discussed with the Medical Monitor. All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

**Table 2: Schedule of Procedures**

| Clinic Visit (V) | Visit 1 Screen | Visit 2 | Call | Visit 3 | Call | Visit 4 | Call | Visit 5 | Call | Visit 6 | Visit 7 | Visit 8/ ED Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day (D)** | **Week -4 to Day -1** | **Day 1** | **Visit 2 +1 day** | **Week 4 (-3 to +7 days)** | **Visit 3 +1 day** | **Week 8 (-3 to +7 days)** | **Visit 4 +1 day** | **Week 12 (-3 to +7 days)** | **Visit 5 +1 Day** | **Week 16 (±1 Week)** | **Week 20 (±1 Week)** | **Week 24 (±1 Week)** |
| Informed Consent | X | | | | | | | | | | | |
| Eligibility Assessment | X | X | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination (height, weight, BMI) | X | | | | | | | | | | | |
| Medical/Ocular History | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital Signs[a] | X | X | | X | | X | | X | | X | | |
| Safety Laboratory[b] | X | X | | X | | X | | X | | X | | |
| [redacted] | | X | | | | | | | | | | |
| Study Drug Administration (KVD001 Injection) or Sham Procedure | | X | | X | | X | | X | | | | |
| Urine Pregnancy Test (women) | X | X | | X | | X | | X | | X | | |
| Adverse Events[c] | X | X | X | X | X | X | X | X | X | X | X | X |

**Table 2 Schedule of Procedures (Cont'd)**

| Clinic Visit (V) | Visit 1 Screen | | Visit 2 | | Call | Visit 3 | | Call | Visit 4 | | Call | Visit 5 | | Call | Visit 6 | | Visit 7 | | Visit 8/ ED Visit | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day (D) | Week -4 to Day -1 | | Day 1 | | Visit 2 +1 day | Week 4 (-3 to +7 days) | | Visit 3 +1 day | Week 8 (-3 to +7 days) | | Visit 4 +1 day | Week 12 (-3 to +7 days) | | Visit 5 +1 day | Week 16 (±1 Week) | | Week 20 (±1 Week) | | Week 24 (±1 Week) | |
| **OCULAR** | **SE** | **FE** | **SE** | **FE** | | **SE** | **FE** | | **SE** | **FE** | | **SE** | **FE** | | **SE** | **FE** | **SE** | **FE** | **SE** | **FE** |
| BCVA[d,e] | X | X | X | X | | X | X | | X | X | | X | X | | X | X | X | X | X | X |
| Slit Lamp Biomicroscopy[d] | X | X | X | X | | X | X | | X | X | | X | X | | X | X | X | X | X | X |
| Dilated Indirect Ophthalmoscopy[d] | X | X | X | X | | X | X | | X | X | | X | X | | X | X | X | X | X | X |
| IOP[f] | X | X | X | X | | X | X | | X | X | | X | X | | X | X | X | X | X | X |
| Fundus Photography[d] | X | X | X | | | X | | | X | | | X | | | X | | X | | X | |
| SD-OCT[d] | X | X | X | X | | X | X | | X | X | | X | X | | X | X | X | X | X | X |

Abbreviations: AEs = Adverse events; BCVA = Best corrected visual acuity; BMI = Body mass index; ED Visit = Early discontinuation visit; FE = Fellow eye; IOP = Intraocular pressure; SD-OCT = Spectral domain optical coherence tomography; SE = Study eye.

[a] Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature. Vital signs will be taken prior to and approximately 30 minutes after study drug

[b] Safety labs are detailed in Section 6.2.2.

[c] AEs to be recorded from time of signing of informed consent form

[d] Procedure will be performed prior to study drug administration or sham procedure on applicable visits.

[e] BCVA will be performed prior to all other ophthalmic procedures.

[f] IOP will be taken prior to and within 60 minutes following study drug administration or sham procedure at applicable visits. Pre-study drug administration IOP must be performed prior to dilation. Post study-drug administration IOP must be performed by unmasked personnel.

.

## 7.2 Procedures by Visit

Prior to any study activities, subjects will be asked to read and sign an ICF that has been approved by an Independent IEC/IRB and the Sponsor and which complies with regulatory requirements.

All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

Ophthalmic procedures are proposed to occur in the following order at Visits 2-5:

- BCVA (must be performed prior to all other ophthalmic procedures)
- Slit lamp biomicroscopy
- Pre-Injection IOP/IOP at visits with no study drug administration (must be done prior to dilation)
- Dilated indirect ophthalmoscopy
- Fundus photography
- SD-OCT
- Intravitreal injection
- Post-Injection IOP

### *7.2.1* Screening Phase (Weeks -4 to Day -1 [Visit 1])

Subjects will undergo screening during a visit that can occur up to 4 weeks prior to the Day 1 Visit. Following full discussion of the study and the signing of ICF, a screening subject ID number will be assigned. All subjects will be assessed for eligibility against the inclusion and exclusion criteria.

The following screening and baseline assessments will be performed:

- Obtain subject's full medical history, including ophthalmic ocular history with DME disease history, concomitant illnesses/diseases and medications, therapies and supplements taken within the past 3 months, previous participation in interventional clinical studies in the past three months;
- Record demographic information including race, ethnicity and date of birth;
- Conduct the following ophthalmic measurements and examinations in both study eye and fellow eye in accordance with procedures as described in Section 6.3.7;
  - BCVA;
  - Slit lamp biomicroscopy;
  - IOP (prior to dilation);
  - Dilated indirect ophthalmoscopy;
  - Fundus photography;
  - SD-OCT;
- Collect blood and urine samples per Section 6.3;
- Perform measurements of height (meters [m], without shoes) and weight (kilogram [kg], without shoes or overcoat). Calculation of body mass index (BMI) will be automated in the database;
- Vital signs (Blood pressure [BP], PR, respiratory rate, and body temperature [ºC]) – BP and PR will be recorded after subject has been supine for 5 minutes;
- Urine pregnancy test (women of childbearing potential);

- Perform eligibility check, evaluating all results of the screening assessment results against the inclusion and exclusion criteria;
- All AEs reported after signing of the ICF will be recorded;
- Review the study procedures and study visit schedule with the subject.

### *7.2.2* Treatment Phase

7.2.2.1 Day 1 and Weeks 4, 8, and 12 (Visits 2, 3, 4, and 5)

Visits are to occur within -3 to +7 days for Weeks 4, 8, and 12. Subjects should attend Clinic Visit 2 within 4 weeks of screening.

The following assessments will be performed:

- Reconfirm eligibility (Day 1 only);
- Collect blood and urine samples per Section 6.2.2;
- [redacted]
- Collect any changes to medical or ocular history;
- Record any AEs;
- Record any change to the concomitant medication;
- Urine pregnancy test (women of childbearing potential);
- Vital signs (BP, PR, respiratory rate, and body temperature [ºC]) – BP and PR will be recorded after subject has been supine for 5 minutes. Vitals signs will be collected prior to and approximately 30 minutes after study drug administration or sham procedure;
- Conduct the following ophthalmic measurements and examinations in both study eye and fellow eye (except fundus photograph) in accordance with procedures as described in Section 6.3.7;
  - BCVA;
  - Slit lamp biomicroscopy;
- IOP will be collected performed prior to and within 60 minutes (Post study-drug administration IOP must be performed by unmasked personnel) after study drug administration or sham procedure. Pre-study drug administration IOP must be conducted prior to dilation;
  - Dilated indirect ophthalmoscopy;
  - Fundus photography (SE only);
  - SD-OCT;
- Administer the study drug administration or sham procedure to the study eye.

7.2.2.2 Post–treatment Follow–up Call

Approximately twenty-four (24) hours after each study drug administration or sham procedure on Day 1 and Weeks 4, 8, and 12), subjects will be contacted by telephone to evaluate any reported AEs and changes in concomitant medications. In the event of any reported AEs, the subjects will return to the clinic for assessment.

### *7.2.3* Follow–up Phase

Following Week 12 (Visit 5) of study drug administration or sham procedure, subjects will be followed up monthly at the clinic for 12 weeks (Weeks 16, 20, and 24 [Visits 6, 7, and 8, respectively]).

7.2.3.1 Weeks 16, 20, and 24 (Visits 6, 7, and 8)

Visits are to occur within ± 1 week of the target visit date. At the visit the following procedures will be conducted:

- Collect blood and urine samples per section 6.2.2 (Week 16 only);
- Collect any changes to medical or ocular history;
- Record any AEs;
- Record any change to the concomitant medication;
- Urine pregnancy test (women of childbearing potential) (Week 16 only);
- Vital signs (BP, PR, respiratory rate, and body temperature [ºC]) – BP and PR will be recorded after subject has been supine for 5 minutes (Week 16 only);
- Conduct the following ophthalmic measurements and examinations in both study eye and fellow eye in accordance with procedures as described in Section 6.3.7;
  - BCVA;
  - Slit lamp examination biomicroscopy;
  - IOP (prior to dilation);
  - Dilated indirect ophthalmoscopy;
  - Fundus photography (SE only);
  - SD-OCT;

### *7.2.4* Early Discontinuation Visit

If any subject discontinues the trial early, every effort should be made to complete the Week 24/early discontinuation (ED) evaluations as soon as possible and, whenever possible, prior to starting any new medication or treatment (including rescue treatment). All attempts will be made to not discontinue the subject unless necessary.

If a study subject completes an early discontinuation evaluation for the purpose of receiving rescue treatment, then the medications used as rescue treatment will be detailed in the respective concomitant medications section of the study's EDC system.

# 8 STATISTICAL METHODS

The statistical considerations summarized in this section outline the plan for data analysis of this study.

Before unmasking, a separate statistical analysis plan (SAP) will be finalized, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described and justified in the final integrated study report.

Subjects will be randomized by the IRT in a 1:1:1 ratio to 1 of the 3 treatment groups: KVD001 Injection (6 µg/eye or 3 µg/eye) or sham. Allocation to the treatments will be stratified by baseline BCVA (≤55 letters vs >55 letters) and CST at Screening (≤450 µm vs >450 µm) as determined by the study center.

## 8.1 Study Subjects

### *8.1.1* Disposition of Subjects

The number and percentage of subjects entering and completing each phase of the study will be presented, stratified by treatment. Reasons for withdrawal post-randomization will also be summarized.

### *8.1.2* Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as “minor” or “major” in cooperation with the Sponsor. Major deviations from the protocol that have the potential to impact the efficacy results will lead to the exclusion of a subject from the Per Protocol Set (PPS). Deviations will be defined prior to unmasking.

### *8.1.3* Analysis Sets

The following analysis sets have been defined for this study:

| | |
|---|---|
| Full Analysis Set (FAS): | All randomized subjects following the principle of intention-to-treat (ITT). Subjects will be included in the analysis according to the treatment to which they were randomized. |
| Per-Per Protocol Set (PPS): | All randomized subjects who are compliant with the study protocol, i.e., who do not experience any major protocol deviations. Subjects will be included in the analysis according to the treatment received. |
| Safety Set (SAF): | All randomized subjects who received at least one dose of study treatment. Subjects will be included in the analysis according to the treatment received. |

The primary efficacy analysis will be based on the FAS and a secondary analysis will also be performed based upon the PPS, to assess the sensitivity of the analysis to the choice of analysis set. All safety analyses will be based upon the SAF.

Demographic and baseline characteristics will be evaluated for the FAS and for the PPS. If one or more subject(s) received incorrect trial drug, these data will also be presented for the SAF.

## 8.2 General Considerations

All statistical tests will be two-sided and will be performed at the 5% level of significance, unless otherwise stated.

Continuous data will be summarized by treatment group using descriptive statistics (number, arithmetic mean, median, standard deviation [SD], minimum, and maximum). Categorical data will be summarized by treatment group using frequency tables (frequencies and percentages).

All analyses will be carried out using SAS Version 9.4 or higher or using other validated software.

**Analysis and data conventions:**

Definition of baseline

The baseline assessment will be the latest, valid pre-dose assessment available.

Visit windows

Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the Investigator.

Unscheduled assessments

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than one laboratory value is available for a given visit, the first valid observation will be used in summaries and all observations will be presented in listings. It is noted that invalid laboratory data may not be used (from hemolyzed samples, mishandled samples, quantity not sufficient, or other conditions that would render values invalid).

Unit of Analysis

Ophthalmic safety endpoints will be analyzed for both eyes. Non-ophthalmic safety endpoints will be analyzed with subject as the unit of analysis. For efficacy endpoints, the unit of analysis will be the study eye.

Missing data conventions

In general, data will not be imputed for safety analysis. The primary and secondary efficacy data analyses will be performed on the FAS [redacted] An analysis using observed data only will also be performed in both the FAS and PPS. Additionally, [redacted] the FAS for the analysis of the primary and secondary efficacy variables. No exploratory efficacy endpoints or safety endpoints will be imputed. Additional details will be provided in the SAP.

Multiplicity Considerations

No multiplicity adjustments are planned in this exploratory Phase 2a study.

Other considerations

Since central randomization will be used, no testing for treatment by center interaction will be conducted. No multiplicity adjustments are planned.

Any outliers that are detected during the masked review of the data will be investigated. If necessary, queries will be issued to the Investigator, to either correct or confirm the outlier.

## 8.3 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographic data, medical history, concomitant diseases, and concomitant medications will be summarized via descriptive statistics, as appropriate, (overall and stratified by treatment group).

Medical history, concomitant medications and AEs will be coded to MedDRA and WHO Drug dictionaries, as appropriate, for the purpose of summarization.

## 8.4 Treatment Compliance

IVT injection compliance for the study eye will be assessed by determining if subjects received one, two, three or four IVT injections.

## 8.5 Efficacy Analyses

All efficacy variables will be displayed in subject listings.

### *8.5.1* Primary Efficacy Analysis

The primary efficacy endpoint is change from baseline in BCVA letter count in the study eye at Week 16. Change from baseline in BCVA letter count will be calculated as Week 16 BCVA letter count minus Day 1 BCVA letter count such that a negative difference indicates a worsening in vision. In addition, treatment comparisons between each dose of the KVD001 Injection and the sham will be calculated as KVD001 Injection minus sham, such that a positive result indicates more letters gained in the KVD001 Injection treatment group.

#### 8.5.1.1 Hypothesis to be Tested

The null hypothesis is that the effects changes from baseline in BCVA letter count at Week 16 for each dose of the KVD001 Injection and the sham procedure on BCVA are identical:

H0: $\mu_k - \mu_s = \mu_k - \mu_s = 0$,

where $\mu_k$ is the effect change from baseline in BCVA letter count at Week 16 for each dose of the KVD001 Injection and $\mu_s$ is the effect of change from baseline in BCVA letter count at Week 16 for the sham procedure. The alternative hypothesis is that the effect change from baseline in BCVA letter count at Week 16 for each dose of the KVD001 Injection is larger than the effect of change from baseline in BCVA letter count at Week 16 for the sham procedure on BCVA:

Ha: $\mu_k - \mu_s > 0$.

#### 8.5.1.2 Statistical Methods

The study eye ETDRS letter scores including changes from baseline will be summarized using continuous descriptive statistics. An analysis of covariance (ANCOVA) model will be used to compare the change from baseline in BCVA letter count at Week 16 between each dose of the KVD001 Injection and the sham. The ANCOVA model will include treatment as a main effect and baseline BCVA letter count as a covariate. Least-squares means (LSMeans) for each treatment group, the LSMeans difference between each dose of the KVD001 Injection group and the sham group, the corresponding CIs and the p-values will be presented.

As a sensitivity analysis, treatment group differences for changes from baseline in BCVA letter count will be evaluated using a mixed model repeated measures (MMRM) ANCOVA fitted with treatment group, visit and the treatment by visit interaction as categorical variable terms with baseline BCVA letter score and baseline CST as covariates with contrasts included for each visit. LSMeans and 95% confidence intervals for each treatment group, the LSMeans difference between each dose of the KVD001 Injection and sham, the corresponding confidence intervals, and the p-values will be presented for each visit.

#### *8.5.2* Secondary Efficacy Analyses

The secondary efficacy endpoints are:

- Change from baseline in CST as measured by Spectral Domain OCT (SD-OCT)
- Proportion of eyes with a ≥2 step improvement from baseline in DRSS score
- Change from baseline in BCVA letter count as measured by ETDRS
- Proportion of study eyes with ≥5, ≥10, and ≥15 BCVA letter change from baseline (gain and loss).

Change from baseline in BCVA letter count in the study eye at Week 24 and change from baseline in CST in the study eye as measured by SD-OCT at Week 16 and Week 24 will be analyzed using the same method described for the primary efficacy analysis. Note that change from baseline in CST will be in favor of KVD001 if the treatment difference is <0.

The proportion of study eyes with improvement of 2 or more steps on the ETDRS DRSS score between the sham procedure group and each of the KVD001 injection groups will be summarized by visit using discrete summary statistics, including 95% asymptotic normal CIs for each treatment group. The difference in proportions between each of the KVD001 groups and the sham procedure group will be analyzed at Week 16 and Week 24 using a Pearson's chi-squared test. 95% asymptotic normal CIs for the differences in proportions will also be calculated. Fisher's exact tests and exact CIs will be employed in cases of expected counts <5.

The proportion of study eyes with ≥5, ≥10 and ≥15 BCVA letter change (gain and loss) between baseline and Weeks 16 and 24 will be analyzed using the same method described for the proportion of study eyes with improvement of 2 or more steps on the ETDRS DRSS score.

### 8.6 Safety Analyses

Safety endpoints include AEs, manifest refraction/BCVA, slit lamp biomicroscopy, dilated ophthalmoscopy, IOP, SD-OCT, ETDRS DRSS, physical exam findings, laboratory test results, and vital signs.

#### *8.6.1* Adverse Events

AEs will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it 1) occurs after the first dose of randomized study treatment or 2) if it is present prior to receipt of randomized study treatment but worsens in severity or increases in frequency after the first dose of randomized study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ

class, preferred term and strongest relationship; by system organ class and preferred term for SAEs; and by system organ class, preferred term, and day of onset. Separate analyses will be performed for ocular specific and all AEs (including systemic). AEs will be classified by System Organ Class (SOC) and preferred term in the MedDRA coding dictionary. AEs will be tabulated both as the total events (regardless of relationship to treatment) and as drug-related events. The number of subjects with one or more events versus no events will be calculated for each treatment.

Subject listings of all AEs will be provided as well as listings of deaths, SAEs, and AEs leading to discontinuation.

The following summaries will be provided:

- Relationship between AE SOC and verbatim text;
- On-treatment AEs: number and percentage of subjects reporting each AE, each AE leading to withdrawal, each SAE, each drug-related SAE, each fatal AE, and most frequent by treatment;
- Post-treatment AEs: number and percentage of subjects reporting each AE;
- Listing of all AEs;
- Summary of Most Frequent AEs.

### *8.6.2* Laboratory Assessments

Laboratory assay results include hematology, clinical chemistry, liver enzymes, electrolytes, and urinalysis. Each of the continuous parameters will be summarized using continuous descriptive statistics for each treatment group and for all subjects at each visit. Changes from baseline will also be summarized for each treatment group and for all subjects where appropriate. Each categorical parameter will be summarized using frequency counts and percentages for each treatment group and for all subjects. A shift table of the changes from baseline will also be presented.

The high/low criteria will be determined based on the reference ranges provided by the laboratory. The actual values and change from baseline values for each laboratory assessment will be summarized by treatment group. Summaries of assessments outside the normal range and the changes from baseline relative to the normal range will also be produced. A subject listing of laboratory assessments will also be produced and will include changes from baseline at each visit. Data from subjects who have values outside the normal range will be specified in this listing.

### *8.6.3* Vital Signs

Vital sign measurements, including pulse, respiratory rate, blood pressure (SBP, DBP), body temperature, height, weight and BMI, will be summarized by visit and time point using continuous descriptive statistics for each treatment group and for all subjects. Change from baseline to each visit will also be summarized for each treatment group and for all subjects. Systolic and diastolic BP, heart rate, respiration rate, and body temperature will be summarized by treatment group at each visit and for the maximum/minimum post-baseline. The change from baseline values will also be summarized. A subject listing will also be produced and will include changes from baseline at each visit.

### *8.6.4* Physical Examination

A subject listing of the Visit 1 (Screening) physical examination findings will be produced.

### *8.6.5* Slit Lamp Biomicroscopy

A slit-lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, iris/pupil, lens, and eyelid will be performed at each visit. The findings will be graded as normal or abnormal [non-clinically significant (NCS) or clinically significant (CS)]. The findings will be summarized for each treatment group and for all subjects at each visit for each eye (study eye and fellow eye). The findings will be summarized using counts and percentages for each treatment group and for all subjects combined at each visit for each eye (study eye and fellow eye). Shift tables for the slit-lamp biomicroscopy parameters will also be provided comparing each follow-up visit to baseline. A subject listing of the slit-lamp biomicroscopy examination parameters will also be produced.

### *8.6.6* Indirect Dilated Ophthalmoscopy

A dilated ophthalmoscopy examination of the vitreous, macula, optic nerve, peripheral retina, and choroid will be performed at each visit. The findings will be graded as normal or abnormal (NCS or CS). The findings will be summarized using frequency counts and percentages by treatment group and for all subjects at each visit for each eye (study eye and fellow eye). A shift table of changes from baseline will also be presented. Cup-to-disc ratio is also reported for each visit and will be summarized using continuous descriptive statistics. Change from baseline will also be summarized by treatment group for each eye (study eye and fellow eye). A subject listing of the dilated ophthalmoscopy examination parameters will also be produced.

### *8.6.7* Intraocular Pressure

IOP of both eyes will be assessed. IOP will be summarized using continuous descriptive statistics for each treatment group and for all subjects at each visit for each eye (study eye and fellow eye). Change from baseline will also be summarized for each treatment group for each eye (study eye and fellow eye). Categorical summary statistics will also be presented using the following categories: ≤5, 6 to 14, 15 to 21, 22 to 29, and ≥30 mmHg for each visit and using the following categories: ≤-15, -14 to -10, -9 to -5, -4 to 0, 1 to 4, 5 to 9, 10 to 14, 15 to 19, and ≥20 mmHg for change from baseline to each visit. A subject listing of IOP will also be produced.

### *8.6.8* Best Corrected Visual Acuity and Manifest Refraction

Best-Corrected visual acuity of both eyes will be measured consistent with the standard procedure developed for the ETDRS. The number of letters read correctly will be counted and the total BCVA letter score will be reported. The total BCVA letter score will be summarized for each treatment group using continuous descriptive statistics at each visit for each eye (study eye and fellow eye). Change from baseline will also be summarized by treatment group and visit for each eye (study eye and fellow eye).

The number of subjects (by eye) with a gain or loss in BCVA letter score ≥15, ≥10, and ≥5 from baseline will be summarized using counts and percentages for each treatment group at each visit.

A subject listing of BCVA and manifest refraction will also be produced.

### *8.6.9* SD-OCT

The SD-OCT parameter values, including changes from baseline will be summarized for each visit using continuous descriptive statistics. A subject listing of SD-OCT parameters will also be produced.

#### *8.6.10* ETDRS DRSS

The ETDRS DRSS scores including changes from baseline will be summarized for each visit using continuous descriptive statistics. A subject listing of ETDRS DRSS will also be produced.

## 8.7 Interim Analyses

No interim analyses are planned.

## 8.8 Determination of Sample Size

The proposed sample size (41 per treatment group) will provide approximately 80% power to detect a difference in change from baseline of 5 letters between either of the KVD001 treatment groups and sham based on a two-sided, two-sample t-test with significance level 0.05 and assuming a pooled SD of 7.5 letters.

# 9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

## 9.1 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation. Site qualification visits may be waived, per the CRO's SOPs, if the site has participated in a study with the CRO within the past 12months.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each subject. All information recorded on the eCRF system for this study must be consistent with the subjects' source documentation (i.e., medical records).

### *9.1.1* Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

## 9.2 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the eCRF. All source documents from which eCRF entries are derived should be placed in the subject's medical records. Measurements for which source documents are usually available include laboratory assessments, and study specific examinations.

The original eCRF entries for each subject may be checked against source documents at the study site by the Ora site monitor.

Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

### *9.2.1* Data Collection

The Investigators (and appropriately authorized staff) will be given access to an on-line web-based EDC) system which is 21 CFR Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and right to

the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each subject included in the study and should reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the subject's visit or assessment. The Investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the eCRF.

Computerized data–check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on–line directly by the Investigator or by authorized staff. Off–line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Investigator will be required to electronically sign off the clinical data.

Data about all study product dispensed to the subject and any dosage changes will be tracked on the eCRF.

## 9.3 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual subject's source medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on–site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures Ora and the Sponsor of the necessary support at all times.

## 9.4 Data Processing

All data will be entered by site personnel into the EDC system/eCRF (as detailed in Section 9.2.1).

The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction sheets for unresolved queries will be sent to the study monitors for resolution with the Investigator. The database will be updated on the basis of signed corrections.

Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Reference List (DRL), which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical

conditions and AEs will be coded using the medical dictionary for regulatory activities (MedDRA) terminology.

Previous and concomitant diseases as well as AEs will be coded with MedDRA.

The versions of the coding dictionaries will be provided in the Clinical Study Report.

## 9.5 Archiving Study Records

According to International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

## 9.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the Good Clinical Practice (GCP) guidelines of the ICH, and of the Declaration of Helsinki (1996). The study also will be carried out in keeping with local legal requirements.

## 9.7 Informed Consent

Before each subject is admitted to the study, informed consent will be obtained from the subject (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country. This consent form must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The date the consent was obtained must also be documented in the eCRF system.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

## 9.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug Application (IND) under which the study is being conducted.

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

## 9.9 Duration of the Study

For an individual subject, the maximum duration of the study for each subject will be up to 28 weeks (including up to 4 weeks for screening, up to 12 weeks of treatment period, and up to 12 weeks for follow–up).

## 9.10 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study;
- Failure to enroll subjects at an acceptable rate;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

## 9.11 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be identified on eCRF system and other documents submitted to Ora by their subject number, initials and/or birth date, not by name. Documents not to be submitted to Ora that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

## 9.12 Other Ethical and Regulatory Issues (optional)

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties – Regulatory Authorities, Investigators, and IRB/IECs.

A significant safety issue is one that has a significant impact on the course of the clinical study or program (including the potential for suspension of the development program or amendments to protocols) or warrants immediate update of informed consent.

## 9.13 Publication Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance. Details are provided in a separate document.

## 11 REFERENCE LIST

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