CLINICAL PROTOCOL

PHASE 2 DOUBLE-MASKED, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY AND EFFICACY OF SUBCUTANEOUSLY ADMINISTERED AKB-9778 15MG ONCE DAILY OR 15MG TWICE DAILY FOR 12 MONTHS IN PATIENTS WITH MODERATE TO SEVERE NON-PROLIFERATIVE DIABETIC RETINOPATHY

Compound:	AKB-9778
US IND Number:	113,322
Protocol Number:	AKB-9778-CI-5001
Phase:	Phase 2
Date:	Final Version 16 Sept 2016 Amendment #1 01 Dec 2016 Amendment #2 05 Jan 2017 Amendment #3 06 March 2017 Amendment #4 11 April 2017 Amendment #5 18 Sept 2017
Sponsor:	Aerpio Therapeutics LLC 9987 Carver Road Suite 420 Cincinnati, OH 45242

1 STUDY CONTACTS

For study related and administrative questions, please contact:

Laura Gambino, BS
Director, Project Management
Aerpio Therapeutics LLC
9987 Carver Road, Suite 420
Cincinnati, OH 45242
Mobile Telephone: (513) 253-9411
Email: lgambino@aerpio.com

For clinical and subject related issues or questions, please contact:

Barbara Withers, PhD
Senior Director, Clinical Operations
Aerpio Therapeutics LLC
9987 Carver Road, Suite 420
Cincinnati, OH 45242
Mobile Telephone: (513) 256-3592
Email: bwithers@aerpio.com

Mitchell Brigell, PhD
Vice President, Clinical Development
Aerpio Therapeutics LLC
9987 Carver Road, Suite 420
Cincinnati, OH 45242
Mobile Telephone: (513) 432-7790
Email: mbrigell@aerpio.com

Steve Pakola, MD
Chief Medical Officer
Aerpio Therapeutics LLC
9987 Carver Road, Suite 420
Cincinnati, OH 45242
Mobile Telephone: (914) 309-3406
Email: spakola@aerpio.com

1.1 Protocol Approval

19Sep2017
Mitchell Brigell, PhD Date
Vice President, Clinical Development
Aerpio Therapeutics LLC

19-SEP-2017
Steve Pakola, MD Date
Chief Medical Officer
Aerpio Therapeutics LLC

19 sept 2017
Barbara Withers, PhD Date
Senior Director, Clinical Operations
Aerpio Therapeutics LLC

19Sept2017
Laura Gambino, BS Date
Director, Project Management
Aerpio Therapeutics LLC

1.2 Investigator Agreement

I confirm that I have read and that I understand this protocol, the Investigator Brochure, and other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization Guidance for Industry, Good Clinical Practice E6.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.
- Terms outlined in the Clinical Trial Agreement.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Name of Facility

_____

Location of Facility (City, State)

TABLE OF CONTENTS

2 PROTOCOL SUMMARY

Protocol Number: AKB-9778-CI-5001
Protocol Title: Phase 2 Double-masked, Placebo-Controlled Study To Assess The Safety And Efficacy Of Subcutaneously Administered AKB-9778 15mg Once Daily Or 15mg Twice Daily For 12 Months In Patients With Moderate To Severe Non-Proliferative Diabetic Retinopathy

Study Objectives:	**Primary Objective:** **1.** To assess the effects of AKB-9778 15mg once daily or 15mg twice daily for 12 months on severity of diabetic retinopathy in subjects with moderate to severe non-proliferative diabetic retinopathy (NPDR) **Secondary Objective:** **1.** To assess the safety and tolerability of AKB-9778 15mg once daily or 15mg twice daily for 12 months in subjects with moderate to severe NPDR **2.** To determine the AKB-9778 systemic exposure based on sparse PK sampling in subjects with NPDR **Exploratory Objectives:** **1.** To explore the potential benefit of AKB-9778 on renal function in subjects with NPDR **2.** To explore the relationship between AKB-9778 systemic exposure and efficacy and safety in subjects with NPDR **Exploratory Efficacy Sub Study Objectives (To be conducted at a subset of sites)** **1.** To explore the effects of AKB-9778 on optical coherence tomography angiography (OCT-A) in subjects with NPDR **2.** To explore the effects of AKB-9778 on retinal function as measured by electroretinogram (ERG) assessment in subjects with NPDR **3.** To explore the effects of AKB-9778 on peripheral retinal abnormalities using ultra-wide field (UWF) fundus photography and UWF fluorescein angiography
Study Endpoints:	**Primary Efficacy Endpoint** **1.** Percentage of subjects with an improvement in study eye severity of diabetic retinopathy (DR) (Early Treatment Diabetic Retinopathy Study (ETDRS) DR Severity Score or DRSS) of ≥ 2 steps at Month 12 **Secondary Efficacy Endpoints** **1.** Mean change from baseline in DRSS in the study eye at Month 12 **2.** Patient level (binocular) change from baseline in DRSS (according to methods of Klein et al, 2001) at Month 12 **3.** Proportion of subjects with a worsening in the study eye DRSS of ≥ 2 steps at Month 12 **4.** Proportion of subjects with an improvement or worsening in the study eye DRSS of ≥ 3 steps at Month 12 **5.** Proportion of patients developing center-involved DME or PDR or PDR-related outcomes during study **6.** Primary and secondary endpoints (1 through 4) assessed at Months 3, 6 and 9 **7.** Primary and secondary assessments in all fellow eyes, fellow eyes that meet all eligibility criteria (qualified fellow eyes), and either eyes (i.e. best response)

	Exploratory Efficacy Endpoints: **1.** Change from baseline in urine-albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) at Month 12 **Exploratory Efficacy Sub-Study Endpoints:** **1.** Mean change from baseline in ERG parameters at Month 12 **2.** Mean change from baseline in indices of macular perfusion, as measured by OCT-A, at Month 12 **3.** Mean change from baseline in area of peripheral non-perfusion, peripheral leakage, and peripheral retinopathy using UWF imaging, at Month 12 **Safety Endpoints:** **1.** Incidence and severity of systemic and ocular adverse events (AEs) **2.** Change from baseline in body system assessments **3.** Change from baseline in vital sign measurements **4.** Change from baseline in ECG parameters **5.** Change from baseline in clinical laboratory assay results (blood chemistry, hematology, fecal occult blood and urinalysis) **6.** Change from baseline in intraocular pressure (IOP) **7.** Change from baseline in slit lamp examination parameters **8.** Change from baseline in dilated funduscopic examination parameters **9.** Change from baseline in fluorescein angiogram (FA) parameters **10.** Mean change from baseline in ETDRS Best Corrected Visual Acuity (BCVA) letter score in the study eye at Month 12 **11.** Proportion of subjects with a decrease of ≥15 letters in ETDRS BCVA at Month 12 (compared to baseline)
Study Population:	Subjects with moderate to severe NPDR (ETDRS Level 43 – 53 inclusive), 18 through 80 years of age (inclusive), no evidence of central involved DME and ETDRS BCVA letter score ≥ 70 (Snellen 20/40 or better).
Study Design:	Phase 2 randomized, double-masked, placebo controlled, multi-center study, to evaluate the safety and efficacy of 12 months of subcutaneous AKB-9778 administered either 15 mg QD or 15 mg BID in subjects with moderate to severe NPDR. Pharmacokinetic assessments are included as an exploratory endpoint. Exploratory efficacy assessments (OCT-A, UWF imaging and non-invasive ERG) will also be included at a subset of sites. Blood samples will be retained for biomarker and genetic analysis.
General Statistical Methods and Types of Analyses:	**Analysis Populations** **<u>Safety Population</u>** The safety population will include all enrolled subjects who receive at least one dose of study medication. All safety analyses will be conducted using the safety population. **<u>Modified Intent-to-Treat Population</u>** The modified intent-to-treat (MITT) population will include all enrolled subjects who receive at least one dose of study medication. The primary efficacy analysis will be conducted using the MITT population. **<u>Per Protocol Population</u>**

	The per protocol (PP) population will consist of all subjects in the MITT population who do not have major protocol deviations considered to affect the primary efficacy variable DRSS, have completed a minimum of 12 months of treatment and have been at least 70% compliant. Sensitivity analyses of the primary efficacy variables will be conducted using the PP population. **Sample Size** Estimates for sample size calculations are derived from published data from the analysis of the effect of ranibizumab (Lucentis®) and aflibercept (Eylea®) intravitreal administration regimens on DR severity score in the RISE/RIDE studies and VIVID/VISTA studies, respectively, in which 28-46% of subjects improved by ≥ 2 steps after 12 months of treatment. With 45 evaluable subjects per treatment group, the study has > 85% power (based on Fisher's Exact Test and a 2-sided alpha =0.05) to demonstrate a statistically significant improvement in proportion of subjects improving by ≥ 2 steps on the ETDRS severity scale, assuming underlying rates for active and placebo of 30% and 5%, respectively. Assuming 10% drop-out/non-evaluable rate, a sample size of 50 subjects per treatment arm (approximately 150 total) has been selected. **Efficacy Analyses** All efficacy data will be summarized by treatment group and time point using appropriate descriptive statistics. Summaries will be presented for both the MITT and PP populations. The primary hypotheses to be tested is that AKB-9778 15mg twice daily and AKB-9778 15mg once daily will be superior to placebo in the improvement of DR as measured by the ETDRS severity scale change from baseline at 12 months. The primary hypotheses will be tested in the MITT population using a Fisher's Exact Test with a 2-sided 5% significance level. To adjust for multiplicity, a pre-specified testing order will be used. AKB-9778 15mg twice daily will be tested first, and AKB-9778 15mg once daily will be tested second. Secondary and exploratory endpoints will be analyzed without adjustment for multiplicity. Continuous variables will be analyzed using ANCOVA models and dichotomous variables will be analyzed using the same approach as outlined for the primary endpoint. Additional exploratory analyses will be conducted to understand the relationship between exposure and response. **Interim Safety Analyses** On an ongoing basis throughout the conduct of the study, multiple layers of planned safety monitoring will be conducted. These include weekly masked reviews by the Aerpio Medical Monitor, monthly masked reviews by the Aerpio Clinical Safety Review Team (CSRT), and quarterly masked reviews by the Safety Assessment Committee These reviews are detailed in a separate document (AKB-9778 Safety Surveillance Plan).
Study Medication:	**Subcutaneous treatments:** • 15 mg AKB-9778 (in 100 mg/mL Hydroxypropyl-Beta-Cyclodextrin [HPβCD]) subcutaneous injection: To be provided as sterile pre-filled ready-to-inject syringes • Placebo (Phosphate-Buffered Saline) subcutaneous injection: To be provided as sterile pre-filled ready-to-inject syringes
Duration of Treatment:	48 weeks
Duration of Participation:	Screening period: up to 4 weeks; Baseline and Treatment period: 48 weeks; Post-treatment Follow-up period: 4 weeks. The Screening, Baseline, Treatment, and Follow-up periods will require subject participation for approximately 56 weeks.
Number of Subjects:	Approximately 150 subjects (50 per treatment group)

Number of Study Centers:	Approximately 50 sites
Volume of Blood Drawn:	Hematology (8 X 4 mL) Chemistry (14 X 3.5 mL) Serum Pregnancy (1 X 2.5 mL) Pharmacokinetic Samples (4 X 6 mL) Exploratory Biomarker (2 X 3 mL) Genetic Sample (1 X 8.5 mL) Total volume blood drawn for entire study: Approximately 134 mL per subject.

3 LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine transaminase (SGPT)
Ang1	Angiopoietin 1
Ang2	Angiopoietin 2
AST	Aspartate transaminase (SGOT)
AUC	Area under the curve
BA	Benzyl alcohol
BCVA	Best corrected visual acuity
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
Cmax	Maximum plasma drug concentration
CPK	Creatine phosphokinase
CRF	Case report form
CSRT	Clinical Safety Review Team
CST	Central Subfield Thickness
CYP	Cytochrome
CV	Cardiovascular
dL	deciliter
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic retinopathy severity score
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ETDRS	Early Treatment Diabetic Retinopathy Study
ENT	Ears, nose and throat
eNOS	Endothelial nitric oxide synthase
EOT	End of treatment
ERG	Electroretinogram
FA	Fluorescein angiograms
FDA	Food and Drug Administration
FOBT	Fecal Occult Blood Test
g	gram
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
HbA1C	Hemoglobin A1c
HEENT	Head, ears, eyes, nose and throat
Hgb	Hemoglobin
HPβCD	Hydroxypropyl Beta Cyclodextrin
HPTPβ	Human Protein Tyrosine Phosphatase β
HR	Heart Rate
ICH	International Conference on Harmonisation

IND	Investigational New Drug
IOP	Intra-ocular pressure
IRB	Institutional Review Board
IRMA	Intra-retinal microvascular abnormalities
IVT	Intravitreal
IWRS	Interactive web response system
kg	kilogram
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
LFTs	Liver function tests
MAD	Multiple-ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular (cell) volume
MedDRA	Medical Dictionary for Regulatory Activities
µL	microliter
µm	micrometer
mg	milligram
mL	milliliter
ms	millisecond
MITT	Modified intent-to-treat
MTD	Maximum tolerated dose
MPV	Mean platelet volume
MDRD	Modification of Diet in Renal Disease
NF	National Formulary
NPDR	Non-proliferative diabetic retinopathy
NVE	Neovascularization elsewhere
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography angiography
PBS	Phosphate-Buffered-Saline
PD	Pharmacodynamic
PDR	Proliferative Diabetic Retinopathy
PK	Pharmacokinetic
POC	Proof of Concept
PP	Per protocol
PRN	as needed
PRP	Panretinal scatter photocoagulation
QA	Quality Assurance
QC	Quality Control
QD	Once daily
RBC	Red blood cell
RDW	Red cell distribution width
RVO	Retinal vein occlusion
SAC	Safety Assessment Committee
SAD	Single ascending dose
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SD OCT	Spectral domain optical coherence tomography
SDH	Sorbitol dehydrogenase

SHR	spontaneously hypertensive rats
SSP	Safety Surveillance Plan
TEAE	Treatment emergent adverse event
TIBC	Total Iron Binding Capacity
Tie2	Tyrosine kinase with immune globulin-like and EGF-like domains2
Tmax	Time to Cmax
TSAT	Trasnferrin Saturation
t1/2	Half-life
UACR	Urine-albumin-to-creatinine ratio
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
UWF	Ultra-wide field
VEGF	Vascular endothelial growth factor
VE-PTP	Vascular endothelial-protein tyrosine phosphatase
WHO	World Health Organization
WBC	White blood cell
WKY	Wistar-Kyoto

4 BACKGROUND INFORMATION

Diabetes is estimated to affect 8.3% of the adult population, 382 million people worldwide, and this number is expected to rise to 592 million people by 2035 (Guariguata et al., 2014). Diabetic retinopathy (DR) is a frequent complication of diabetes that may result in blindness. The incidence of DR increases with duration of diabetes. The prevalence of DR in the diabetic population is approximately 33%, with approximately 10% having vision threatening conditions of macular edema or proliferative retinopathy (Yau et al., 2012). By 20 years after disease diagnosis, nearly 100% of type 1 diabetics and 60% of type 2 diabetics develop DR (Fong et al., 2004a,b). In the Wisconsin Epidemiologic Study of Retinopathy, the 25-year cumulative rate of retinopathy progression in Type 1 diabetics was 83%, with 43% of this population progressing to proliferative retinopathy (Klein et al., 2008) and 29% progressing to macular edema (Klein et al., 2009). Based on these data, it is clear that diabetic retinopathy will increase as a public health problem, with both aging of the US population and increasing prevalence of diabetes over time.

The severity of DR has been standardized using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading of standard 7-field fundus photographs. There is extensive evidence to show that as DR severity increases, the likelihood of development of macular edema or high-risk proliferative diabetic retinopathy (PDR) increases (Davis et al., 1998; Klein et al., 2001). Thus, early detection and treatment of DR would dramatically reduce both visual disability associated with diabetes as well as the impact of this visual loss on health economics.

In pivotal trials of intravitreal anti-VEGF (vascular endothelial growth factor) effects on diabetic macular edema (DME), it was observed that treatment also had beneficial effects on DR. After 1 year of treatment with Eylea®, 33.5% of subjects treated monthly and 28.4% of subjects treated bi-monthly improved by ≥ 2 steps on the ETDRS severity scale, compared to 10.9% in the laser treatment group (Korobelnik et al., 2014). Similarly, in the RISE and RIDE trials with Lucentis®, 46.9% of subjects treated with 0.3 mg monthly and 46.8% of subjects treated with 0.5 mg monthly for 2 years had a ≥ 2 step improvement in DR, compared to 6.8% of subjects treated with sham injections (Ip et al., 2012). There was also a decrease in the percent of subjects who worsened by ≥ 2 steps after 2 years of treatment (2.5%, 2.0%, and 12.4% in the 0.3 mg Lucentis, 0.5 mg Lucentis, and sham groups, respectively). On the basis of these data, Lucentis and Eylea have been approved for the treatment of DR in patients with DME. However, the efficacy of anti-VEGF therapy for the treatment of DR in patients without center-involved DME is unproven. Two trials have recently been initiated to test the efficacy of Eylea in this population (the PANORAMA study - NCT02718326 sponsored by Regeneron; and Protocol W - NCT02634333 sponsored by DRCR.net). However, it is important to note that eyes with non-proliferative diabetic retinopathy (NPDR) and no DME have little visual dysfunction and thus the burden of multiple binocular intravitreal anti-VEGF injections may be unacceptable in this population. The objective of the present study is to examine the efficacy of AKB-9778 subcutaneous administration in the treatment of NPDR in patients without DME.

AKB-9778 is a first-in-class molecule in development for the treatment of diabetic eye disease, including DME and DR. AKB-9778 is a small molecule Tie2 (tyrosine kinase with immunoglobulin-like and EGF-like domains 2) activator that works through inhibition of VE-PTP (vascular endothelial-protein tyrosine phosphatase), otherwise known as HPTPβ (human protein tyrosine phosphatase β), enhancing Tie2 activation and signaling. Tie2 is a receptor

tyrosine kinase that is expressed principally in vascular endothelial cells and serves as the receptor for the angiopoietin family of secreted polypeptides. Over the last decade, the Tie2/angiopoietin pathway has been identified as a key modulator of endothelial function and vascular stability (Augustin et al., 2009; Milner et al., 2009; Brindle et al., 2006; Fiedler et al., 2006; Peters et al., 2004). Members of the angiopoietin family are ligands for Tie2; angiopoietin 1 (Ang1) is an agonist and angiopoietin 2 (Ang2) functions as a context dependent antagonist. The bulk of evidence indicates that Ang1/Tie2 signaling promotes normal vascular integrity. Conversely, in settings where Ang2 is upregulated, as in patients with diabetic retinopathy, Tie2 signaling is blunted and the vasculature is destabilized promoting vascular leak and enabling pathologic angiogenesis.

VE-PTP is an endothelial tyrosine phosphatase that dephosphorylates Tie2, further reducing Tie2 signaling. Inhibition of VE-PTP with AKB-9778 overrides Ang2 and restores Tie2 signaling. Importantly, AKB-9778-mediated Tie2 activation results in activation of the PI3 kinase/Akt/endothelial nitric oxide synthase (eNOS) pathway, a critical pathway in maintaining endothelial function and vascular integrity. Thus, AKB-9778 promotes vascular stability through enhanced Tie2 activation resulting in improved endothelial function, reduced vascular leak and inflammation, and resistance to pathologic angiogenesis.

In multiple preclinical vascular disease models, vascular stabilizing effects of AKB-9778 resulted in decreased vascular leak and/or suppression of pathologic neovascularization. In models of retinopathy, AKB-9778 dramatically reduced VEGF-driven retinal edema and neovascularization and prevented retinal detachment (Shen et al., 2014). The vascular stabilizing properties of AKB-9778 may be beneficial in the treatment and prevention of a broad range of retinal pathology including nonproliferative and proliferative diabetic retinopathy, diabetic macular edema, neovascular age-related macular degeneration, and retinal vein occlusion, for which current therapy is not optimal.

4.1 Rationale

Please see the AKB-9778 Investigator Brochure for additional discussion and information for the following section.

AKB-9778 is a small molecule that inhibits VE-PTP. This inhibition selectively increases the phosphorylation of Tie2 and augments Ang-1 signaling pathways through Tie2 that lead to vascular stabilization and protection against vascular leak and pathologic angiogenesis.

Two clinical studies in subjects with DME have been performed with AKB-9778, evaluating respectively 1 month and 3 months of treatment (Campochiaro et al., 2015, 2016). AKB-9778 was well tolerated in these studies with no safety issues identified. The completed TIME-2 Proof of Concept study (Campochiaro, 2016) has shown that SC dosing of AKB-9778 15 mg twice daily (BID) may be of value in the treatment of DME when used in conjunction with Standard of Care anti-VEGF therapy and that AKB-9778 monotherapy may be effective in the treatment of NPDR.

In the present study, the efficacy of AKB-9778 will be further evaluated in subjects with moderate to severe NPDR and no center-involved macular edema.

4.2 Summary of Nonclinical Experience

Please see the AKB-9778 Investigator Brochure for additional discussion and information for the following section.

A comprehensive nonclinical program has been conducted with AKB-9778 including evaluation in multiple retinopathy models, safety pharmacology studies, pharmacokinetic (PK) and metabolism studies, toxicology studies in rats, dogs, and monkeys, embryo-fetal development studies in rats and rabbits, and genotoxicity studies. The nonclinical program conducted to date supports evaluation of the intended 15 mg QD and BID AKB-9778 hydroxypropyl-beta-cyclodextrin (HPβCD) dose formulation regimens for a duration of 12 months in the current clinical study. Please see the AKB-9778 Investigator Brochure for additional information.

AKB-9778 has excellent SC bioavailability and demonstrates linear, dose-dependent increases in exposure following SC administration in rats, dogs and monkeys.

In the Good Laboratory Practices (GLP) nonclinical safety studies, AKB-9778 formulated as a solution in 10% HPβCD demonstrated an excellent safety profile and was well tolerated by SC administration in rats, dogs, and monkeys. The primary target tissues for AKB-9778 were identified as injection sites and liver in rat, dog and monkey; skin/subcutis (vascular) in dog and monkey; and gastrointestinal (GI; vascular) in dog.

In the 6-month rat study elevations in AST and ALT were correlated with microscopic observations of scattered, individual, minimally necrotic hepatocytes. Similar findings were observed in the shorter duration (28- and 91-day) rat studies. In dogs, adverse liver findings have only been observed in the 28-day toxicity study, at the high dose, and included one incidence of mild randomly distributed foci of mild necrosis, associated with centrilobular vacuolation; non-adverse findings included hepatocellular degeneration also associated with centrilobular vacuolation, and one incidence of mild, randomly distributed microgranulomas in the liver.

In the dog 9-month study, reversible, non-adverse and minimal panlobular hypertrophy of the liver was observed in all dose groups without any associated changes in liver transaminases. In the 28-day monkey study there was no test article-related mortality and no definitive test article-related mortality in the 273-day monkey study. In the 273-day study, one of the 16 monkeys at 22.5 mg/kg (33-fold the clinical exposure at 15 mg BID) was sacrificed on Day 109 with cholestatic liver injury and associated anemia which developed over a minimum of several weeks. The initial inciting event leading to early termination was not clear based on full evaluation of all available data and the relationship to test article is uncertain. The different characteristics of the liver responses in rat, dog, and monkey suggest different processes and/or pathogenesis for the liver effects in each species. For guidance on assessment and monitoring of potential liver findings refer to the Investigator's Brochure.

In rat, dog, and monkey, injection sites had findings related to the subcutaneous injection procedure (repeated injection of a limited number of injection sites on animals) with exacerbation by the presence of AKB-9778. SC injections of AKB-9778 as a solution in these nonclinical studies were generally well tolerated by rats, dogs and monkeys with only sporadic or transient observation of injection site redness, thickening, or scabbing. These findings were correlated histopathologically with focal SC hemorrhage, inflammation, fibrosis, and necrosis that were observed to largely recover. In early clinical trials with the AKB-9778 HPβCD

formulation, few adverse effects at the injection site were reported for injection volumes of less than 1 mL and mild to moderate transient pain was reported for injection volumes of 1 mL or greater.

In the 9-month dog toxicity study, broadly distributed dermal-localized nodules were observed on all dogs at 15 and 30 mg/kg/day and one nodule was observed on one male dog at 6 mg/kg/day. The majority of nodules were identified microscopically as focal angiectasis, characterized as ectatic, blood-filled vessels with varying degrees of thrombosis that was occasionally associated with papillary endothelial hyperplasia; and one nodule in a high dose dog identified as benign hemangioma. The nodules ranged in size between 1 and 50 mm in diameter and appeared to slowly enlarge or remain static in size. The majority of nodules were persistent, but a few nodules were self-limiting while AKB-9778 dosing continued. The dermal nodules were observed to rapidly resolve upon drug withdrawal. In addition, largely GI tract-localized minimal to mild angiectasis was observed by microscopic examination at all dose levels in dog (at exposures 6- to 24-fold the human exposure at 15 mg BID) and not present in the vehicle control group. The vascular findings were not associated with any clinical observations, serum chemistry, or other microscopic changes. In the rat 6-month study, minimal focal angiectasis was observed by microscopic examination in the uterus with cervix of one high-dose rat (at higher AUC exposure than exposures assessed in dog) and was considered incidental. There were no skin nodules or GI-related findings in rat. In the 9-month monkey study, a solitary dermal nodule on the tail of one high dose animal was characterized as angiectasis with resolving thrombosis, and associated with AUC exposure higher than exposures assessed in dog. There were no GI-related findings in monkey. These observations suggest an increased sensitivity of the dog to vascular effects of AKB-9778. No unusual or unexpected dermal findings have been observed in clinical studies with AKB-9778. For guidance on assessment and monitoring of potential vascular effects refer to the Investigator's Brochure.

A consistent finding in both rat and dog was a non-adverse decrease in blood pressure. In normotensive Wistar-Kyoto rats (WKY) and spontaneously hypertensive rats (SHR), blood pressure was decreased (the decrease in systolic pressure was greater than the decrease in diastolic pressure [systolic > diastolic]) with a compensatory increase in heart rate. Similarly, in the dog cardiovascular (CV) study, blood pressure was decreased (systolic > diastolic) with a compensatory increase in heart rate. Changes in blood pressure in both species were transient (4-6 hours), correlated with the drug plasma profile, and appeared to plateau with increasing dose, consistent with a pharmacological effect. As mentioned previously, activation of Tie2 results in endothelial nitric oxide synthase (eNOS) activation, which generates the potent vasodilator, nitric oxide (NO). AKB-9778 activates Tie2 and eNOS in cultured vascular endothelial cells, which supports a pharmacologic basis for vasodilation and decreased blood pressure.

Another consistent finding in dog was a non-adverse increase in cholesterol and triglycerides without microscopic correlate. These changes resolved during the recovery period and were not associated with microscopic changes. In early clinical trials with AKB-9778, no clinically meaningful changes in clinical chemistry (including total cholesterol and triglycerides) have been observed.

4.3 Summary of AKB-9778 Clinical Experience

Please see the AKB-9778 Investigator Brochure for additional discussion and information for the following section.

To date, AKB-9778 has been evaluated in six completed early phase studies: a Phase 1a single ascending dose (SAD) study (AKB-9778-CI-2001) in healthy male volunteers, a Phase 1 pharmacokinetic-pharmacodynamic crossover single dose study of an extended release suspension formulation (AKB-9778-CI-3001), a 1-month Phase 1b multiple ascending dose (MAD) study in subjects with DME (AKB-9778-CI-2002), a 3-month Phase 2a POC study in subjects with DME (AKB-9778-CI-2003), a Phase 1 pharmacokinetic-pharmacodynamic crossover single dose study evaluating extended release solution and suspension formulations (AKB-9778-CI-3002); and a Phase 1 repeat-dose, PK/tolerability study evaluating extended release solution formulations (AKB-9778-CI-3003). AKB-9778 is also being evaluated in two ongoing studies: a single-center, 3-month Phase 2a POC study in subjects with retinal vein occlusion (RVO) (AKB-9778-CI-4001) and a Phase 1 ADME study (AKB-9778-CI-3004).

The initial Phase 1a study, (Study AKB-9778-CI-2001) was a double-masked, placebo controlled, SAD study conducted to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of 6 single ascending subcutaneous doses of AKB-9778 including one administered as a divided dose in healthy male volunteers. Six cohorts of eight subjects each were randomized to receive either AKB-9778 or placebo (6:2). AKB-9778 doses evaluated over a single day of dosing were 5, 10.5, 20, 40, or 80 mg administered as a single dose, or 120 mg [(administered as 2 doses, 60 mg each, separated by 12 hours (i.e. 60 mg BID)]. Exposure following single ascending doses of AKB-9778 was dose proportional with no evidence of accumulation when administered as 2 doses separated by 12 hours (60 mg BID). Absorption and elimination were rapid (T_{max} ~ 15-30 minutes and $T_{1/2}$ ~ 1-2 hours). Single doses of AKB-9778 through 40 mg were generally well tolerated. At doses of 60, 80, and 120 mg (60 mg BID), an increase in the type and frequency of systemic AEs consistent with the exaggerated vasodilatory pharmacology of AKB-9778 was observed. These events were transient and generally resolved within 2-8 hours post-dose. At doses ≥ 60 mg, orthostatic symptomology observed during a 3-5 minute standing blood pressure (BP) assessment improved upon return of subjects to supine position, and resolved by 1-3 hours post-dose without treatment other than oral fluids. There were no severe or serious adverse events (SAEs) and no clinically significant changes or trends in safety laboratory tests, electrocardiogram (ECG) parameters, vital signs (except orthostatic BP), or physical exams in AKB-9778 or placebo treated subjects.

Study AKB-9778-CI-2002, a Phase 1b, open-label, MAD cohort study, was conducted to assess the safety, tolerability, pilot efficacy, PK and pharmacodynamic (PD) effects of 28-day repeat subcutaneous doses of AKB-9778 in subjects with DME. Four dose cohorts were administered 5, 15, 22.5 and 30 mg AKB-9778 BID, respectively. Twenty-six subjects in total were enrolled. Consistent with plasma exposure profiles in the healthy volunteer study, exposure in DME subjects increased with increasing dose levels of AKB-9778 with no evidence of significant accumulation. Absorption and elimination were rapid with an elimination half-life of approximately 1 hour. All AKB-9778 doses were generally well tolerated. There were no SAEs. Adverse events, consistent with the exaggerated vasodilatory pharmacology of AKB-9778, emerged at AKB-9778 doses of 22.5 and 30 mg BID and included dizziness, headache, and presyncope/syncope. These events were transient, usually occurred within the first hour after

dosing, and generally resolved within 5 minutes to one hour after onset. There were no clinically meaningful abnormalities or changes from baseline in safety laboratory tests (chemistry, hematology, and urinalysis), ECG parameters, vital signs or physical exams. In the 22.5 and 30 mg BID dose groups, consistent modest decreases in resting systolic BP (with corresponding modest increases in heart rate (HR)) were observed following dosing (30 mg >22.5 mg). These effects were largely asymptomatic and transient, and the timing of the effects correlated with the rapid AKB-9778 absorption and elimination plasma concentration-time curve. Pilot efficacy evaluations, including assessments of retinal thickness and visual acuity, suggest that AKB-9778 exhibited biologic activity.

AKB-9778-CI-2003 was a Phase 2 proof of concept (POC) study which further explored the efficacy of AKB-9778 in DME when administered for 3 months. In this trial, AKB-9778 was evaluated as monotherapy (subcutaneous administration of 15 mg BID), and in combination with ranibizumab intravitreal (IVT) injection. A ranibizumab active control group was also evaluated. AKB-9778 was well tolerated in subjects when administered BID either as monotherapy or as combination therapy with monthly ranibizumab IVT injection. There were no meaningful imbalances among treatment groups in either ocular or non-ocular treatment emergent adverse events (TEAEs), and no deaths or treatment-related SAEs were reported. Transient effects on baseline BP and HR following Day 1 dosing were observed, but the effects were not of clinical concern, and after 3 months (end of treatment), there were no differences in BP and HR between treatment groups. Hematology and blood chemistry did not yield clinically meaningful results for any treatment group, and clinically significant changes in physical examination, slit-lamp biomicroscopy parameters, intraocular pressure evaluations, and indirect dilated ophthalmoscopy evaluations were few and distributed similarly among treatment groups. When used in combination with ranibizumab, AKB-9778 demonstrated a statistically significant improvement in the reduction of central subfield thickness (CST) that also was statistically significantly greater than the improvement seen in the use of ranibizumab alone. Analysis of diabetic retinopathy severity score (DRSS) showed evidence that AKB-9778 monotherapy increased the percent of eyes that gain 2 or more steps in DRSS compared to placebo and had an effect on DRSS similar to ranibizumab (Campochiaro et al., 2016).

The previously described studies utilized an AKB-9778 formulation prepared using HPβCD as a solubilizing agent. A recently completed Phase 1 SAD study, AKB-9778-CI-3002, evaluated the safety, tolerability and bioavailability of an AKB-9778 solution formulation utilizing 1.5% benzyl alcohol (BA) as a solubilizing agent relative to AKB-9778 in 12.5% HPβCD.

Study AKB-9778-CI-3002, conducted in healthy subjects, evaluated the single-dose PK, hemodynamic effects (BP and HR), and the safety and tolerability of two dose levels (15 and 30 mg) of AKB-9778 containing 1.5% BA relative to 15 mg AKB-9778 containing 12.5% HPβCD. All formulations and doses evaluated in the study were safe and well tolerated. Similar to the results of the previous clinical studies, all formulations and doses of AKB-9778 demonstrated a small, transient reduction in BP and increase in HR within first hour after dosing.

Study AKB-9778-CI-3003, conducted in healthy subjects, evaluated 7-day BID subcutaneous administration of three different formulations of AKB-9778. In this study a 1.5% BA formulation was used to test 15 mg and 30 mg doses of AKB-9778, a 3.0% BA formulation was used to test 30 mg, 45 mg, and 60 mg AB-9778 doses, and a 12.5% HPβCD formulation was used to test 15 mg AKB-9778. Placebo injections of 1.5% BA and 3.0% BA were also tested. All

doses were given subcutaneously BID for 7 days (volume 0.75 ml). The trial was randomized and double-masked. The 15 mg AKB-9778 in 12.5% HPβCD formulation was well tolerated both systemically and locally. The AKB-9778 in BA formulations, while being well tolerated systemically, demonstrated injection site reactions (mild to moderate in intensity) in at least 2 subjects in each of the treatment arms. Injection site reactions were also observed in the 3% BA vehicle arm. Therefore, the current study will evaluate the AKB-9778 in an HPβCD formulation.

The totality of the nonclinical and clinical data support continued clinical development of AKB-9778 as a treatment for DR. The current clinical study, AKB-9778-CI-5001, is a Phase 2 study which will explore the safety and efficacy of 15 mg AKB-9778 in the treatment of subjects with moderate to severe NPDR in the absence of center-involved DME when administered QD or BID for 12 months (48 weeks).

4.4 Potential Benefits and Risks

4.4.1 Potential Benefits and Risks of AKB-9778

Please see the AKB-9778 Investigator Brochure for additional discussion and information for the following section.

Collectively, the nonclinical pharmacology data in diverse models is consistent with the proposed mechanism whereby AKB-9778 inhibits VE-PTP resulting in Tie2 activation and improves endothelial function and vascular stabilization, supporting the potential efficacy of VE-PTP inhibition with AKB-9778 in a broad range of retinal pathology. The completed clinical Phase 2a study in subjects with DME shows that Tie-2 activation via AKB-9778 enhances treatment of macular edema when combined with an anti-VEGF inhibitor and has evidence of efficacy as monotherapy in the treatment of NPDR.

The safety of VE-PTP inhibition with AKB-9778 has been explored in nonclinical safety studies, in multiple nonclinical pharmacology studies and in seven clinical studies.

Clinically, AKB-9778 has shown no evidence of significant safety issues to date. A transient, generally asymptomatic reduction in blood pressure is observed reflecting the vasodilatory pharmacodynamic effect of Tie-2 activation. At doses above the 15 mg dose used in the Phase 1b AKB-9778-CI-2002 study, vasovagal events (presyncope/syncope) have been observed following the first dose of AKB-9778. A vasovagal event was observed after the first dose in 1/144 (0.7%) subjects in the Phase 2 AKB-9778-CI-2003 study. This subject did not experience any such events during the subsequent 3 months of dosing. No other vasovagal events were observed in this study. In both studies there was a significant correlation between baseline BP and change in BP. Specifically, subjects with higher BP had greater reductions in BP.

Based on nonclinical studies and clinical studies conducted to date, identified risks include transient injection site reactions, hepatotoxicity, hemodynamic effects, hematologic and plasma lipid effects, and vascular effects.

In the nonclinical rat studies, findings of reversible and acute, individual hepatocellular necrosis of minimal severity were observed that correlated with elevations in AST and ALT in some animals. In dogs, adverse liver findings have only been observed in the 28-day toxicity study, at the high dose, and included one incidence of mild randomly distributed foci of mild necrosis,

associated with centrilobular vacuolation; non-adverse findings included hepatocellular degeneration also associated with centrilobular vacuolation, and one incidence of mild, randomly distributed microgranulomas in the liver. In the dog chronic 9-month study, reversible, non-adverse and minimal panlobular hypertrophy of the liver was observed in all dose groups without any associated changes in liver transaminases. In the monkey chronic 9-month study, one of the 16 monkeys at 22.5 mg/kg (33-fold the clinical exposure at 15 mg BID) was sacrificed on Day 109 with cholestatic liver injury and associated anemia which developed over a minimum of several weeks. In prior AKB-9778 clinical trials, in subjects treated for 3 months with AKB-9778 15mg BID, 0/113 had transaminase (ALT or AST) elevation >5X upper limit of normal (ULN) at any monthly assessment timepoint; 1/113 subjects (1/16 RVO patients; 0/97 DME patients) had a single occurrence of asymptomatic ALT elevation >3X but < 5X ULN at the end of treatment. This subject had an ALP slightly above ULN at pre-treatment and 2.05X ULN at the end of treatment, with all other labs (including AST, bilirubin and total protein) normal throughout the study. ALT and ALP levels were normal on repeat assessment 4 weeks later. The rate of LFT findings observed to date in patients treated with AKB-9778 is in the range reported for placebo groups in clinical trials (Llanos et al, 2010), particularly given the absence of any cases associated with elevated bilirubin levels.

In the subchronic (28-day) dog and monkey studies, decreases in hemoglobin and hematocrit were observed at the high doses with no microscopic correlate and were considered possibly associated with effects at the injection sites. However, in the chronic rat, dog and monkey studies, except for the single monkey described above with cholestatic liver injury and associated anemia, decreases in hemoglobin or hematocrit were not observed. Non-adverse increases in cholesterol and triglycerides were observed in dogs in all pivotal studies with no associated microscopic changes. These changes resolved within the recovery periods. No significant hematologic or plasma lipid abnormalities were observed in the 9-month monkey study. In all clinical trials with AKB-9778 to date, no clinically meaningful changes in hematological parameters (including hemoglobin and hematocrit) or plasma lipids (including total cholesterol and triglycerides) have been observed.

Dermal nodules, characterized microscopically as angiectasis (dilated, blood filled vessels), have been observed in the chronic 9-month dog toxicity study and with a single incidence in one high-dose monkey in the chronic 9-month monkey study; however, no unusual dermal findings have been observed in human clinical studies of durations of up to 3 months. Whether ectasias will be seen when patients are dosed for longer periods is unknown. In the chronic dog study, angiectasis was also identified microscopically largely in the GI tract after the 9-month dosing period. These changes were asymptomatic (i.e. there was no bleeding, loss of appetite, or other observable clinical abnormalities of the GI tract) at exposures up to 24-fold above the human clinical exposure.

The current clinical study employs robust safety monitoring to assess for potential adverse effects. Safety assessments in the current study include body system assessments, vital sign monitoring, clinical laboratory assessments (including blood chemistry, hematology, fecal occult blood testing, and urinalysis), vision and ocular assessments.

On an ongoing basis throughout the conduct of the study, a variety of planned safety monitoring reviews of available study data will be conducted (as detailed in Section 6.4 Oversight of Safety and in the AKB-9778 Safety Surveillance Plan). These include weekly reviews conducted by the

Aerpio Medical Monitor, monthly masked reviews by the Aerpio Clinical Safety Review Team (CSRT), and quarterly masked reviews by the Safety Assessment Committee (SAC: composed of members independent of the clinical team including Aerpio physician/cardiologist, a non-sponsor independent physician experienced in the assessment of clinical trial safety data, a non-sponsor independent physician with expertise in gastrointestinal/hepatology safety assessment, and a non-sponsor independent physician/ophthalmologist with expertise in ophthalmology safety assessment).

Given the safety history of AKB-9778 and the robust safety monitoring implemented in this study, there is anticipated to be minimal risk of drug-related severe adverse effects as a result of participation in this study.

In nonclinical reproductive toxicology studies (rats and rabbits), AKB-9778 was not associated with embryo-fetal abnormalities. Additionally, in the chronic repeated-dose rat (6-month) and dog (9-month) toxicity studies, there was no evidence of reproductive organ toxicity. Nonetheless, enrollment of women of child bearing potential and non-vasectomised male subjects will remain limited to subjects willing and able to use acceptable methods of contraception.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective

1. To assess the effects of AKB-9778 15 mg once daily or 15 mg twice daily for 12 months on severity of diabetic retinopathy in subjects with moderate to severe NPDR

5.2 Secondary Objective

1. To assess the safety and tolerability of AKB-9778 15 mg once daily or 15 mg twice daily for 12 months in subjects with moderate to severe NPDR
2. To determine the AKB-9778 systemic exposure based on sparse PK sampling in subjects with NPDR

5.3 Exploratory Objectives

1. To explore the potential benefit of AKB-9778 on renal function in subjects with NPDR
2. To explore the relationship between AKB-9778 systemic exposure and efficacy and safety in subjects with NPDR

5.4 Exploratory Efficacy Sub-Study Objectives (To be conducted at a subset of sites)

1. To explore the effects of AKB-9778 on optical coherence tomography angiography (OCT-A) in subjects with NPDR
2. To explore the effects of AKB-9778 on retina function as measured by electroretinogram (ERG) assessment in subjects with NPDR
3. To explore the effects of AKB-9778 on peripheral retinal abnormalities using ultra-wide field (UWF) fundus photography and UWF fluorescein angiography

5.5 Primary Efficacy Endpoints

1. Percentage of subjects with an improvement in study eye severity of diabetic retinopathy (DR) (ETDRS DR Severity Score or DRSS) of ≥ 2 steps at Month 12

5.6 Secondary Efficacy Endpoints

1. Mean change from baseline in DRSS in the study eye at Month 12
2. Patient level (binocular) change from baseline in DRSS (according to methods of Klein et al, 2001) at Month 12
3. Proportion of subjects with a worsening in the study eye DRSS of ≥ 2 steps at Month 12
4. Proportion of subjects with an improvement or worsening in the study eye DRSS of ≥ 3 steps at Month 12
5. Proportion of patients developing center-involved DME or PDR or PDR-related outcomes event during study
6. Primary and secondary endpoints (1 through 4) assessed at Months 3, 6 and 9
7. Primary and secondary assessments in all fellow eyes, fellow eyes that meet all eligibility criteria (qualified fellow eyes), and either eye (i.e. best response)

5.6.1 Exploratory Efficacy Endpoints:

1. Change from baseline in urine-albumin-to-creatinine ratio (UACR) and estimated glomerular (eGFR) at Month 12

5.6.2 Exploratory Efficacy Sub-Study Endpoints

1. Mean change from baseline in ERG parameters at Month 12
2. Mean change from baseline in indices of macular perfusion, as measured by OCT-A, at Month 12
3. Mean change from baseline in area of peripheral nonperfusion, peripheral leakage, and peripheral retinopathy using UWF imaging, at Month 12

5.6.3 Safety Endpoints:

1. Incidence and severity of systemic and ocular AEs
2. Change from baseline in body system assessments
3. Change from baseline in vital sign measurements
4. Change from baseline in ECG parameters
5. Change from baseline in clinical laboratory assay results (blood chemistry, hematology, fecal occult blood, and urinalysis)
6. Change from baseline in intraocular pressure (IOP)
7. Change from baseline in slit lamp examination parameters
8. Change from baseline in dilated funduscopic examination parameters

9. Change from baseline in fluorescein angiogram (FA) parameters
10. Mean change from baseline in ETDRS best corrected visual acuity (BCVA) letter score in the study eye at Month 12
11. Proportion of subjects with a loss of ≥15 letters in BCVA at Month 12 (compared to baseline)

6 STUDY DESIGN

6.1 Study Design

This is a Phase 2 randomized, double-masked, placebo controlled, multi-center study, to evaluate the safety and efficacy of 12 months (48 weeks) of subcutaneous AKB-9778 administered 15 mg QD or 15 mg BID in subjects with moderate to severe NPDR. Exploratory evaluations include pharmacokinetic assessments, as well as exploratory efficacy assessments (OCT-A, UWF imaging and non-invasive ERG) at a subset of sites. Blood samples will be retained for biomarker and genetic analysis.

Subjects will participate in the study for approximately 56 weeks (Screening period up to 4 weeks, Baseline and Treatment periods for 48 weeks, and Follow-up period for 4 weeks).

The study will be conducted at approximately 50 investigative sites.

Subjects will be randomized 1:1:1 to either AKB-9778 15mg QD, AKB-9778 15mg BID, or placebo treatment groups. Fifty (50) subjects are planned per group. The treatment groups are as follows:

- Active Group: SC AKB-9778 15 mg (QD); To maintain masking, subjects will receive BID dosing with masked study medication administered as one dose of active and one dose of matching placebo
- Active Group: SC AKB-9778 15 mg (BID)
- Placebo Group: SC Phosphate-Buffered-Saline (PBS) (BID)

Subjects will self-administer study medication as SC injections in the abdomen (preferably) around the same time every morning and evening, if possible (See Section 8.3.5). The Investigator, all study-site personnel, Central Image Reading Center personnel, and subjects will be masked to treatment assignment during the entirety of the study.

For safety monitoring throughout the conduct of the study, ocular image data (fundus photographs, including red free images, fluorescein angiography, and OCT) for both the study and fellow eye will be read locally by the Investigator.

All ocular image data will be transmitted to a Central Image Reading Center. Modified 7-Field or 4-Wide Field color fundus photos will be graded for ETDRS DRSS by the Central Image Reading center. The Central Image Reading center will confirm study eye eligibility based on ocular imaging criteria. The Central Image Reading Center will provide the Screening DRSS value to investigative sites which will be used for randomization stratification based on Screening photos (See Section 8.3.2). Ocular images analyzed at the Central Image Reading

Center will be used for final statistical analyses. Reading center personnel will be masked to subject treatment and the reading and grading will be done in a masked fashion.

Randomization will be stratified by study eye screening ETDRS DRSS (levels 43, 47 and 53 equally distributed between the treatment groups). The number of study eyes with moderate severity of DR (level 43) will be limited to 50.

Spot UACR and eGFR will be assessed as exploratory assessments to evaluate for any potential effects on renal function. UACR will be evaluated at Baseline, Month 6, Month 9, and Month 12 (EOT). eGFR will be evaluated at Screening, Baseline, Month 6, Month 9, and Month 12 (EOT).

Plasma samples will be collected at specified times on Day 1 and Month 6 visit for PK assessments. These samples will be analyzed for AKB-9778 using validated bioanalytical methods.

A blood sample will be retained for exploratory genetic analysis that may provide insight into the role of the VE-PTP/Tie2 pathway in diabetic retinopathy and an individual subject's response to AKB-9778 treatment. Similarly, blood samples collected at baseline and Month 12 End of Treatment (EOT) will be retained for exploratory analysis of biomarkers in plasma associated with VE-PTP inhibition and Tie2 activation. Once results of the study are known, the Sponsor will determine the value of conducting the genetic and biomarker assessments.

Subjects will be seen at the investigative site every 4 weeks while participating in the study. At each monthly visit, subjects will undergo blood pressure and heart rate monitoring and visual acuity assessments. Subjects will also be questioned about any symptoms since their prior visit, and any adverse events and changes or additions to concomitant medications will be documented. Subjects will undergo blood sampling for clinical laboratory assessments (monthly for chemistry and every other month for hematology assessments). Fecal occult blood will be evaluated at Screening, Month 6, Month 9, and Month 12 (EOT). Subjects will collect their stool specimens at home and ship directly to the central clinical laboratory for testing; Investigative sites will distribute instructions and supplies for specimen collection and shipping. Every three months, subjects will also undergo a battery of comprehensive ocular assessments at the investigative site including slit lamp biomicroscopy, IOP, dilated indirect ophthalmoscopy, SD-OCT, fundus photography and fluorescein angiography (at Months 6 and 12 only). Exploratory efficacy assessments (OCT-A, UWF imaging and non-invasive ERG) will also be included at a subset of sites.

In addition to the assessments at the study site visits, at Screening and every three months during the treatment period, subjects will be visited at their homes by a home healthcare nurse, who will conduct body system assessments and review status of specimen collection for fecal occult blood testing (on relevant visits). The home health care nurse will also conduct the 1 month Follow-Up visit. At this visit, the nurse will collect medical history and conduct a body system assessment. If the home healthcare nurse identifies any potential AEs during the home visit, the nurse will communicate directly to the study site and the Investigator will be responsible for determination of AEs and any necessary follow-up with the subject. The home healthcare nurse visits are anticipated to provide an additional measure of safety oversight.

The safety and tolerability of AKB-9778 will be determined by incidence and severity of treatment emergent AEs and changes from baseline in ECG, vital sign measurements, clinical

laboratory assay results (blood chemistry, hematology, fecal occult blood, and urinalysis), BCVA, IOP, slit lamp examinations, funduscopic examinations and fluorescein angiograms (FA).

6.2 Rationale for Study Design

This Phase 2 study is being conducted to assess the safety and efficacy of AKB-9778 15 mg QD and AKB-9778 15 mg BID when administered daily for 12 months (48 weeks) in subjects with moderate to severe NPDR and no center-involved DME.

6.3 AKB-9778 Dose Justification

In two previous studies of AKB-9778 in subjects with DME, a 15 mg BID dose regimen using the HPβCD formulation has been well tolerated for up to 1 month and 3 months of treatment, respectively. The AKB-9778 dose regimen selected for this study is anticipated to be well tolerated based on nonclinical toxicology studies and clinical evaluation in humans and should allow for evaluation of efficacy without undue safety risk for participating subjects. Additionally, this dose regimen was associated with an increased percent of DME subjects achieving at least a 2-step improvement in DRSS compared to placebo. To evaluate if less frequent administration may also achieve efficacy, an AKB-9778 15 mg QD dose regimen arm is also included in this study.

6.4 Oversight of Safety

On an ongoing basis throughout the conduct of the study a variety of planned safety monitoring reviews of available study data will be conducted. These include weekly reviews conducted by the Aerpio Medical Monitor, monthly masked reviews by the Aerpio Clinical Safety Review Team (CSRT), and quarterly masked reviews by the Safety Assessment Committee (SAC: composed of members independent of the clinical team including Aerpio physician/cardiologist, a non-sponsor independent physician experienced in the assessment of clinical trial safety data, a non-sponsor independent physician with expertise in gastrointestinal/hepatology safety assessment, and a non-sponsor independent physician/ophthalmologist with expertise in ophthalmology safety assessment). Ad hoc review by any review committee will be conducted anytime an important safety signal is identified. If unmasked reviews are needed to understand a potential safety signal, these will be conducted by the SAC. These reviews are detailed further in the AKB-9778 Safety Surveillance Plan.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 General Criteria

Subjects will be recruited for screening by investigative Sites.

To be eligible for this study, a subject must provide valid informed consent and must meet all of the following criteria. No study procedures (including screening tests) may be performed until after the informed consent process has been conducted and the subject has legally signed.

A subject number will be allocated to each subject at the Screening visit. If during the course of the Screening tests and procedures, a subject does not meet the eligibility criteria or does not continue in the study, the subject will be considered a Screening failure (not a withdrawal).

7.2 Subject Eligibility Criteria

7.2.1 Subject-Level Inclusion Criteria

1. Males and non-pregnant females between 18 to 80 years of age, inclusive.
2. Body mass index (BMI) between 18 to 40 kg/m^2, inclusive.
3. Diagnosis of diabetes mellitus (type 1 or type 2). Any one of the following will be considered to be sufficient evidence that diabetes is present:
    a. Current regular use of insulin for the treatment of diabetes for at least the 3 months prior to screening.
    b. Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes for at least the 3 months prior to screening.
    c. Documented diabetes (type 1 or type 2) as classified by the American Diabetes Association (ADA) and/or World Health Organization (WHO) criteria.
4. At least one eye meets the study eye criteria listed below.
5. Ability, in the opinion of the Investigator, and willingness to return for all scheduled visits and assessments.
6. Ability to compliantly self-administer subcutaneous study medication twice daily for 12 consecutive months.
7. Understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure.

7.2.2 Subject-Level Exclusion Criteria:

1. For females of child-bearing potential: pregnant or breast-feeding or intending to become pregnant within the next 12 months.
2. Females of child-bearing potential who are unable or unwilling to use an acceptable method of contraception (Refer to Section 9.1.3, Contraception and Pregnancy Avoidance Measures).
3. Non-vasectomized male subjects who are unable or unwilling to use an acceptable method of contraception (Refer to Section 9.1.3, Contraception and Pregnancy Avoidance Measures).
4. Hemoglobin A1C (HbA1C) ≥ 12.0% at Screening.
5. Uncontrolled hypertension defined as resting (sitting) systolic BP of ≥180 mmHg or a diastolic BP of ≥100 mmHg at Screening. Must be on a stable (≥ 6 weeks) antihypertensive regimen.
6. Resting (sitting) systolic BP of <100 mmHg at Screening.
7. A history of symptomatic orthostatic hypotension, vasovagal syndrome, syncope, or presyncope within one year prior to Screening.

8. Initiation of nitrate medications or history of nitrate-associated orthostatic symptoms within one month prior to Screening.
9. History of stroke, transient ischemic attack, congestive heart failure > NYHA Class 2, angina, or acute coronary syndrome within 3 months prior to Screening or any acute cardiology medical issues within 30 days prior to screening.
10. Coronary-artery bypass graft, percutaneous intervention (e.g., cardiac, cerebrovascular, aortic), or major cardiac surgery within 3 months prior to Screening or anticipated need during study participation.
11. If atrial fibrillation is present, then it must have been continuously present for >2 months with adequate rate control (ventricular response <95 BPM) with no plans to return the subject to sinus rhythm during the study confirmed by either their primary care physician or cardiologist.
12. QTcF > 470 ms.
13. Major surgery within 28 days prior to Screening or major surgery planned during the study. Major surgery is defined as a surgical procedure that is more extensive than fine needle biopsy/aspiration, placement of a central venous access device, removal/biopsy of a skin lesion, or placement of a peripheral venous catheter.
14. Serum transaminase ([AST] and [ALT]) levels > 2X the upper limit of normal (ULN). (May be repeated once).
15. History of clinically significant chronic liver disease (defined as any complication of liver disease, ascites, varices, hepatic encephalopathy, hepatocellular cancer).
16. History of chronic renal failure (stage 4 or 5).
17. History of gastrointestinal bleeding within the last year, or any history of bleeding due to arteriovenous malformation.
18. Ferritin < 30 ng/ml in combination with a transferrin saturation (TSAT) < 20%.
19. Fecal occult blood > 4.0 mg total hemoglobin/g feces as determined by the central laboratory.
20. Presence of New York Heart Classification congestive heart failure class III or IV.
21. Severe aortic stenosis.
22. Chronic anticoagulation with warfarin, a direct acting anticoagulant, or antiplatelet agent (other than low dose aspirin).
23. History of any solid organ transplant or bone marrow transplant, requiring immunosuppressive medications.
24. Any history of alcohol or drug abuse within the previous year prior to Screening.
25. Previous treatment with AKB-9778.
26. Use of an investigational medication or device or participation in an investigational study within 30 days or 5 half-lives of the investigational medication, whichever is longer, preceding Screening, or ongoing or scheduled participation in another investigational study during the current study.

27. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the Investigator's judgment, would make the subject inappropriate for study entry.
28. Current treatment for serious systemic infection.
29. History of allergy to fluorescein.
30. Subject is expecting to move out of the area of the clinical site to an area not covered by another clinical site during the conduct of the study.

7.3 Ocular Eligibility Criteria

For a subject to be included in the study, at least one eye must meet all ocular inclusion and exclusion criteria. If both eyes meet all ocular eligibility criteria, then the eye with the worse ETDRS DRSS should be designated the study eye, and the other eye designated as a qualified fellow eye; in this case, the Central Image Reading Center will confirm selection of the study eye.

7.3.1 Study Eye / Qualified Fellow Eye Inclusion Criteria:

1. Moderate to severe NPDR (ETDRS Level 43 – 53 inclusive) as confirmed by the Central Image Reading Center
2. No evidence of center involved DME on SD-OCT as confirmed by the Central Image Reading Center
3. No history of treatment for DME or DR within 12 months prior to Day 1 and no history of treatment with Iluvien® within 36 months prior to Day 1
4. ETDRS BCVA letter score ≥ 70 (Snellen 20/40 or better)

7.3.2 Study Eye /Qualified Fellow Eye Exclusion Criteria

1. A decrease in visual acuity due to causes other than DR (e.g., foveal atrophy, pigment abnormalities, dense subfoveal hard exudates, previous vitreoretinal surgery, non-retinal condition, substantial cataract).
2. Any other ocular disease that may cause substantial reduction in visual acuity, including iris neovascularization, retinal detachment, visually significant epiretinal membrane, vitreomacular traction, vitreous hemorrhage or fibrosis, ocular inflammation (uveitis), other retinal inflammatory or infectious diseases.
3. Evidence of active ocular infection (e.g., blepharitis, keratitis, scleritis, or conjunctivitis).
4. History of non-infectious uveitis.
5. High myopia (-8 diopter or more correction).
6. History of prior pars plana vitrectomy.
7. History of prior PRP

8. Evidence of neovascularization on clinical examination, including active neovascularization of the iris or angle neovascularization
9. Evidence of neovascularization on FA within the area of the Modified 7-Field fundus photographs as confirmed by the Central Image Reading Center.
10. History of any ocular surgery within 3 months prior to Day 1.
11. Uncontrolled glaucoma defined as IOP ≥ 30 mmHg on maximum IOP reduction therapy.
12. Media opacity, pupillary constriction (i.e. senile miosis), or poor subject cooperation that, in the opinion of the investigator, would interfere with any study procedures, evaluations or interpretation of data.
13. Any ocular condition that, in the opinion of the investigator, may require intervention, interfere with the study procedures, or interfere with evaluations of efficacy or safety or interpretation of data collected in the study.

7.4 Waivers

No waivers will be granted in the study.

7.5 Replacement of Subjects

Subjects withdrawn for reasons other than lack of efficacy (treatment for PDR or DME) may be replaced.

7.6 Discontinuation of Study Medication/Withdrawal of Subjects

Subjects will discontinue study medication for any of the following conditions:

- In the opinion of the Investigator, it is medically necessary
- The subject withdraws consent
- Major toxicity considered to be related to study medication
- The investigator obtains the treatment code for the subject
- Administrative reasons, such as, subject non-compliance or a major protocol violation
- Upon request of the Subject, Sponsor, Institutional Review Board (IRB) or regulatory agency
- Study termination

In addition to the above reasons for study medication discontinuation, if the subject meets criteria for treatment of PDR or DME (e.g. Anti-VEGF, steroids, laser, vitrectomy) in the study eye or qualified fellow eye, study medication may be discontinued at the discretion of the principal investigator and the subject.

- *Criteria for treatment of PDR or DME in the study eye or qualified fellow eye are given in Appendix B. Non-qualified fellow eyes may be treated at the discretion of the Investigator.*
- *Refer to Section 8.4.3 for additional details regarding assessments to be conducted prior to treatment of PDR or DME.*

Once it is identified that a subject will discontinue study medication, the subject should undergo all EOT (Month 12/Early Withdrawal) assessments (See Section 9.3.2.16) as soon as possible after study medication is stopped. The subject will then enter the 1-month Follow-up period provided that the subject has not withdrawn consent.

If a subject does not return for a scheduled site visit or complete a homecare nurse visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome by completing the End of Treatment (Month 12/ Early Withdrawal) assessments.

The Investigator must document the primary reason for discontinuation of study medication on the appropriate case report form (CRF). If the reason for discontinuation of study medication is a clinical AE, monitoring will continue until the AE resolves or the Investigator assesses the AE as chronic or stabilized.

8 STUDY PRODUCT AND TREATMENT OF SUBJECTS

8.1 Study Medication, Supplies and Storage

AKB-9778 and matching placebo will be provided as sterile pre-filled syringes. The pre-filled syringes will be packaged in kits containing a one-week supply of study medication (seven "AM" doses and seven "PM" doses). Kits will be shipped by the Sponsor or its designated supplier/distributor to the investigative site. Study medication will be provided as masked supplies. Syringes containing doses to be administered in the morning will be labelled "AM" and syringes containing doses to be administered in the evening will be labelled "PM".

The Investigator or designated study personnel will be responsible for study medication supply accountability (Section 8.5) and dispensing study medication and supplies to subjects.

AKB 9778

AKB-9778 is supplied as a sterile solution for subcutaneous administration packaged in a clear glass pre-filled syringe sealed with a Flurotec-coated stopper. Each syringe is filled to a volume of 0.75 mL which delivers a dose of 15 mg AKB-9778.

The drug product formulation contains 20 mg/mL AKB-9778, 100 mg/mL HPβCD (United States Pharmacopeia [USP]) and 25 mg/mL dextrose, USP. The formulation is controlled to pH 5.0 - 8.5 with an osmolality of between 250 and 350 mOsm/kg.

Placebo

The matching placebo formulation is supplied as a sterile solution for subcutaneous administration packaged in a clear glass pre-filled syringe sealed with a Flurotec-coated stopper. Each syringe is filled to a volume of 0.75 mL.

The placebo formulation (PBS) contains 8 mg/mL sodium chloride, USP, 1.5 mg/mL sodium phosphate dibasic, USP, and 0.6 mg/mL sodium phosphate monobasic, USP. The formulation is controlled to pH 5.0 - 8.5 with an osmolality of between 250 and 350 mOsm/kg.

8.1.1 Storage and Handling of Study Medication

At the investigational site, study medication will be locked under controlled access and maintained at USP/National Formulary (NF) Controlled Room Temperature 15ºC - 30ºC (59ºF - 86ºF) inclusive, with excursions permitted of up to and including 40ºC (104ºF) for no more than 24 hours.

The subject will be directed to store study medication in a secure location away from children at ambient temperature.

8.2 Dispensing Procedures

Assignment of masked study medication for dispensing will be made using an interactive web response system (IWRS).

The Investigator will maintain a Drug Accountability Form itemizing all masked medication dispensed to and returned from each subject during the study.

At Day 1 and visits on Months 1 through 11, subjects will be provided with sufficient supply for 1 month (4 weeks) of dosing plus overage to allow for some flexibility in study visit scheduling.

At the Day 1 visit, the subject will also be provided with a tote bag which contains ancillary supplies for dosing (e.g., sterile wipes, band aids, sharps container).

Subjects should be instructed to bring all unused study medication to each monthly study visit for product accountability. Full sharps containers should be returned and replaced as necessary. Subject dosing diaries should be returned at each monthly visit and subjects will be questioned regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication.

All unused and returned study medication should be retained at the investigative site and must be returned to the Sponsor or its designee for destruction. If authorized by the Sponsor, investigative sites that have SOPs for destruction of study medication on site may destroy study medication once accountability procedures have been completed.

8.3 Treatment of Subjects

The Treatment period will last 12 months (48 weeks).

8.3.1 Treatment Group Assignments

Subjects meeting all eligibility criteria will be randomized 1:1;1 to either AKB-9778 15 mg QD, AKB-9778 15 mg BID, or Placebo treatment groups. Fifty (50) subjects are planned per group. The treatment groups are as follows:

- Active Group: SC AKB-9778 15 mg (BID)
- Active Group: SC AKB-9778 15 mg (QD)
- Placebo Group: SC PBS (BID)

8.3.2 Randomization and Allocation to Treatment Group

Approximately 150 subjects will be treated in the study.

Using a central IWRS randomization system, eligible subjects will be assigned in a double-masked fashion 1:1:1 to one of the 3 treatment groups. To maintain balance between treatment groups with respect to DR severity, randomization will be stratified by Screening ETDRS DRSS (levels 43, 47 and 53). The number of study eyes randomized with Screening ETDRS DRSS level 43 will be capped at 50.

8.3.3 Masking in the Study

This study will be conducted in a double-masked manner.

Treatment group assignment will be done through a central randomization system and completed using an IWRS.

Study medication will be shipped as masked supplies.

All investigative site staff will be masked to study treatment assignment

Subjects will be masked to treatment assignment during the entirety of the study.

Central Image Reading Center personnel will be masked to treatment assignment for the entirety of the study and the reading and grading will be done in a masked fashion.

Blood specimens will be obtained from subjects for PK analysis in a manner that maintains treatment masking. Select personnel at the bioanalytical contract laboratory will be unmasked to subject treatment in order to permit analyses of samples from active treatment subjects only.

8.3.4 Unmasking

Unmasking of the Investigator is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment is necessary for the proper management of the subject. When possible, the Investigator should first discuss the unmasking request with the Sponsor and or Medical Monitor prior to unmasking. If treatment is unmasked, the subjects should be discontinued from the study.

8.3.5 Study Drug Administration

Subjects will be responsible for self-administering study medication and will receive training during the Day 1 visit.

On Day 1, Within 30 minutes to 1 hour prior to dosing, the subject should eat a meal or snack and drink 1-2 glasses of fluids preferably juice or electrolyte-containing as per the subject's usual diet management.

Following the first dose of study medication on Day 1, subjects should remain seated for the first 30 minutes, when not conducting study assessments.

On Day 1, subjects will be dosed with the AM dose at the site, regardless of the time of day. Subjects will only self-administer the AM dose of study medication on Day 1. The subject will self-inject BID on a morning and evening schedule as detailed below. Subjects will dose BID except for Day 1 when the subject will administer the first dose of study medication at the site using the AM dose (regardless of the time of day) and will begin the BID dosing schedule on Day 2; the PM dose will ***not*** be administered on Day 1. Subjects will only use AM syringes for dose administration in the morning and PM syringes for dose administration in the evening.

Subjects should administer their daily doses around the same time every morning and evening, if possible. If a dose is missed, this dose should be skipped and the subject should maintain the morning and evening dosing schedule. Subjects will maintain a study medication diary noting time and location of injection. Subjects should be encouraged to follow their normal diet and maintain fluid intake (per their diabetes management).

Study medication will be administered subcutaneously in the abdomen (preferably) following standard subcutaneous administration practices. A distance of at least 3 cm between injection site and the midline, and between injection site and any scar should be maintained. The subject should avoid tender, bruised, red or indurated areas and should maintain a distance of at least 3 cm between consecutive injections. If possible, subjects should not dose in the same quadrant of the abdomen between consecutive injections. If the subject does not prefer to inject in the abdomen, the subject is allowed to dose in other standard regions for subcutaneous administration (e.g., upper arm or thigh); the location of the injection site will be identified in the subject medication diary.

For subjects on injectable hypoglycemic drugs (e.g., insulin or GLP-1 analogues), it is preferable that a separate anatomical region be used for study drug administration. For example, if the subject usually injects insulin or GLP-1 analogue in the upper arm, then study drug would preferably be injected in the abdomen.

Before injection, the skin at the injection site should be cleaned and prepared with a skin disinfectant. Care must be taken to ensure the study medication is not injected into a blood vessel.

The subject must be able to compliantly self-administer study medication. If the subject lives with a caretaker, the caretaker is allowed to assist the subject with dosing.

8.4 Prior and Concomitant Therapy

8.4.1 General

All medications taken within 30 days prior to the start of study medication through the Month 12 EOT visit should be recorded on the appropriate CRF.

Diabetes management is left to the subject's medical care provider.

Subjects will take allowed non-study medication including insulin or oral-hyperglycemia agents per their normal routine. (For additional details see Section 9.1.4).

Procedural ophthalmic medications are not required to be recorded (e.g., fluorescein dye, dilating drops, etc.).

8.4.2 Investigational Medications

Study subjects should not have received any investigational medication or participated in an investigational study within 30 days or 5 half-lives of the investigational medication, whichever is longer, preceding Day 1.

Additionally, ongoing or scheduled participation in another investigational study during the current study through the Month 12 visit is not allowed.

8.4.3 Treatment of PDR or DME

Criteria for treatment of PDR or DME in the study eye or qualified fellow eye during the study are summarized in Appendix B. Treatment of PDR of DME in a non-qualified fellow eyes is at the discretion of the Investigator. Treatment will be recorded on the appropriate CRFs.

Subjects who receive treatment for PDR or DME in a study eye or qualified fellow eye may discontinue study medication at the discretion of the Investigator and subject. Subjects who remain in the trial will continue study medication.

The following scenarios apply depending on eye being treated for PDR or DME.

- For a study eye or qualified fellow eye requiring treatment, the Sponsor Medical Monitor should be informed prior to initiation of treatment. Additionally,
    - If the subject will discontinue study medication, the subject should undergo all EOT (Month 12/Early Withdrawal assessments (See Section 9.3.2.16) as soon as possible after study medication is stopped. EOT procedures should be conducted **prior** to treatment for PDR or DME in the study eye or qualified fellow eye. Treatment for PDR or DME will be in accordance with criteria in Appendix B; following treatment, the subject will enter the 1-month Follow-up period.
    - If the subject will continue study medication, consult the Sponsor Medical Monitor to determine appropriate ocular assessments to be conducted prior to treatment for PDR or DME. Treatment for PDR or DME will be in accordance with criteria in Appendix B.
- For a non-qualified fellow eye requiring treatment:
    - The subject will remain in the study and study assessments will be conducted per protocol prior to any treatment for PDR or DME. Treatment for PDR or DME in a non-qualified fellow eye is at the discretion of the Investigator.

8.5 Product Accountability and Destruction

Product accountability should be an ongoing process throughout the study. All study medication must be accounted for and any discrepancies explained.

Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date or retest date is provided to the Investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the master drug log is completed for all subcutaneous study medication received at the site and that all required fields are complete, accurate, and legible.
- Review of temperature log, and that the study medication is stored in locked access controlled conditions.
- Verifying the subject individual drug accountability log is completed for each subject and that all required fields (units dispensed, returned, used, compliance) etc., are complete accurate and legible.

If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

Prior to site close-out, a representative from the Sponsor will perform clinical study material accountability and reconciliation.

At the end of the study, the Investigator will retain all the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the Sponsor.

The Investigator or designated study personnel is responsible for keeping accurate records of the study medication received from the Sponsor or its designee, all supplies retained in inventory at the site, and study medication dispensed to and returned from each subject. This record will be maintained on a Drug Accountability Log that accurately reflects the accountability of the study medication at all times.

During the study, the Investigator will be notified of any expiry dates or retest date extensions of study medication. If an expiry date notification is received during the study, the site must complete all instructions outlined in the notification, including segregation of expired study material for return to the Sponsor or its designee for destruction.

At the end of the study, any unused study medication must be returned to the Sponsor or its designee for destruction. If an investigative site has SOPs for destruction of study medication on site, the Sponsor may authorize destruction of at the investigative site following completion of accountability procedures.

9 STUDY PROCEDURES AND SCHEDULE OF ACTIVITIES

Please see Appendix A for a detailed table of the Schedule of Activities.

A one-month duration in this study is defined as 4 weeks/28 days. The 12-month Treatment period is 48-weeks/336 days.

This study includes the following periods and visits:

- Screening visit (up to 28 days prior to Baseline)
- Baseline visit (pre-dosing period on Day 1)
- Treatment Period (Days 1 through Month 12 (Week 48)); including:
    - Investigative site visits on Day 1, Day 7 (phone-call), and monthly (i.e., every 4 weeks) thereafter until the Month 12 (Week 48) EOT visit
    - Homecare nurse visits on Screening and Months 3, 6, 9, 12 (EOT)
- Follow-Up Period 1 Month (4 weeks) Post-Treatment

The following sections describe the procedures to be completed during the study. Subjects are to be assessed by the same Investigator or site personnel whenever possible.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained prior to the subject entering into screening for the study and before any protocol-specific procedures are performed (see Section 15.3).

9.1.2 Documentation of Screen Failures

Investigators will maintain a log of pre-screened subjects and indicate who was brought in for informed consent and Screening or who was not. For subjects not brought in for informed consent and Screening, the reason(s) for not passing the pre-screen will be documented by the Investigator.

Investigators must account for all subjects who sign informed consent and will maintain a log of subjects screened and indicate who was randomized or screen-failed. If the subject is found not to be eligible prior to randomization, the reason(s) for ineligibility/screen fail must be documented by the Investigator.

Subject numbers assigned to subjects who fail screening will not be re-used.

9.1.3 Contraception and Pregnancy Avoidance Measures

9.1.3.1 Summary of AKB-9778 Reproductive Toxicology Studies

In nonclinical animal embryo-fetal development studies, there was no evidence of external fetal teratogenic effects, or of skeletal or visceral malformations, at dose levels up to the highest doses tested; 180 mg/kg/day in rats and 140 mg/kg/day in rabbits. In rats and rabbits, decreased maternal body weight and food consumption were observed at these high doses.

Fertility and peri-postnatal development studies have not yet been conducted with AKB-9778, and there are no data on the transmission of AKB-9778 in breast milk or the effect of AKB-9778 on infants.

9.1.3.2 Guidance for Study AKB-9778-CI-5001

Due to the unknown effects of AKB-9778 on sperm and the developing fetus, all subjects must agree to use adequate contraception throughout the study and for 30 days after administration of last dose of any study medication.

Adequate contraception is defined as follows:

Female subjects must be surgically sterile, postmenopausal (for at least one year), or have negative pregnancy test results at Screening (serum) and at Baseline (urine).

Female subjects not surgically sterile or postmenopausal (for at least one year), and non-vasectomized male subjects must practice at least one of the following methods of birth control:

- total abstinence from sexual intercourse (minimum one complete menstrual cycle prior to Screening visit, throughout the study, and for 30 days after the last dose of study medication)
- a vasectomized partner or partner of non-child bearing potential

- hormonal contraceptives (oral, parenteral, Nexplanon, or transdermal) for at least three months prior to study drug administration
- double-method of birth control and must include condoms in addition to one other method: spermicide, IUD, diaphragm with spermicide, hormonal contraceptive, bilateral tubal ligation, Essure procedure.

Female subjects may not donate eggs (ova, oocytes) during this study and for 30 days after the last dose of study medication.

Male subjects must not donate sperm during the study and for at least 60 days after the last dose of any study drug.

9.1.4 Diet, Fluid and Activity Control

Subjects should be encouraged to follow their normal diet and maintain fluid intake (per their diabetes management).

Subjects will take allowed non-study medication including insulin or oral-hyperglycemia agents per their normal routine. Subjects will monitor blood sugar as per their normal routine. Diabetes management is left to the subject's medical care provider.

Subjects are to refrain from physical activity greater than their normal level of activity for the duration of the study.

Subjects will be advised that it is important to refrain from excessive alcohol intake for the duration of the study.

Subjects taking medication for erectile dysfunction (e.g., Viagra®, Cialis®, Levitra®), should not take this medication within 2 hours before or after study medication.

For three days prior to and during the days of stool sample collection for fecal occult blood testing, subjects are to refrain from eating any red meat (beef, pork or lamb). Also, for three days before and during the days of stool sample collection, subjects will avoid taking aspirin. However, subjects taking daily low dose aspirin are allowed to continue their aspirin but must not change their dose.

On Day 1 and on Month 6, within 30 minutes to 1 hour prior to dosing at the site, the subject should eat a meal or snack and drink 1-2 glasses of fluids preferably juice or electrolyte containing as per the subject's usual diet management. Following dosing on the Day 1 and Month 6 visits, subjects should remain seated for the first 30 minutes, when not conducting study assessments.

9.1.5 Laboratory Accreditation and Reference Ranges

The Investigator and the Sponsor will maintain a copy of the laboratory accreditation and the reference ranges for the central laboratory used for clinical laboratory evaluations.

9.2 Study Procedures and Evaluations

Please see the Schedule of Activities presented in Appendix A for designated time points for assessments.

9.2.1 Clinical Evaluations

The following clinical evaluations will be conducted during the course of the study.

- Medical/ophthalmic history and demographics: Relevant medical history (with particular emphasis on previous medical conditions that may lead to exclusion) and significant ongoing medical conditions or diseases should be documented. Ophthalmic history should include treatment history for DR/DME.
- Body System Assessments: Body systems to be evaluated include general appearance, HEENT (head, ears, eyes, nose and throat), cardiovascular, respiratory, abdomen/gastrointestinal (including query of any changes in bowel habit frequency, consistency, or color), musculoskeletal, and skin (including query of any skin abnormalities noted as well as direct observation of skin of head, neck, chest, abdomen, back and extremities). Subjects will be instructed that if they note any abnormalities between visits they should contact their study doctor so that any such findings can be assessed.
- Height (at Screening only), weight, and temperature
- 12-Lead ECG: A standard 12-lead ECG will be obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes and prior to vital sign assessments and blood draws when possible. With the subject in a supine position, obtain the 12-lead tracing. Each 12-lead ECG must be recorded with a paper speed of 25 mm/sec and printed as a paper copy. The Investigator (or a qualified observer) will interpret the ECG and record the results including the following parameters: heart rate, PR interval, QT interval, QRS interval, and QTcF (corrected).

  In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTcF values are in the acceptable range.

  All abnormal rhythms will be reviewed by the study physician for the presence of rhythms of potential clinical concern. The Investigator should utilize medical judgment in the reporting of AEs and SAEs as well as determination of additional cardiac work-up. A printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents. An ECG will be performed at the Screening, Month 6, and Month 12 (EOT) visits.
- Vital Signs: Vital signs include blood pressure and heart rate. Vital sign assessments should be taken prior to blood draws when possible. The subject should be seated, with legs uncrossed and feet resting comfortably on the floor, for at least 5 minutes prior to measuring blood pressure and heart rate.
- ETDRS Best Corrected Visual Acuity (BCVA): Visual acuity of both eyes will be assessed using the ETDRS protocol at 4 meters.
- Slit Lamp Biomicroscopy: Slit-lamp biomicroscopy will include examination of the cornea, conjunctiva, anterior chamber, iris/pupil, lens, and eyelid of both eyes. Findings

will be graded as normal, abnormal not clinically significant, or abnormal clinically significant.

- Intraocular Pressure (IOP): IOP will be assessed with either applanation tonometry or tonopen; the method should be consistent throughout the study.
- Dilated Indirect Ophthalmoscopy: Dilated indirect ophthalmoscopy will be performed to assess the vitreous, macula, optic nerve, and peripheral retina of both eyes. Findings will be graded as normal, abnormal not clinically significant, or abnormal clinically significant.
- SD OCT: Spectral domain optical coherence tomography (SD OCT) will be utilized to assess retinal characteristics of both eyes. The OCT instrument type used throughout the study must be consistent for an individual subject. OCT imaging data will be transmitted to a central reading center for independent analysis. Detailed instructions for imaging and data transfers will be provided in the study-specific imaging manual.
- Fundus Photography: Modified 7-Field or 4-Wide Field color fundus photographs (including red free images) of both eyes will be taken to evaluate retinal anatomy. Photographs will be transferred to a central reading center. Detailed instructions for imaging and data transfers will be provided in the study-specific imaging manual.
    - For sites participating in the UWF imaging sub-study, ***in addition to*** Modified 7-Field or 4-Wide Field color fundus photographs, UWF color fundus photographs should be taken using the Optos P200Tx or Optos California system. Parameters obtained are detailed further in this section under "UWF imaging".
- Fluorescein Angiography (FA): Retinal vasculature of both eyes will be evaluated by fluorescein angiography (FA). FA images will be transferred to a central reading center. Detailed instructions for imaging and data transfers will be provided in the study-specific imaging manual.
    - For sites participating in the UWF imaging sub-study, ***in lieu of*** standard FA, UWF FA images should be taken using the Optos P200Tx or Optos California system. Parameters obtained are detailed further in this section under "UWF Imaging".
- Adverse Event Assessments: Beginning with informed consent and through final protocol required visit, the Investigator and study personnel will review each subject's laboratory and clinical evaluation findings and query the subject directly regarding AEs (see Section 10). If a home healthcare nurse identifies any potential AEs during a home visit, the nurse will communicate directly to the study site and the Investigator will be responsible for determination of AEs and any necessary follow-up with the subject. Subjects must be followed for AEs until the final required protocol visit or until all drug-related toxicities and serious adverse events have resolved (or are considered chronic/stable), whichever is later.
- Concomitant Medication Recording: All medications, both prescription and non-prescription, and including vitamins, herbals, topicals, inhaled, and intranasal, taken within 30 days prior to the start of study medication and through the Month 12 EOT visit

should be recorded on the appropriate CRF. At each study visit, subjects will be asked whether they have started or discontinued any medication since their previous study visit. This includes single use or PRN (as needed) medication use. All medications and treatments, including vitamin supplements, over-the-counter medications, and oral herbal preparations must be recorded in the CRFs.

- Exploratory Efficacy Sub-Study Evaluations (to be conducted at a subset of sites):
    - OCT-A – OCT-angiography should be obtained from both eyes using a SD OCT machine according to instructions provided by the manufacturer
    - ERG – Flicker ERGs will be obtained from both eyes using the RETeval system (LKC Technologies, Gaithersburg MD). Responses will be obtained from electrodes placed on the skin under light-adapted conditions. Parameters obtained will include flicker ERG amplitude, ERG peak latency, and pupillary response to each of 3 different flicker intensities. RETeval score will also be derived from these data (Maa et al, 2015).
    - UWF imaging – UWF FA and UWF color fundus photographs will be obtained using the Optos P200Tx or Optos California instrument following procedures specified in the study specific imaging manual. As described previously, UWF FA will be performed ***in lieu of*** standard FA, but UWF photographs will be obtained ***in addition to*** standard Modified 7-Field or 4-Wide Field color fundus photographs. UWF fundus photographs are only obtained on visits when UWF FA is performed (e.g. Screening, Month 6, and Month 12 (EOT). Parameters obtained from UWF FA include area of peripheral non-perfusion, area of peripheral leakage. Parameters measured in UWF color fundus photographs include peripheral microaneurysms, vitreous hemorrhage, venous beading, intra-retinal microvascular abnormalities (IRMA) and neovascularization elsewhere (NVE).

9.2.2 Laboratory Evaluations:

All samples collected (with the exception of urine pregnancy tests) will be sent to a central clinical laboratory.

If to be conducted at the same time points, blood sampling should occur after vital sign assessments and ECGs have been conducted.

Samples for clinical laboratory evaluations (hematology, chemistry, fecal occult blood testing, and urinalysis assays) and Screening serum pregnancy tests will be analyzed at the central laboratory. The Investigator is responsible for reviewing laboratory results for clinical significance.

The central laboratory is also responsible for distribution of PK samples to the respective PK laboratory for analysis. Once the results of the study are known, the Sponsor will determine if biomarker and genetic analyses will be conducted and will direct the central clinical laboratory on distribution of samples for biomarker and genetic analyses to the appropriate laboratories.

The following clinical laboratory evaluations will be conducted during the course of the study:

- Pregnancy test: A serum pregnancy test will be performed at Screening for females of childbearing potential. The investigative site will perform a urine pregnancy test at the Baseline, Month 6 and Month 12 EOT visits. The Screening and Baseline results must be available and must be negative before the subject takes the first dose of any study medication on Day 1. At each monthly visit, the site will query subjects of childbearing potential regarding the potential for pregnancy.
- Hematology: The complete blood count (CBC) will include: hemoglobin (Hgb), hematocrit, red blood cell (RBC) count, mean corpuscular (cell) volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), white blood cell (WBC) count with differential (neutrophils, immature granulocytes, lymphocytes, monocytes, eosinophils, basophils), platelet count, reticulocyte count and HbA1C. Hematology will be assessed every other month except for HbA1C which will be assessed at Screening, Baseline, Month 6, and Month 12 (EOT) visits.

  Chemistry: The serum chemistry will include the following assays: sodium, potassium, bicarbonate, chloride, calcium, phosphorus, glucose, creatinine, blood urea nitrogen (BUN), creatinine phosphokinase (CPK), uric acid, albumin, total protein, total bilirubin, alkaline phosphatase, alanine transaminase ((ALT (SGPT)), aspartate transaminase (AST (SGOT)), lactate dehydrogenase (LDH), total cholesterol, triglycerides, ferritin, serum iron, total iron binding capacity (TIBC) and transferrin saturation (TSAT). Chemistries will be assessed monthly. eGFR will be determined on serum chemistry samples collected at the Screening, Baseline, Month 6, Month 9, and Month 12 (EOT) visits.
- Fecal occult blood testing: A small amount of stool will be collected on 3 separate days as per standard procedure to measure fecal blood levels using the HemoQuant test (Rockey et al, 1999; Barber et al, 2002; Harewood et al, 2002). At the Screening, Month 6, Month 9, and Month 12 (EOT) site visits, Investigative sites will distribute instructions and supplies for home specimen collection to the subject. For 3 days prior to and during the days of stool sample collection, subjects will refrain from eating red meat and taking high dose aspirin as detailed in Section 9.1.4. Subjects will collect their specimens and are responsible for shipping to the central laboratory for testing; specimen collection and shipping should be conducted within one week following the site visit.
- Urinalysis: Urinalysis will include bilirubin, blood, glucose, ketones, pH, protein, specific gravity and microscopic examination (only if urinalysis is positive for blood or protein).
- Urine-albumin-to-creatinine ratio (UACR): UACR will be determined on urine samples collected at the Baseline, Month 6, Month 9, and Month 12 (EOT) visits; subjects should refrain from heavy exercise 24 hours before these visits.
- Pharmacokinetic analysis: Analysis of plasma samples for AKB-9778 concentration determinations will be performed by a central PK laboratory using a validated Liquid Chromatography-Mass Spectrometry and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) method. Detailed instructions for processing and shipment of samples will be provided by the Sponsor or Central laboratory

- Biomarker analysis in Plasma: Biomarkers will be assessed in plasma samples. Detailed instructions for processing and shipment of samples for biomarker analyses will be provided by the Sponsor or Central laboratory.
- Genetic analysis: Detailed instructions for processing and shipment of samples for biomarker analyses will be provided by the Sponsor or Central laboratory.

9.3 Schedule of Activities

The Schedule of Activities is presented in Appendix A and shows the timing of planned study procedures to be conducted at the study site and at the home care nursing visits. Every effort should be made to adhere to the procedure schedule and all assessments should be completed at each study visit.

The Screening, Baseline, Treatment, and Follow-up Periods will require subject participation for approximately 56 weeks.

Study procedures, clinical assessments (including laboratory assays), and PK, biomarker and genetic sampling will be performed as indicated in the Schedule of Activities.

Subjects will be responsible for self-administration of study medication which is provided in prefilled sterile syringes. The subject will self-inject BID on a morning and evening schedule as detailed in Section 8.3.5. Subjects will dose BID with the exception of Day 1 when the subject will dose the first (AM) dose at the clinic and will begin the BID dosing schedule on Day 2. No PM dose will be taken on Day 1.

At the visit on Day 1, the site will train the subject on SC study medication administration and dosing diary completion. After the pre-dose activities have been completed, the subject will self-administer the AM dose of study medication.

After the subject has completed the EOT visit, no further subcutaneous dosing will occur.

Study visits on Day 1, Month 6 and Month 12 EOT should be scheduled for the morning. The remainder of the site visits should also be scheduled for the morning when possible. Subjects will maintain a daily study medication diary and will record timing and location of dose.

At the site visits on Day 1 and Months 1 through 11, subjects will be dispensed subcutaneous study medication and dosing supplies.

Subjects discontinuing study medication sooner than the planned 12-month dosing period or withdrawing from the study should complete the Month 12 EOT assessments including the EOT assessments at the EOT site visit (See Section 9.3.2.16) and the EOT homecare nurse visit (See Section 9.3.3.5).

Detailed descriptions of procedures and activities to be followed during each site and homecare nurse visit are presented in the following sections. For specific time points please refer to the Schedule of Activities in Appendix A. Procedures and activities to be conducted at the investigative site are presented in Section 9.3.2 followed by procedures to be conducted at the homecare nurse visits presented in Section 9.3.3.

9.3.1 Visit Windows

Plasma PK samples collected at 30 and 90 minutes after dosing of study medication on Day 1 and Month 6 should be collected within ±10 minutes of the target time. If for any reason, the sampling time point for a given sample falls outside of the visit window, the sample must still be collected. For all samples; the exact time of sample collection will be recorded.

Blood pressure and heart rate evaluations performed must be conducted within ±20 minutes of the designated time.

Subjects will only use AM syringes for dose administration in the morning and PM syringes for dose administration in the evening. Subjects should administer their daily doses around the same time every morning and evening, if possible. If a dose is missed, this dose should be skipped and the subject should maintain the morning and evening dosing schedule.

The Day 7 phone call must be conducted within ±3 days.

Site visits scheduled for Months 1 through 12 should be conducted within 28 days times the study month number ±3 days relative to the baseline visit (e.g. Month 1 visit window is 28 ±3 days from Day 1, Month 2 visit window is 56 ±3 days from Day 1, etc.).

Homecare nurse visits scheduled for Screening, Months 3, 6, 9 and 12 should be conducted within 1 week after the corresponding site visit. The Follow-up homecare visit occurs 4 weeks ±3 days after the EOT visit at the site.

The fecal occult blood specimen collection and shipping to the Central Laboratory should be conducted by the subject within the week following the corresponding site visit.

9.3.2 Activities to be conducted at the Study Site

9.3.2.1 Screening Visit

The Screening visit must be performed within 28 days prior to dosing. The Investigator will maintain a log of subjects screened and indicate who was enrolled or excluded and the reason for exclusion (Section 9.1.2).

After obtaining informed consent and receiving a unique subject number, subjects will undergo a number of screening activities.

If possible, all screening activities should be conducted on the same day. At the Screening visit, the following activities/procedures will be performed:

- Informed consent obtained
- Assignment of subject number
- Review of eligibility criteria
- Demographics
- Medical/ophthalmic history including treatment history for DR/DME
- Temperature, height and weight
- 12 Lead ECG (prior to vital signs and blood draws)
- Vital signs:
    - sitting blood pressure and heart rate measurements
- Eye and Vision Exams:

  - ETDRS BCVA
  - slit-lamp biomicroscopy
  - IOP
  - dilated indirect ophthalmoscopy
  - SD OCT
  - fundus photography (and UWF fundus photography at select sub-study sites)
  - fluorescein angiography (or UWF fluorescein angiography at select sub-study sites)
- Laboratory Procedures
  - serum pregnancy test for women of childbearing potential
  - hematology
  - clinical chemistry
- Concomitant Medication recording
- AE monitoring
- Dispense instructions and kit for subject to perform home fecal occult blood specimen collection

9.3.2.2 Baseline Period (Pre-Treatment, Day 1)

Eligible randomized subjects will be dosed at the Site on Day 1. At Baseline on Day 1, the following activities/procedures will be performed prior to any dosing of study medication:

- Interim medical/ophthalmic history
- Vital signs (to be performed within 2 hours prior to dosing and prior to blood draws):
  - sitting blood pressure and heart rate measurements
- Eye and Vision Exams:
  - ETDRS BCVA
  - slit-lamp biomicroscopy
  - IOP
  - dilated indirect ophthalmoscopy
  - ERG (at select sub-study sites)
  - OCT-A (at select sub-study sites)
- Laboratory Procedures
  - urine pregnancy test for women of childbearing potential (results must be known prior to dosing)
  - hematology
  - clinical chemistry
  - urinalysis
  - biomarker blood sampling
  - blood sampling for genetic analysis
- Concomitant Medication recording as needed
- AE monitoring

9.3.2.3 Treatment Period – Day 1

Following Baseline on Day 1, the following activities/procedures will be performed at the site

- Train subject on self-administration of study medication and diary completion. Distribute diaries.
- Subjects should eat a snack or meal and drink 1-2 glasses of fluid (See Section 9.1.4) within 1 hour to 30 minutes prior to dosing.
- Dose administration:
  - Subjects will self-dose the AM dose in the seated position and remain seated for 30 minutes following dosing.
- Sitting blood pressure and heart rate measurements will be conducted at 30 and 90 minutes after dosing. These assessments are to be conducted prior to any blood draws.
  - *If a subject develops symptoms of lightheadedness, presyncope, or of possible hypotension, consistent with medical practice it is recommended that the blood pressure and heart rate be re-measured and the subject placed in the supine position until symptoms resolve. The Investigator should also contact the study medical monitor.*
- PK blood sampling at 30 and 90 minutes after dosing. Sampling is to be conducted after blood pressure and heart rate measurements are completed.
- AE monitoring
- Concomitant Medication recording as needed
- Dispense 1 month supply of study medication kits and study medication diary.

9.3.2.4 Treatment Period – Day 7 (Week 1 Phone call)

- AE monitoring and AE recording since last visit
- Question subject regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication

9.3.2.5 Treatment Period – Month 1 Visit (Week 4)

- Vital signs:
  - sitting blood pressure and heart rate measurements
- Eye and Vision Exams:
  - ETDRS BCVA
- Laboratory Procedures
  - clinical chemistry
- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit
- Dispense 1 month supply of study medication kits

9.3.2.6 Treatment Period – Month 2 Visit (Week 8)

- Vital signs:
  - sitting blood pressure and heart rate measurements
- Eye and Vision Exams:
  - ETDRS BCVA
- Laboratory Procedures
  - hematology

  - clinical chemistry
- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit
- Dispense 1 month supply of study medication.

9.3.2.7 Treatment Period – Month 3 Visit (Week 12)

- Vital signs
  - sitting blood pressure and heart rate measurements
- Eye and Vision Exams:
  - ETDRS BCVA
  - slit-lamp biomicroscopy
  - IOP
  - dilated indirect ophthalmoscopy
  - SD OCT
  - fundus photography
  - ERG (at select sub-study sites)
  - OCT-A (at select sub-study sites)
- Laboratory Procedures
  - clinical chemistry
- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit
- Dispense 1 month supply of study medication kits

9.3.2.8 Treatment Period – Month 4 Visit (Week 16)

- Vital signs
  - sitting blood pressure and heart rate measurements
- Eye and Vision Exams:
  - ETDRS BCVA
- Laboratory Procedures
  - hematology
  - clinical chemistry
- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit
- Dispense 1 month supply of study medication kits

9.3.2.9 Treatment Period – Month 5 Visit (Week 20)

- Vital signs
  - sitting blood pressure and heart rate measurements
- Eye and Vision Exams:
  - ETDRS BCVA
- Laboratory Procedures

  - clinical chemistry
- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit
- Dispense 1 month supply of study medication kits

9.3.2.10 Treatment Period – Month 6 Visit (Week 24)

Given that post-dose PK sample collection is included in this visit, subjects will be instructed to not administer their AM dose prior to their visit and to bring their AM dose along with other study medication in kits, as the AM dose will be administered in the clinic.

- Weight and Temperature
- 12 Lead ECG (prior to vital signs and blood draws)
- Vital signs
  - sitting blood pressure and heart rate measurements
- Eye and Vision Exams:
  - ETDRS BCVA
  - slit-lamp biomicroscopy
  - intraocular pressure
  - dilated indirect ophthalmoscopy
  - SD OCT
  - fundus photography (and UWF fundus photography at select sub-study sites)
  - fluorescein angiography (or UWF fluorescein angiography at select sub-study sites)
  - ERG (at select sub-study sites)
  - OCT-A (at select sub-study sites)
- Laboratory Procedures
  - urine pregnancy test for women of childbearing potential
  - hematology
  - clinical chemistry
  - urinalysis
- Subjects should eat a snack or meal and drink 1-2 glasses of fluid (See Section 9.1.4) within 1 hour to 30 minutes prior to dosing.
- Dose administration:
  - Subjects will self-dose AM dose in the seated position and remain seated for 30 minutes following dosing.
- Sitting blood pressure and heart rate measurements will be conducted at 30 and 90 minutes after dosing. These assessments are to be conducted prior to any blood draws.
- PK blood sampling at 30 and 90 minutes after dosing. Sampling is to be conducted after blood pressure and heart rate measurements are completed.
- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit

- Dispense 1-month supply of study medication kits
- Dispense instructions and kit for subject to perform home fecal occult blood specimen collection

9.3.2.11 Treatment Period – Month 7 Visit (Week 28)

- Vital signs
  - sitting blood pressure and heart rate
- Eye and Vision Exams:
  - ETDRS BCVA
- Laboratory Procedures
  - clinical chemistry
- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit
- Dispense 1 month supply of study medication kits

9.3.2.12 Treatment Period – Month 8 Visit (Week 32)

- Vital signs
  - sitting blood pressure and heart rate
- Eye and Vision Exams:
  - ETDRS BCVA
- Laboratory Procedures
  - hematology
  - clinical chemistry
- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit
- Dispense 1 month supply of study medication kits

9.3.2.13 Treatment Period – Month 9 Visit (Week 36)

- Vital signs
  - sitting blood pressure and heart rate measurements
- Eye and Vision Exams:
  - ETDRS BCVA
  - slit-lamp biomicroscopy
  - intraocular pressure
  - dilated indirect ophthalmoscopy
  - SD OCT
  - fundus photography
  - ERG (at select sub-study sites)
  - OCT-A (at select sub-study sites)
- Laboratory Procedures
  - clinical chemistry
  - urinalysis

- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit
- Dispense 1 month supply of study medication kits
- Dispense instructions and kit for subject to perform home fecal occult blood specimen collection

9.3.2.14 Treatment Period – Month 10 Visit (Week 40)

- Vital signs
  - sitting blood pressure and heart rate
- Eye and Vision Exams:
  - ETDRS BCVA
- Laboratory Procedures
  - hematology
  - clinical chemistry
- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit
- Dispense 1-month supply of study medication kits

9.3.2.15 Treatment Period – Month 11 Visit (Week 44)

- Vital signs
  - sitting blood pressure and heart rate
- Eye and Vision Exams:
  - ETDRS BCVA
- Laboratory Procedures
  - clinical chemistry
- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit
- Dispense 1-month supply of study medication kits

9.3.2.16 Treatment Period – Month 12 End of Treatment Visit (Week 48)

- 12 Lead ECG (prior to vital signs and blood draws)
- Weight and temperature
- Vital signs
  - sitting blood pressure and heart rate measurements
- Eye and Vision Exams:
  - ETDRS BCVA
  - slit-lamp biomicroscopy
  - intraocular pressure
  - dilated indirect ophthalmoscopy
  - SD OCT
  - fundus photography (and UWF fundus photography at select sub-study sites)

  - fluorescein angiography (or UWF fluorescein angiography at select sub-study sites)
  - ERG (at select sub-study sites)
  - OCT-A (at select sub-study sites)
- Laboratory Procedures
  - urine pregnancy test
  - hematology
  - clinical chemistry
  - urinalysis
  - biomarker blood sampling
- AE monitoring and AE recording since last visit
- Concomitant Medication recording as needed since last visit
- Collect returned used supplies and review medication use since last visit
- Dispense instructions and kit for subject to perform home fecal occult blood specimen collection

9.3.3 Activities to be conducted at the Homecare nurse visit

Homecare nurse visits scheduled for Screening, Months 3, 6, 9 and 12 should be conducted within 1 week after the corresponding site visit. The Follow-up homecare visit occurs 4 weeks ±3 days after the EOT visit at the site. Nurse visits will likely occur at subject's home; however alternate locations acceptable to the subject are allowed (e.g. investigative site).

Investigative sites will distribute instructions and kits for the subject to perform home fecal occult blood specimen collection and shipping to the Central Laboratory; nurses will review status of specimen collection and shipping with subjects on corresponding homecare visits.

During homecare nurse visits, if any change in status, the nurse will contact the Investigator, so that the Investigator can assess for any new adverse event or change in status of existing adverse event, and document and report accordingly.

9.3.3.1 Screening Visit

- Body systems assessment
- Review Status of fecal occult blood testing

9.3.3.2 Treatment Period – Month 3 Visit (Week 12)

- Body systems assessment

9.3.3.3 Treatment Period – Month 6 Visit (Week 24)

- Body systems assessment
- Review status of fecal occult blood testing

9.3.3.4 Treatment Period – Month 9 Visit (Week 36)

- Body systems assessment
- Review status of fecal occult blood testing

9.3.3.5 Treatment Period – Month 12 Visit (Week 48)

- Body systems assessment
- Review status of fecal occult blood testing

9.3.3.6 Follow-up Period -1 Month (4 weeks) Post-Treatment Visit (Week 52)

- Medical history since last visit
- Body systems assessment

10 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events (AEs)

An adverse event (AE) is any untoward medical occurrence in a patient or trial subject administered a drug or biologic (medicinal product) or using a medical device; the event does not necessarily have a causal relationship with that treatment or usage.

AEs include the following:

- All suspected adverse medication reactions.
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a preexisting illness (see paragraph below on Preexisting Conditions).
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness), the accident (e.g., fall secondary to dizziness), and any adverse outcome (e.g., hip fracture secondary to the fall) should be reported as three separate adverse events.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (e.g., elevated liver enzymes in a subject with jaundice) should be described under Comments on the report of the clinical event (e.g., jaundice) rather than listed as a separate adverse event.

Procedures – Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy noted under Comments.

Preexisting Conditions – In this trial, a preexisting condition (i.e., a disorder present before the adverse event reporting period) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

Abnormal Test Findings – All laboratory test results will be reviewed by the Investigator. The Investigator will utilize his/her judgment in determining if out of range laboratory values are clinically significant and should denote this using the abbreviation "CS" on the laboratory report for source documentation. Laboratory tests that are labeled as clinically significant should be reported as AEs, either separately or as part of a description of a symptomatic AE. If there are significant changes in a laboratory report from a previous visit that are determined to be clinically significant, these should also be reported as AEs. Any abnormal laboratory value which requires treatment or further diagnostic testing and/or results in discontinuation from study should be reported as AEs.

10.1.2 Serious Adverse Events (SAEs)

Each adverse event is to be classified by the Investigator as SERIOUS or NONSERIOUS. An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death
- Is life -threatening (see paragraph below on Life-threatening)
- Requires in -patient hospitalization or prolongation of existing hospitalization (see paragraph below on Hospitalization)
- Results in persistent or significant disability/incapacity (see paragraph below on Disability)
- Is a congenital anomaly/birth defect

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

The term serious also includes any other event that the Investigator or Sponsor judges to be serious or which is defined as serious by the regulatory agency in the country in which the event occurred. If there is any doubt whether the information constitutes an AE or SAE, the information is to be treated as an SAE.

Life-threatening – Any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis of a more severe nature can be fatal.

Hospitalization – Hospitalization is defined as an overnight admission with observation of a minimum of 24 hours. A hospitalization planned before the start of the study for a preexisting condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a

total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the course of the study).

Disability – Defined as a substantial disruption in a person's ability to conduct normal life functions.

10.1.3 Severity

The Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

MILD:	Does not interfere with subject's usual function
MODERATE:	Interferes to some extent with subject's usual function
SEVERE:	Interferes significantly with subject's usual function

Note the distinction between the gravity and the intensity of an adverse event. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

10.2 Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs at each site visit following the initiation of treatment.

10.3 Reporting

Each AE is to be classified by the Investigator as SERIOUS or NONSERIOUS. This classification of the gravity of the event determines the reporting procedures to be followed. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

All AEs that occur in study subjects during the adverse event reporting period specified in the protocol must be reported, WHETHER OR NOT THE EVENT IS CONSIDERED MEDICATION RELATED.

10.3.1 Reporting Period

The AE reporting period for this study begins from the time of informed consent and ends at the final protocol required visit.

IN ADDITION, any known untoward event that occurs subsequent to the AE reporting period that the Investigator assesses as possibly or probably related to the study medication should also be reported as an AE.

10.3.2 Reporting AEs

NONSERIOUS AEs are to be reported on the adverse event case report forms.

10.3.3 Reporting SAEs

Serious adverse events should be reported on both the clinical trial adverse event CRF *and* the Serious Adverse Event Report Form.

Note: Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

Any SAE, regardless of causal relationship, must be reported to the Sponsor within 24 hours after the Investigator becomes aware of the SAE by completing and sending an SAE report form. Compliance with this time requirement is essential so that the Sponsor may comply with its regulatory obligations.

The initial SAE report should be completed as fully as possible but should contain, at a minimum:

- A description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name and site identification number
- Name of the suspected medicinal product (not applicable for double-masked studies)
- Causality assessment

Follow-Up information relating to an SAE must be reported to the clinical safety contact at the Sponsor within 24 hours of receipt by the Investigator by sending a completed SAE report form with new information. The subject should be observed and monitored carefully until the condition resolves or stabilizes.

All deaths are to be thoroughly investigated and reported. Autopsy reports are to be obtained, if possible.

The Sponsor and/or its designee are responsible for reporting SAEs to all applicable regulatory agencies and the central ethics committees within the required timeline.

The Investigator is responsible for submitting required safety information to their local IRB. This information includes but is not limited to any safety alert letter received from the Sponsor and any SAEs occurring at their site.

10.3.4 Relationship to Study Medication

The causal relationship of the AE to study drug will be assessed by both the Investigator and the Sponsor. The following definitions will be used in assessment.

Probably Related: The AE follows a reasonable temporal sequence from the time of drug administration. It follows a known response pattern to the study drug. The AE cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs.

Possibly Related: The AE follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs.

Unrelated: The AE does not follow a reasonable temporal sequence from administration of the product or the AE is clearly related to other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.

10.3.5 Follow-Up of Unresolved Events

All AEs should be followed until they are resolved or the Investigator assesses them as chronic or stable or the subject's participation in the trial ends (i.e., until a final report is completed for that subject).

In addition, all serious adverse events and those nonserious events assessed by the Investigator as possibly or probably related to the study medication should continue to be followed even after the subject's participation in the trial is over. Such events should be followed until they resolve or until the Investigator assesses them as "chronic" or "stable."

10.4 Exposure *In Utero*

If any study subject becomes or is found to be pregnant while receiving study medication during the treatment period or within 30 days of discontinuing the study medication, the Investigator is to submit this information on a Pregnancy Notification Cover Sheet along with a completed Serious Adverse Event Form. This must be done irrespective of whether an AE has occurred. Pregnancy during this time frame of the female partner of a male subject should also be reported. To ensure subject safety, each pregnancy must be reported to the Sponsor's Medical Monitor or CRO designee within 24 hours of awareness of the pregnancy.

If the pregnancy of a female study participant is discovered during the study, study medication should be discontinued.

The Investigator will follow the subject (or female partner of a male subject) until completion of the pregnancy and will follow the neonate up to 1 month of birth.

Within 24 hours of awareness, Investigator sites will notify the Sponsor's Medical Monitor or CRO designee of abnormal pregnancy outcomes. Normal outcomes may be reported within 5 days of awareness. Reporting of outcome will be provided on the Pregnancy Reporting Form.

In addition to reporting the outcome on the Pregnancy Reporting Form, if the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion, stillbirth, neonatal death within one month of birth, or congenital anomaly [including that in an aborted fetus]), the Investigator should also follow the procedures for reporting a SAE within 24 hours of awareness.

Additional information about pregnancy outcomes follows:

- Note that "spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within one month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after one month that the Investigator assesses as possibly or probably related to the in utero exposure to the study medication should also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth.

- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

11 DATA ANALYSIS

11.1 Sample Size Determination

Estimates for sample size calculations are derived from published data from the analysis of the effect of ranibizumab (Lucentis) and aflibercept (Eylea) intravitreal administration regimens on DR severity score in the RISE/ RIDE studies and VIVID/VISTA studies, respectively, in which at least 28-46% of subjects improved by ≥ 2 steps after 12 months of treatment.

With 45 evaluable subjects per treatment group, the study has >85% power (based on Fisher's Exact Test and a 2-sided alpha =0.05) to demonstrate a statistically significant improvement in percent of subjects improving by ≥ 2 steps on the ETDRS severity scale, assuming underlying rates for active and placebo of 30% and 5%, respectively. Assuming 10% drop-out/non-evaluable rate, a sample size of 50 subjects per treatment arm (approximately 150 total) has been selected.

11.2 Study Populations

11.2.1 Safety Populations

The safety population will include all enrolled subjects who receive at least one (1) dose of study medication. All safety analyses will be conducted using the safety population.

11.2.2 Efficacy Populations

11.2.2.1 Modified Intent-to-Treat Population

The modified intent-to-treat (MITT) population will include all enrolled subjects who receive at least one dose of study medication. The primary efficacy analysis will be conducted using the MITT population.

11.2.2.2 Per Protocol Population

The per protocol (PP) population will consist of all subjects in the MITT population who do not have major protocol deviations considered to affect the primary efficacy variable DRSS, have completed a minimum of 12 months of treatment and have been at least 70% compliant. Sensitivity analyses of the primary efficacy variables will be conducted using the PP population.

11.3 Analysis of Demographics and Baseline Variables

Descriptive statistics (e.g., number of subjects, mean, standard deviation (SD), median, minimum, and maximum) will be generated for selected continuous variables (age, selected laboratory assays, vital signs, etc.) for each treatment group and for all subjects. The number and percentage of subjects in each class of categorical demographic and baseline variables (e.g., ethnicity, and race) will be tabulated for each treatment group and for all subjects. Individual subject demographic and baseline characteristic data will be listed.

11.4 Disposition of Subjects

The number and percentage of subjects who are enrolled, complete the study, discontinue study medication, or withdraw from the study including reasons for study medication discontinuation or study withdrawal will be summarized along with the number and percentage of subjects in each of the analysis populations (safety, MITT, and PP) in tabular format by treatment group and for all subjects. Individual subject disposition data will be listed.

11.5 Study Days and Assessment Windows

Study days will be numbered relative to the first day of dosing. The start of study (Day 1) will be defined as the date on which a subject takes the first dose of any study medication, as recorded on the CRF. Relative to study start, days will be numbered …-2, -1, 1, 2, ... with Day -1 being the day prior to the start of study medication (Pre-Dose).

Recorded data will be assigned to evaluation/assessment windows. If more than one clinical evaluation is made within a window for a particular visit, the record with the worst assessment will be used for the assessment in that window.

11.6 Safety Analysis

All subjects who receive at least one dose of any study medication will be included in the safety analysis. All safety endpoints are listed in Section 5.6.3.

All AEs reported during the study period will be recorded and coded using MedDRA terminology. An AE will be considered as treatment-emergent if it has an onset during the treatment period or is pre-existing and worsens after the first dose of study medication is administered. The incidence of all reported treatment-emergent adverse events (TEAEs) will be summarized using system organ class and preferred term by treatment group and overall, using counts and percentages. Separate analyses will be performed for ocular and non-ocular TEAEs. These summaries will also be provided for treatment related TEAEs and TEAEs by severity. For ocular TEAEs, the subject will be considered to have had the TEAE if at least one eye had the TEAE.

Continuous safety endpoints collected at each visit will be summarized with number of subjects, mean, standard deviation (SD), median, minimum, and maximum for each treatment group and for all subjects. Qualitative variables collected at each visit will be summarized using counts and percentages for each treatment group and for all subjects. Summaries will also include change from baseline and shift tables, where appropriate. Individual subject safety data will be listed.

11.7 Efficacy Analyses

All efficacy endpoints are listed in Sections 5.5 and 5.6. All efficacy data will be summarized by treatment group and time point using appropriate descriptive statistics. Summaries will be presented for both the MITT and PP populations. Due to the small number of subjects that are expected to be enrolled at each center, all summaries and analyses will be performed using data pooled across centers.

The primary hypotheses to be tested is that AKB-9778 15mg twice daily and AKB-9778 15mg once daily will be superior to placebo in the improvement of DR as measured by the ETDRS severity scale change from baseline at 12 months. Specifically, the primary endpoint is the

percentage of subjects with an improvement in study eye severity of DR (ETDRS DR Severity Score or DRSS) of ≥ 2 steps at Month 12 without need for treatment of PDR or DME (by IVT, laser, or vitrectomy) in the study eye. The primary hypotheses will be tested in the MITT population using a Fisher's Exact Test with a 2-sided 5% significance level. To adjust for multiplicity, a pre-specified testing order will be used. AKB-9778 15mg twice daily will be tested first, and AKB-9778 15mg once daily will be tested second. Details of how missing data will be handled for the primary endpoint, along with sensitivity analyses to assess the impact of missing data will be outlined in the statistical analysis plan (SAP).

Secondary and exploratory endpoints will be analyzed without adjustment for multiplicity, and all inferential analyses will use a 2-sided 5% significance level. Continuous variables will be analyzed using ANCOVA models and/or repeated measures mixed effect models and dichotomous variables will be analyzed using the same approach as outlined for the primary endpoint. Details of how missing data will be handled for secondary and exploratory endpoints will be provided in the SAP.

Exploratory analyses will be conducted to understand the relationship between exposure and response and details of these analyses will be outlined in the SAP.

11.8 Pharmacokinetic Analyses

AKB-9778 plasma concentrations will be summarized by treatment group and nominal sampling time using descriptive statistics. Individual subject pharmacokinetic data will be listed.

Additional analyses including the potential relationship of plasma concentration and selected safety and efficacy parameters and/or subject demographic variables will be performed.

11.9 Pharmacodynamic Analyses

Blood samples collected at baseline and Month 12 End of Treatment (EOT) will be retained for exploratory analysis of biomarkers in plasma. Once results of the study are known, the Sponsor will determine the value of conducting these analyses.

11.10 Exploratory Genetic Analyses

For subjects who have provided consent for genetic sampling, a blood sample will be retained for exploratory genetic analysis that may provide insight into the role of Tie2 in diabetic retinopathy and an individual subject's response to AKB-9778 treatment. Once results of the study are known, the Sponsor will determine the value of conducting these analyses.

12 DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms (CRFs)

Case Report Forms (CRFs) are required and should be completed for each included subject. The completed original CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor. CRFs for this study will be electronic (eCRFs).

The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms. The CRFs must be signed by the Investigator (for electronic CRFs, they can be signed electronically) to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs and source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are contained in the subject's chart at the hospital or the physician's office. In these cases, data collected on the CRFs must match the data in those charts.

12.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs, SAE forms, source documents, detailed records of drug disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to the International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever time period is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

13 QUALITY CONTROL (QC) AND QUALITY ASSURANCE (QA)

13.1 Study Site Monitoring Visits

During study conduct, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol, Good Clinical Practice (GCP), and applicable local regulations are being followed. The monitors will review source documents to confirm that the data recorded on CRFs is accurate. The Investigator/institution will allow Sponsor monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may also be subject to QA audits and Regulatory Inspections performed by the Sponsor or companies working with or on behalf of the Sponsor, and/or review by the IRB, and/or to inspection by appropriate regulatory authorities

It is important that the Investigator and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

13.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator should consult with the Sponsor or designee (and IRB, as required) to determine the appropriate course of action.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the Sponsor or its designee (and IRB, as required) immediately. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessments.

14 TRIAL DISCONTINUATION/INVESTIGATIVE SITE TERMINATION

The Sponsor reserves the right to discontinue the study prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating subjects within a time period specified by the Sponsor to inform them of the decision to discontinue the trial.

The study may also be put on hold or discontinued by IRB or Regulatory Authority.

14.1 Criteria for Premature Termination or Suspension of the Study

The following criteria may result in either temporary suspension or early termination of the study:

- New information regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

The Sponsor reserves the right to discontinue the trial for other valid administrative reasons.

14.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found to be in significant violation of GCP, protocol, contractual agreement, or is unable to ensure adequate performance of the study or guarantee safety of participating subjects.

14.3 Procedures for Premature Termination or Suspension of the Study or Investigational Site(s)

In the event that the Sponsor elects to terminate or suspend the study or the participation of an Investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable Investigational sites during the course of termination or study suspension.

15 ETHICS

15.1 Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

15.2 Institutional Review Board (IRB)

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, (e.g., recruitment advertisements, if applicable) from the IRB prior to implementation. All correspondence with the IRB should be retained in the Investigator File. Copies of IRB approvals should be forwarded to the Sponsor.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB and the Sponsor in writing immediately after the implementation.

15.3 Subject Information and Consent

It is the responsibility of the Investigator, or a person designated by the Investigator, to give each subject (or the subject's acceptable representative), prior to inclusion in the study, potential benefits of participation, and the possible risks involved. The Investigator should ensure all questions the subject may have regarding participation are answered. The process must be conducted in a language understood by the subject. The subject must be informed about their right to withdraw from the trial at any time without consequence.

Furthermore, it is the responsibility of the Investigator, or a person designated by the Investigator, to obtain a freely signed informed consent from each subject or the subject's legally acceptable representative prior to inclusion in the trial. The Investigator will retain the original of each subject's signed consent form. The subject (or the subject's acceptable representative) must be provided a copy of the signed form.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and the Sponsor before use. The Investigator must re consent subjects on updated material as required by the IRB and local regulatory, and legal requirements.

15.4 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that comes to the attention of the Investigator.

15.5 Subject Confidentiality

All parties will ensure protection of subject personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, the Sponsor will maintain high standards of confidentiality and protection of subject personal data.

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA), the Sponsor's designated auditors, and the appropriate IRB to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's CRF).

16 PUBLICATION OF STUDY RESULTS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Sponsor and the Investigator and/or the Investigator's institution. The Sponsor must have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including: Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

17 REFERENCES

Augustin HG, Koh GY, Thurston G, Alitalo K. Control of vascular morphogenesis and homeostasis through the angiopoietin-Tie system. Nat Rev Mol Cell Biol. 2009 Mar;10(3):165-77.

Barber MD, Abraham A, Brydon WG, et al. Assessment of faecal occult blood loss by qualitative and quantitative methods. J R Coll Surg Edinb. 2002 Apr;47(2):491-4.

Brindle NP, Saharinen P, Alitalo K. Signaling and functions of angiopoietin-1 in vascular protection. Circ Res. 2006 April 28; 98(8): 1014–1023.

Campochiaro PA, Khanani A, Singer M, et al; Enhanced benefit in diabetic macular edema from AKB-9778 Tie2 activation combined with vascular endothelial growth factor suppression. Ophthalmology. 2016 Aug;123(8):1722-30

Campochiaro PA, Sophie R, Tolentino M, et al. Treatment of diabetic macular edema with an inhibitor of vascular endothelial-protein tyrosine phosphatase that activates Tie2. Ophthalmology. 2015 Mar;122(3):545-54.

Davis JS, Yeo TW, Piera KA, Woodberry T, Celermajer DS, Stephens DP, et al. Angiopoietin-2 is increased in sepsis and inversely associated with nitric oxide-dependent microvascular reactivity. Crit Care. 2010;14(3):R89. Epub 2010 May 18.

Davis MD, Fisher MR, Gangnon RE, et al. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study Report #18. Invest Ophthalmol Vis Sci. 1998 Feb;39(2):233-52.

Fiedler U, Augustin HG. Angiopoietins: a link between angiogenesis and inflammation. Trends Immunol. 2006 Dec;27(12):552-8. Epub 2006 Oct 12.

Fong DS, Aiello LP, Ferris FL 3rd, Klein R. Diabetic retinopathy. Diabetes Care. 2004;27:2540-53.

Fong DS, Aiello L, Gardner TW, et al; American Diabetes Association. Retinopathy in diabetes. Diabetes Care. 2004;27 Suppl 1:S84-7.

Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Research and Clinical Practice. 2014.

Harewood GC, McConnell JP, Harrington JJ, et al. Detection of occult upper gastrointestinal tract bleeding: performance differences in fecal occult blood tests. Mayo Clin Proc. 2002 Jan;77(1):23-8.

Ip MS, Domalpally A, Hopkins JJ, Wong P, Ehrlich JS. Long-term effects of ranibizumab on diabetic retinopathy severity and progression. Arch Ophthalmol. 2012 Sep;130(9):1145-52.

Klein R, Klein BE, Moss SE. How many steps of progression of diabetic retinopathy are meaningful? The Wisconsin epidemiologic study of diabetic retinopathy. Arch Ophthalmol. 2001 Apr;119:547-53.

Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology, 2008. 115(11): p. 1859-68.

Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. Ophthalmology, 2009. 116(3): p. 497-503.

Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology. 2014 Nov;121:2247-54.

Llanos L, Moreu R, Ortin T, Peiro A, Pascual S, et al. Existence of a relationship between increased serum alanine aminotransferase levels (ALT) detected in premarketing clinical trials and postmarketing published hepatotoxicity case-reports. Alimentary Pharmacology and Therapeutics, Wiley, 2010, 31 (12), pp.1337.

Maa AY, Feuer WJ, Davis CQ, Pillow EK, et al. A novel device for accurate and efficient testing for vision-threatening diabetic retinopathy. J Diabetes Complications. 2016;30(3):524-32.

Milner CS, Hansen TM, Singh H, Brindle NP. Roles of the receptor tyrosine kinases Tie1 and Tie2 in mediating the effects of angiopoietin-1 on endothelial permeability and apoptosis. Microvasc Res. 2009 Mar;77(2):187-91. Epub 2008 Sep 20.

Peters KG, Kontos CD, Lin PC, Wong AL, Rao P, Huang L, et al. Functional significance of Tie2 signaling in the adult vasculature. Recent Prog Horm Res. 2004;59:51-71.

Rockey DC, Auslander A, Geenberg PD. Detection of upper gastrointestinal blood with fecal occult blood tests. Am J Gastroenterology. 1999. Vol. 94(2): 344-350.

Shen J, Frye M, Lee BL, et al. Targeting VE-PTP activates TIE2 and stabilizes the ocular vasculature. J Clin Invest 2014; 124:4564-76.

Yau JW, Rogers SL, Kawasaki R, et al. Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35:556-64.

18 APPENDICES

18.1 Appendix A: Schedule of Activities

Schedule of Activities [A]																	
	Screening	Baseline	Treatment Period [B]														F/U
	Day				Month												
Protocol Activities	Day - 28 to Day - 1	Day 1 Pre-Dose	Day 1	Day 7	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12 (EOT)	EOT + 1M
Informed Consent	X																
Eligibility Criteria	X																
Demographics	X																
Medical/Ophthalmic History	X	X															X
Height Weight and Temperature [C]	X									X						X	
Body System Assessments [D]	X						X			X			X			X	X
ECG [E]	X									X						X	
Vitals [F]																	
Sitting BP and HR	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Eye and Vision Exams																	
ETDRS BCVA	X	X			X	X	X	X	X	X	X	X	X	X	X	X	
Slit Lamp Biomicroscopy	X	X					X			X			X			X	
Intraocular Pressure	X	X					X			X			X			X	
Dilated Indirect Ophthalmoscopy	X	X					X			X			X			X	
SD OCT	X						X			X			X			X	
Fundus Photography[G]	X						X			X			X			X	
Fluorescein Angiography [H]	X									X						X	
OCT Angiography Sub Study [I]		X					X			X			X			X	
ERG Sub Study [I]		X					X			X			X			X	
Laboratory Procedures																	
Serum/Urine Pregnancy [J]	X	X								X						X	
Hematology[K]	X	X				X		X		X		X		X		X	
Chemistry [L]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis [M]		X								X			X			X	
Fecal Occult Blood Test [N]	X									X			X			X	
Biomarker Blood Sampling		X														X	
Blood sampling for Genetic Analyses		X															
PK Blood Sampling [O]			X							X							
Dosing [P]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study medication dispensing & return, diary review [Q]			X		X	X	X	X	X	X	X	X	X	X	X	X	
AE collection [R] [S]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review [T]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
[A] Assessments are conducted at the study site unless otherwise noted.																	

[B] Site visits scheduled for Months 1 through 12 should be conducted within 28 days times the study month number ±3 days relative to the baseline visit. Homecare nurse visits scheduled for Screening, Months 3, 6, 9 and 12 should be conducted within 1 week after the corresponding site visit. The Follow-up homecare nurse visit is to be conducted 4 weeks (± 3 days) after the EOT visit at the investigative site.
[C] Height is collected at screening only.
[D] Body system assessments are conducted at the home care nursing visit.
[E] ECGs will be performed after the subject rests in a supine position for approximately 5 minutes. ECGs should be taken prior to any vital sign assessments or blood draws.
[F] Assessments are conducted prior to any blood draws when possible. On Day 1, sitting BP and HR assessments will be conducted at Baseline (pre-dose) and at 30 and 90 minutes post-dose. On the Month 6 visit, sitting BP and HR assessments will be conducted prior to administration of the AM dose at the site and at 30 and 90 minutes after the AM dose.
[G] For sites participating in the UWF imaging sub study, at the Screening, Month 6 and Month 12 (EOT) vists, UWF fundus photographs will be obtained in addition to standard fundus photographs.
[H] For sites participating in the UWF imaging sub-study, UWF FA will be performed in lieu of FA.
[I] Performed only at sites with required equipment available.
[J] In women of child bearing potential, a serum pregnancy test will be conducted at the Screening visit. Prior to dosing on Day 1, a urine pregnancy test will be conducted on Day 1. At the Month 6 and Month 12 site visits, a urine pregnancy test will be conducted.
[K] HbA1C is conducted at Screening, Baseline, Month 6, and Month 12.
[L] eGFR will be determined on serum chemistry samples collected at the Screening, Baseline, Month 6, Month 9, and Month 12 (EOT) visits.
[M] UACR is measured at Baseline, Month 6, Month 9, and Month 12 (EOT) visits; subjects should refrain from heavy exercise 24 hours before these visits.
[N] Sites will distribute instructions and materials to subjects for home specimen collection and shipping to the central laboratory. Subjects will collect their specimens and are responsible for shipping to the clinical laboratory for testing; specimen collection and shipping should be conducted within one week following the site visit. Homecare nurses will review status of specimen collection and shipping with subjects.
[O] Subjects are to be instructed prior to the Month 6 visit to NOT take the AM dose prior to their visit and to bring their AM dose to the visit along with other study medication in kits, as the AM dose will be administered in the clinic on this visit. The post-dose PK sample collection on Day 1 and Month 6 is relative to time of dose administration. PK blood sampling is conducted at 30 and 90 minutes after dosing ± 10 minutes. PK blood samples are to be collected after vital signs are conducted.
[P] On Day 1 and Month 6, subjects will administer their AM dose at the site. Prior to dosing on these visits, subjects should eat a snack or meal and drink 1-2 glasses of fluid. Subjects will self-dose in the seated position and remain seated for 30 mins. Subjects will dose BID with the exception of Day 1 when the subject will dose the AM dose at the site and will begin the BID dosing schedule on Day 2.
[Q] At Baseline, subjects will be trained on administration of study medication. Subjects will be provided with a dosing diary and dosing supplies at Day 1, and monthly during the treatment period.
[R] All adverse events (serious and non-serious, and related and non-related) will be documented and recorded through the last protocol specified visit.
[S] If the home healthcare nurse identifies any potential AEs during the home visit, the nurse will communicate directly to the study site and the Investigator will be responsible for determination of AEs and any necessary follow-up with the subject
[T] All concomitant medications received up to and including 28 days prior to the start of study medication through the Month 12 visit will be recorded.

18.2 Appendix B: Criteria for Treatment of PDR or DME in the Study Eye or Qualified Fellow Eye During the Study

Standardizing the criteria to treat PDR or DME during this study will allow for enhanced evaluation of the effect of AKB-9778 monotherapy on diabetic retinopathy. These criteria have been adapted from the DRCR.net Protocol W (http://drcrnet.jaeb.org/Studies.aspx?RecID=340).

If a study eye or qualified fellow eye treated for PDR or DME, study medication may be discontinued at the discretion of the Investigator and subject. If a non-qualified fellow eye requires treatment for PDR or DME, the subject will remain in the study.

- *Criteria for treatment of PDR or DME in the study eye or qualified fellow eye and allowed treatments are presented below. Non-qualified fellow eyes may be treated at the discretion of the Investigator.*
- *Refer to Section 8.4.3 for additional details regarding assessments to be conducted prior to treatment of PDR or DME.*

Treatment for PDR in the study eye or qualified fellow eye should not be given unless at least one of the following is present:

1. Neovascularization of the angle or neovascular glaucoma
2. Neovascularization of the disc (NVD) greater than standard photograph 10A (1/4 to 1/3 disc area)
3. Any NVD *with* pre-retinal or vitreous hemorrhage
4. Neovascularization elsewhere (NVE) greater than ½ disc area *with* pre-retinal or vitreous hemorrhage
5. Vitreous hemorrhage (VH) requiring treatment that is presumed to be from PDR
6. If none of the above is met, Reading Center confirmation of neovascularization within the 7-field fundus photo area should be obtained prior to initiating treatment whenever possible

   Treatment of neovascularization outside of the 7-field fundus photo area without the presence of pre-retinal or vitreous hemorrhage is discouraged (If the Investigator believes treatment for peripheral neovascularization is necessary, the sponsor should be informed prior to initiation).

Treatment for PDR can include:

1. Anti-VEGF IVT
2. PRP / sector Laser photocoagulation
3. Vitrectomy

Treatment for DME in the study eye or qualified fellow eye should not be given unless there is center-involved DME on clinical exam with ≥ 10% increase in CST from baseline and:

1. ≥ 10 letter loss of BCVA at a single visit or
2. 5 to 9 letter loss of BCVA at 2 consecutive visits

Treatment for DME can include:

1. Anti-VEGF or steroid IVT
2. Grid / focal Laser photocoagulation