CLINICAL PROTOCOL SYNOPSIS

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…..TBD
Sponsor:	Aerpio Therapeutics, Inc. 9987 Carver Road Suite 420 Cincinnati, OH 45242

Method of Action and Drug Summary

Aerpio has developed a first-in-class small molecule approach to the treatment of diabetic retinopathy. This approach is based on the discovery that restoration of Tie2 activity directly addresses the pathophysiology of diabetic retinopathy by enhancing endothelial survival and function and improving vascular stability, resulting in decreased vascular leak and reduced pathologic angiogenesis. Importantly, the Tie2/Ang pathway has been implicated in vascular destabilization that precedes ischemia in diabetic eye disease. In a completed Phase 2a study (TIME-2), AKB-9778 subcutaneous administration has demonstrated synergistic benefit with standard of care anti-VEGF therapy in the treatment of DME; subcutaneous AKB-9778 monotherapy also demonstrated the ability to improve underlying diabetic retinopathy by 2 or more steps in both study and fellow eyes without the need for intraocular injections (Campochairo et al., Ophthalmology, 2016). AKB-9778 is therefore being developed as a novel therapy for the treatment of diabetic retinopathy prior to the development of sight-threatening conditions of DME and PDR.

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 **3.** To explore the effects of AKB-9778 on biomarkers in plasma 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

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.** 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.** Mean change from baseline in ETDRS Best Corrected Visual Acuity (BCVA) letter score in the study eye at Month 12 **6.** Proportion of patients developing center-involved DME or PDR or PDR-related outcomes during study. **7.** Primary and secondary endpoints (1 through 4) assessed at Months 3, 6 and 9 **8.** Primary and secondary assessments in all fellow eyes, fellow eyes that meet all inclusion criteria, 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 **2.** Mean change from baseline in biomarkers in plasma at Month 12 **Exploratory Sub-Study Efficacy 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 **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 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.** 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), Central subfield thickness (CST) of < 300 µm 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. Exploratory evaluations include pharmacokinetic and biomarker assessments. Exploratory efficacy assessments (OCT-A and non-invasive ERG) will also be included at a subset of sites. A blood sample will be retained for genetic analysis. See detailed study design description below.
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 40 sites
Volume of Blood Drawn:	Hematology (8 X 2 mL) Chemistry (14 X 1 mL) Serum Pregnancy (1 X 1.5 mL) Pharmacokinetic Samples (4 X 6 mL) Exploratory Biomarker (2 X 3 mL) Genetic Sample (1 X 8 mL) Total volume blood drawn for entire study: Approximately 70 mL per subject.

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 (SC) AKB-9778 administered 15 mg QD or 15 mg BID in subjects with moderate to severe NPDR. Exploratory evaluations include pharmacokinetic and biomarker assessments; and OCT-A, non-invasive ERG and contrast sensitivity assessments at a subset of sites. A blood sample will be retained for 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 40 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 masked 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. 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. Seven-field 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.

Spot UACR and eGFR will be assessed at baseline, and thereafter every 12 weeks as exploratory assessments to evaluate for any potential effects on renal function.

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.

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 only be responsible for providing the fecal occult collection kit and the instructions to the subject for obtaining and shipping to the central laboratory. 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).

In addition to the assessments at the study site visits, at Screening and every three months during the treatment period, subjects will also be visited at their homes by a home healthcare nurse, who will conduct body system assessments (similar to a physical exam) and review status of specimen collection for fecal occult blood testing (on relevant visits). The home health care nurse will also conduct the 12 month Follow-Up visit. At this visit, the nurse will collect medical history and conduct a body system assessment. 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).

Key Inclusion Criteria

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/m2, inclusive.
3. Diagnosis of diabetes mellitus (type 1 or type 2).

4. Ability to compliantly self-administer subcutaneous study medication twice daily for 12 consecutive months.

Subject-Level Exclusion Criteria:

1. Hemoglobin A1C (HbA1C) ≥ 12.0% at Screening.
2. 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.
3. Resting (sitting) systolic BP of <100 mmHg at Screening.
4. A history of symptomatic orthostatic hypotension, vasovagal syndrome, syncope, or presyncope within one year prior to Screening.
5. Initiation of nitrate medications or history of nitrate-associated orthostatic symptoms within one month prior to Screening.
6. Any hospitalization or history of stroke, transient ischemic attack, congestive heart failure > NYHA Class 1, angina, or acute coronary syndrome within 3 months prior to Screening or any acute cardiology medical issues within 30 days prior to screening.
7. 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.
8. QTcF > 470 ms.
9. 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.
10. Serum transaminase ([AST] and [ALT]) levels > 2X the upper limit of normal (ULN). (May be repeated once).
11. History of clinically significant chronic liver disease (defined as any complication of liver disease, ascites, varices, hepatic encephalopathy, hepatocellular cancer).
12. History of chronic renal failure (stage 4 or 5).
13. History of gastrointestinal bleeding within the last year, or any history of bleeding due to arteriovenous malformation.
14. Fecal occult blood > 4.0 mg total hemoglobin/g feces as determined by the central laboratory (collected at home and shipped directly to the central laboratory)
15. Presence of New York Heart Classification congestive heart failure class III or IV.
16. Severe aortic stenosis.
17. Chronic anticoagulation with warfarin, a direct acting anticoagulant, or antiplatelet agent (other than low dose aspirin).
18. History of any solid organ transplant or bone marrow transplant, requiring immunosuppressive medications.
19. History of allergy to fluorescein.

Study Eye / Qualified Fellow Eye Inclusion Criteria:

1. Moderate to very 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 the past 6 months
4. ETDRS BCVA letter score ≥ 70 (Snellen 20/40 or better).

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) that is likely to decrease visual acuity by three lines or more (i.e., cataract would be reducing acuity to 20/40 or worse if eye was otherwise normal).
2. Any other ocular disease that may cause substantial reduction in visual acuity, including iris neovascularization, retinal detachment, visually significant epiretinal membrane, 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 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. History of prior treatment with IVT anti-VEGF or IVT corticosteroid within 12 months prior to Day 1, or history of prior treatment with Iluvien® within 36 months prior to Day 1.
12. Prompt PRP or IVT anti-VEGF or IVT corticosteroid treatment required.
13. History of treatment with any drug that has not received regulatory approval (e.g., off-label use) within 30 days or 5 half-lives of the medication, whichever is longer.
14. Uncontrolled glaucoma defined as IOP ≥ 30 mmHg on maximum IOP reduction therapy.
15. 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.

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	
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			X	
Fundus Photography	X						X			X			X			X	
Fluorescein Angiography	X									X						X	
OCT Angiography Sub Study [G]		X					X			X			X			X	
ERG Sub Study [G]		X					X			X			X			X	
Laboratory Procedures																	
Serum/Urine Pregnancy [H]	X	X														X	
Hematology	X	X				X		X		X		X		X		X	
Chemistry[I]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis		X					X			X			X			X	
Fecal Occult Blood Test [J]	X									X			X			X	
Biomarker Blood Sampling		X														X	
Blood sampling for Genetic Analyses		X															
PK Blood Sampling [K]			X							X							
Dosing [L]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study medication dispensing & return, diary review [M]			X		X	X	X	X	X	X	X	X	X	X	X	X	
AE collection [N] [O]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review [P]	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] Visit windows during Treatment period are ± 3 days for site visits. Homecare nurse visits scheduled for Screening, Months 3, 6, 9 and 12 must 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 postdose. 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] Performed only at sites with required equipment available.

[H] 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 12 site visit, a urine pregnancy test will be conducted.

[I] HbA1C is conducted at Screening, Baseline, Month 6, and Month 12.

[J] Sites will distribute instructions and materials to subjects for home specimen collection and shipping to the clinical 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 the week following the site visit. Homecare nurses will review status of specimen collection and shipping with subjects.

[K] 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.

[L] On Day 1 and Month 6, subjects will dose 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.

[M] 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.

[N] All adverse events (serious and non-serious, and related and non-related) will be documented and recorded through the last protocol specified visit.

[O] 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

[P] 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.