ASCLEPIX THERAPEUTICS, INC.

Phase 1/2a Study of the Safety and Bioactivity of AXT107 in Subjects with Diabetic Macular Edema (DME)

Study Abbreviated Title	CONGO study
Protocol Number:	AXT107-CS101
Study Phase:	1/2a
US IND #:	
Investigational Product:	AXT107
Sponsor Name and Address:	AsclepiX Therapeutics, Inc. 301 W 29th Street, Suite 2004 Baltimore, MD 21211
Serious Adverse Event Reporting:	safetygroup@clinipace.com
Medical Safety Physician Contact Information:	Quan Dong Nguyen, MD Email: safety@asclepix.com Phone: 1-410-802-8321
Investigator Agreement:	I have read the content of this clinical protocol and agree to maintain confidentiality of all information received or developed in connection with this protocol. I agree to conduct the study in compliance with the clinical protocol, GCP, the ethical principles contained within the Declaration of Helsinki, and all applicable regulatory requirements. I agree to initiate this study only upon obtaining written approval by the appropriate IRB or EC, and once I have complied with all financial and administrative requirements of the governing body of the clinical institution and the Sponsor.
PRINCIPAL INVESTIGATOR:	
	Signature/Date: _____ / _____
	Name:
	Address:
	Phone:

ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
AMD	Age-related Macular Degeneration
BCVA	Best Correct Visual Acuity
CRF	Case Report Form
CRO	Clinical Research Organization
CST	Central Subfield Thickness
DFE	Dilated Fundus Examination
DMC	Data Monitoring Committee
DME	Diabetic Macular Edema
DRSS	Diabetic Retinopathy Severity Scale
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FDA	Food and Drug Administration
FP	Fundus Photography
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HGF	Hepatocyte Growth Factor
ICF	Informed Consent
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF-1	Insulin Growth Factor-1
IND	Investigational New Drug
IOP	Intraocular Pressure
IRB	Institutional Review Board
mg	Milligram
mmHg	Millimeters Mercury
MOP	Manual of Procedures
MTD	Maximum Tolerated Dose
N/A	Not Applicable
nAMD	Neovascular (wet) Age-Related Macular Degeneration
NF-kB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
OCT-A	Optical Coherence Tomography Angiography
OU	Both Eyes
PDGF	Platelet Derived Growth Factor
PT	Preferred Term

SAE	Serious Adverse Event
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Study Eye
SOC	System Organ Class
Tie2	Tyrosine kinase with immunoglobulin-like and epidermal growth factor-like
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
VEGF	Vascular Endothelial Growth Factor
VE-PTP	Vascular Endothelial Protein Tyrosine Phosphatase

1. SYNOPSIS

Sponsor: AsclepiX Therapeutics, Inc.	
Name of Investigational Product: AXT107	Study Phase: 1/2a
Name of Active Ingredients: AXT107 is a 20-mer synthetic peptide derived from the non-collagenous domain of collagen IV that inhibits VEGF-A, VEGF-C and activates Tie2.	
Study Title: Phase 1/2a Study of the Safety and Bioactivity of AXT107 in Subjects with Diabetic Macular Edema (DME) – CONGO study	
Objectives: Primary Objective: To evaluate the safety and tolerability of a single injection of three dose levels (0.1 mg/eye, 0.25 mg/eye, or 0.5 mg/eye) of AXT107 in subjects with DME Secondary Objective: To evaluate the bioactivity and duration of action of AXT107 for the treatment of DME	
Methodology: This is an open-label, dose-escalating, 48-week study assessing the safety, tolerability, bioactivity and duration of action of a single intravitreal injection of 0.1 mg (low dose), 0.25 mg (mid dose), or 0.5 mg (high dose) AXT107 in approximately 18 subjects (up to 6 subjects per dose) with DME. Upon providing informed consent, subjects will be sequentially enrolled into the study. Decision regarding dose escalation will be based on the recommendation from the Data Monitoring Committee (DMC). The first 3 eligible subjects will receive the low dose of AXT107 injection. After the 3 low dose subjects complete a 7-day follow-up, the DMC will review their safety data. If an acceptable safety profile is determined by the DMC, 3 additional subjects will be enrolled to receive the mid dose of AXT107 injection. Upon completion of a 7-day follow-up, review of the safety data, and determination of an acceptable safety profile by the DMC for the mid dose subjects, 3 additional subjects will be enrolled to receive the high dose of AXT107 injection. For the first 9 subjects, treatment naïve patients CANNOT be enrolled. After the 9 initial subjects have completed the 7-day follow-up, 9 additional subjects (3 each to receive the low dose, mid dose, and high dose of the study drug) who can be previously treated or treatment naïve may be enrolled. In total, approximately18 subjects with DME will be enrolled and will be followed for 48 weeks. If the maximum tolerated dose (MTD) is not reached after the 0.5 mg group, a higher dose up to 1.0 mg may be tested. All subjects will attend a total of 16 visits: Screening (Day -14 to -1), Baseline (Day 0), Day 1 (Phone call), Week 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48. Stopping rules will be considered upon DMC decision if any of the following events are identified: • Decrease in Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) of ≥ 15 letters (3-line decrease) unrelated to the natural progression of the disease and determined by the Investigator to be related to the study drug in ≥ 2 subject • Intraocular inflammation (anterior or posterior) grade +2 or more in ≥ 2 subjects (using SUN Grading Working Group and Nussenblatt et al grading) • Increase in intraocular pressure (IOP) to ≥ 30mmHg for more than 24 hours post-injection in ≥ 2 subjects despite IOP lowering medication treatment	

- Any other serious ocular or systemic adverse event (AE) that, in the opinion of the Investigator, is related to the study drug in ≥ 1 subject

Rescue therapy with the Investigator's preferred treatment will be allowed starting at Week 12 for any subject who has received injection of AXT107 and for whom there is ≥ 7 letter ETDRS BCVA decrease from Baseline (Day 0) or ≥ 75 µm increase in Central Subfield thickness (CST) compared to the lowest previous visit.

Number of Subjects:

Approximately 18 subjects with diabetic macular edema secondary to type 1 or type 2 diabetes mellitus will be enrolled. The final number of subjects enrolled may be adjusted based on the presence of dose limiting toxicities.

Duration of the Study:

The expected duration of this clinical study is up to 50 weeks, including a 14-day screening phase and 48 weeks of on treatment/ follow up phase.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. 18 years of age or older
2. Type 1 or 2 diabetes mellitus with center-involved DME and with central subfield thickness ≥ 305 µm (females) or 320 µm (males) on Spectralis® Spectral Domain Optical Coherence Tomography (SD-OCT) device or 290 µm (females) or 305 µm (males) on Cirrus® SD-OCT device and with intraretinal or subretinal fluid as evidenced by Spectral Domain Optical Coherence Tomography (SD-OCT) in the study eye at Screening, as confirmed by the Investigator
3. BCVA in the study eye at Baseline (Day 0) between 65 and 23 ETDRS letters (20/40 and 20/320 Snellen equivalent) with BCVA decrement determined by the Investigator primarily attributable to DME
4. BCVA of 34 ETDRS letters or better (20/200 or better Snellen equivalent) in the non-study eye at Baseline (Day 0)
5. Able and willing to give signed informed consent and follow study instructions

Exclusion Criteria:

1. Any signs of high risk proliferative diabetic retinopathy in the study eye and related complications, as determined by the Investigator
2. Previously treated patients who are non-responders to anti-VEGF determined by the Investigator
3. Panretinal photocoagulation within 6 months or macular laser photocoagulation within 3 months from Screening in the study eye
4. Use of intraocular or periocular corticosteroids within 4 months (with the exception of fluocinolone acetonide intravitreal implant which is excluded), Aflibercept within 8 weeks, Ranibizumab and Bevacizumab within 6 weeks from Baseline (Day 0) in the study eye
5. Any concurrent disease that would require medical or surgical intervention during the study in the study eye (e.g. retinal detachment, significant cataract, uncontrolled glaucoma)
6. Any condition that that may preclude improvement in visual acuity or affect the evaluation of the study eye after resolution of DME (e.g. vitreous hemorrhage, macular ischemia, pre-retinal fibrosis involving the macula, pre-retinal macular hemorrhage, visually significant vitreomacular traction, or media clarity insufficient to obtain quality images)
7. Chronic uveitis or ongoing clinically significant infection or inflammation (e.g. keratitis, scleritis) in either eye
8. Previous vitreoretinal surgery, previous filtration surgery, cataract surgery within 3 months or YAG laser capsulotomy within 1 month of Screening in the study eye
9. History of cataract surgery complications (vitreous loss) or aphakia in the study eye

10. History of penetrating ocular trauma in the study eye
11. History of allergy to fluorescein or povidone iodine
12. History or current systemic condition that preclude the safe administration of the study treatment or confound results (e.g. HbA1c > 12% at Screening, uncontrolled hypertension [≥ 180/100] on optimal medical regimen at Screening, systemic anti-VEGF treatment, renal failure requiring dialysis, or renal transplant)
13. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control
14. Participation in an interventional clinical study at Screening

Investigational Product, Dose, and Route of Administration:

Subjects will receive one of the following doses of AXT107 single intravitreal injection in the study eye.

- AXT107 0.1 mg (low dose)
- AXT107 0.25 mg (mid dose)
- AXT107 0.5 mg (high dose)

Control Product, Dose, and Route of Administration:

N/A

Safety Assessments:

- Adverse events (AEs)
- ETDRS BCVA
- IOP
- Slit lamp biomicroscopy
- Dilated fundus exam (DFE)
- Optos (at selected sites only)
- SD-OCT
- OCT-A (at selected sites only)
- Fundus photography (FP)
- Fluorescein angiography (FA)
- Diabetic Retinopathy Severity Scale (DRSS)
- Laboratory evaluation (including ADA assay)
- Vital signs
- Physical examinations
- Pregnancy test

Efficacy Assessments:

- CST (Mean change in CST from Baseline) assessed by SD-OCT and measured by Reading Center
- BCVA (Mean change in ETDRS letters)
- BCVA (Proportion improving ≥5, ≥10, and ≥15 letters from Baseline (Day 0)

Statistical Methods:

Sample Size Determination:

Approximately 18 subjects will be enrolled, with 6 subjects in each dose. The final number of subjects enrolled may be adjusted based on the presence of dose limiting toxicities. This sample size is not planned based on statistical considerations.

Analyses:

Age, sex, race, ethnicity, and baseline assessments will be summarized and listed by dose level. Medical history, history of ocular surgery and procedures, and concomitant medication will also be summarized and listed.

Changes from baseline in BCVA (ETDRS letter score) and retinal thickness (CST) will be summarized by dose level using continuous summary statistics. BCVA change will be summarized using categorical summaries as well, including frequency counts and percentages improving at least 5, 10, and 15 letters.

Verbatim descriptions of AEs will be mapped to MedDRA thesaurus terms and be presented in a data listing. Treatment emergent AEs that occur after the first dose of study medication will be summarized by dose level using frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. Summaries will be presented separately for ocular and non-ocular AEs. All TEAEs will be summarized by severity and study drug relatedness.

BCVA will be summarized at each time point using both continuous summaries (ETDRS letter score), including change from Baseline (Day 0), and categorical summaries, including change from Baseline (Day 0) on an ETDRS chart in the number of lines.

IOP will be summarized at each time point using both continuous summaries, including change from Baseline (Day 0), and categorical summaries for pre-stated categories of change in IOP.

Slit lamp biomicroscopy and ophthalmoscopy measures will be summarized at each measured time point using categorical summary statistics.

FA will be summarized by visit.

DRSS will be summarized at each measured visit and change from Baseline (Day 0) to each measured visit.

Vital signs will be summarized at each visit and for change from Baseline (Day 0) to each visit using continuous summary statistics by treatment group and visit.

Clinical laboratory results will be summarized using both continuous summaries, including change from Baseline (Day 0), and discrete summaries, including frequency and percent of subjects with an abnormal value and shift tables from Baseline (Day 0). Additionally, laboratory data will be presented in data listings.

Exploratory analyses will be performed to summarize the results obtained from the Notal Vision Home OCT device and home M&S® Technology visual acuity measurement.

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3. BACKGROUND

3.1 Introduction

The worldwide prevalence of diabetes was estimated to be more than 8.5% in 2017, for a total of 451 million people affected (Guariguata 2014). With an aging population and increasing prevalence of obesity, it is estimated that 592 million people will have diabetes in 2035. A meta-analysis of 35 population-based studies worldwide suggests that almost 7% of the diabetic population has diabetic macular edema (DME) (Yau 2012). DME occurs due to retinal microvasculature damage, increase in vascular permeability, and loss of blood-retinal barrier leading to interstitial fluid accumulation in the retina, particularly in the region of the macula (Cunha-Vaz 1975, Patelli 2014, Bhagat 2009).

In DME, vascular permeability, angiogenesis, and inflammation play an important role (Campa 2010, Bhagat 2009). Retinal hypoxia and the hypoxia-regulated protein vascular endothelial growth factor (VEGF) play key roles in the pathogenesis of DME (Nguyen 2004, Nguyen 2009). Intravitreal injection (IVT) of a VEGF neutralizing protein, either in the form of an antibody or a chimeric receptor, is first-line treatment for DME and provides benefit in many patients (Nguyen 2006, Nguyen 2012,), but there is a substantial percentage of patients (40 to 60%) in whom anti-VEGF injections are not sufficient to eliminate edema or provide a clinically significant improvement in visual acuity (Heier 2014, Korobelnik 2014). These patients may experience permanent reductions in visual acuity over time from the damaging effects of chronic, recurrent edema (Do 2013, Channa 2014). There is thus still an unmet medical need for agents to treat DME using novel mechanisms.

In addition to VEGF inhibition, Tie2 (Tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains 2) is also being increasingly recognized for its role in regulating vascular permeability. Tie2 is a tyrosine kinase receptor that, like VEGF receptor-2, is located on vascular endothelial cells and has been implicated in the modulation of vascular permeability (Wong 1997, Thurston 1999, Thurston 2000). However, although phosphorylation of VEGF receptor-2 stimulates vascular leakage, phosphorylation of Tie2 activates downstream pathways that suppress vascular leakage and promote vascular stabilization. Angiopoietin 1 is an endogenous full agonist that stimulates phosphorylation of Tie2 (Davis 1996). Angiopoietin 2 is an endogenous weak, partial agonist that competes with angiopoietin 1, thereby suppressing Tie2 phosphorylation (Maisonpierre 1997, Yuan 2009). Tie2 is also regulated by vascular endothelial protein tyrosine phosphatase (VE-PTP), also known as human protein tyrosine phosphatase beta, which is physically associated with Tie2. It dephosphorylates Tie2, thereby reducing Tie2 activation and signaling through the Tie2 pathway (Yacyshyn 2009). Levels of both angiopoietin 2 and VE-PTP are increased by hypoxia, leading to accentuated VEGF-mediated ocular neovascularization and vascular leakage (Hackett 2000, Hackett 2002, Oshima 2004, Oshima 2005, Shen 2014). Preclinical models have shown that VE-PTP inhibition, even in the presence of high angiopoietin 2, restores Tie2 activation (Shen 2014).

The drugs currently used to treat DME are administered IVT and they have a short duration of action; Lucentis® is administered every month and Eylea® is administered monthly initially, and if there is an adequate response it may be dosed every 2 months or administered every 3 months. Frequent dosing is a burden for patients and can also increase the chance of adverse effects related to the injection. Thus, there is a considerable unmet medical need for alternative

treatment options with prolonged treatment duration to reduce treatment burden and new mechanism of action for patients who could not achieve optimal treatment effect from anti-VEGF agents.

AsclepiX Therapeutics, Inc. is developing AXT107 Intravitreal Injection for the treatment of retinal diseases, including diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), and retinal vein occlusion (RVO). AXT107 is a synthetic 20-mer collagen IV–derived peptide which inhibits Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) and activates the vessel stabilizing tyrosine kinase receptor Tie2. AXT107 disrupts integrin αvβ3 to inhibit signaling from VEGFR2 and other growth factors, including PDGF, HGF, and IGF; consequently, choroidal neovascularization and vascular leakage are inhibited. AXT107 disrupts α5β1 and stimulates the relocation of Tie2 and the integrin subunit α5 to cell junctions. AXT107 then activates junctional Tie2 by converting the Ang2 that is abundant in these diseases into a strong agonist, thereby upregulating downstream survival signals, rearranging F actin to strengthen junctions, and, as a result, reducing endothelial junctional permeability. In addition, AXT107 resolves TNFα-induced vascular inflammation in endothelial cells by converting the pro-inflammatory Ang2 into a strong agonist of Tie2 signaling, disrupting the synergism between TNFα and Ang2 while also preventing IκBα degradation directly through Tie2 signaling. This recovery of IκBα prevents NF-κB nuclear localization, thereby blocking NF-κB induced inflammatory responses. Administered intravitreally, AXT107 has anti-angiogenic, anti-permeability, and anti-inflammation effect and induces regression of disease in animal models of retinal neovascularization (Mirando 2020, Silva 2017, Formica 2019).

This Phase 1/2a, open-label, dose-escalating, 48-week study is planned to assess the safety, tolerability, bioactivity, and duration of action of a single intravitreal injection of AXT107 in the study eye of subjects with DME.

3.2 Investigational Product

AXT107 is a 20-mer synthetic peptide made up of naturally-occurring amino acids developed as a first-in-class synthetic peptide that inhibits VEGFR2 and activates Tie2 as a monotherapy agent.

AXT107 will be administered via an intravitreal injection (IVT) to patients with DME. Based on available pharmacodynamic and pharmacokinetics data, three doses, 0.1mg/eye, 0.25mg/eye, 0.5 mg/eye will be tested in this clinical study.

3.3 Summary of Relevant Data

A brief summary of the findings from nonclinical studies is presented below. Please refer to the Investigator's Brochure for detailed study information.

AXT107 was tested in the genetic tet/opsin/VEGF mouse model in which high levels of human VEGF cause massive vascular leakage leading to exudative retinal detachment. In this mouse model, AXT107 prevents retinal detachment more potently than aflibercept. AXT107 also strongly inhibits ischemia-induced retinal neovascularization in an oxygen-induced retinopathy (OIR) model in the mouse. In the rabbit eye nonclinical studies, AXT107 strongly inhibited VEGF induced vascular leakage. Remarkably, in head-to-head studies in which AXT107 was

tested at a human dose equivalent of aflibercept in the rabbit eye, AXT107 inhibited vascular leakage more potently than aflibercept and its activity lasted at least twice as long as aflibercept.

In addition, AXT107 was tested in a retinopathy of prematurity model of angiogenesis in the mouse eyes. The results showed that AXT107 inhibited angiogenesis induced by hypoxia in a dose-dependent manner. This suggested that AXT107 can be used to inhibit neovascularization caused by hypoxia.

Regarding the activation of Tie2, AXT107 was tested in a retinopathy of prematurity mouse model for phosphorylation of Tie2. The study showed that AXT107 induced the phosphorylation of Tie2 when it is present in conditions of hypoxia in which HIF, VEGF and Ang2 are all increased. This result suggested that AXT107 causes an increase in Tie2 phosphorylation in the presence of increased Ang2 which normally causes a decrease in Tie2 phosphorylation.

AXT107 was further tested in a model in which Lipopolysaccharide (LPS) was used to cause vascular leakage in the mouse eye. This model serves as a surrogate for inflammatory diseases of the eye including DME and uveitis. The results demonstrated that AXT107 inhibited LPS induced vascular leakage and has anti-inflammation effect.

Ocular tissue distribution studies have showed the sustained ocular exposure of AXT107 in the retina, choroid, and vitreous of rabbit eyes for up to 12 months.

In the toxicology studies in rabbits and minipigs, AXT107 was well tolerated, no significant ocular toxicity was observed for up to 15 months in rabbits and for up to9 months in minipigs. No systemic exposure was detected at doses up to 1.0 mg/eye and no systemic toxicity was observed.

In summary, nonclinical studies have demonstrated that AXT107 is more potent than aflibercept, has a longer efficacy duration with no detectable systemic exposure.

3.4 Known Risks and Benefits to Human Subjects

This is the first-in-human clinical trial of AXT107. The risks associated with AXT107 are not well understood at this time. The potential risks related to intravitreal injection include conjunctival hyperemia or hemorrhage. Endophthalmitis, vitreous hemorrhage, and retinal detachment are uncommon risks associated with intravitreal injection.

The anticipated benefit of AXT107 as a new treatment option with a different mechanism of action is the potential for a new therapeutic effect with a prolonged duration of action that will ease the burden of frequent treatments for patients with retinal diseases.

3.5 Target Population

The target population for AXT107 is diabetic patients with center-involved diabetic macular edema. In this study, approximately 18 subjects with an existing diagnosis of center-involved DME will be recruited to participate.

4. STUDY OBJECTIVES

The primary objective of this study is to evaluate the safety and tolerability of a single injection of three dose levels (0.1 mg/eye, 0.25 mg/eye, or 0.5 mg/eye) of AXT107 in subjects with DME.

The secondary objective of the study is to evaluate the bioactivity and duration of action of AXT107 for the treatment of DME.

5. INVESTIGATIONAL PLAN

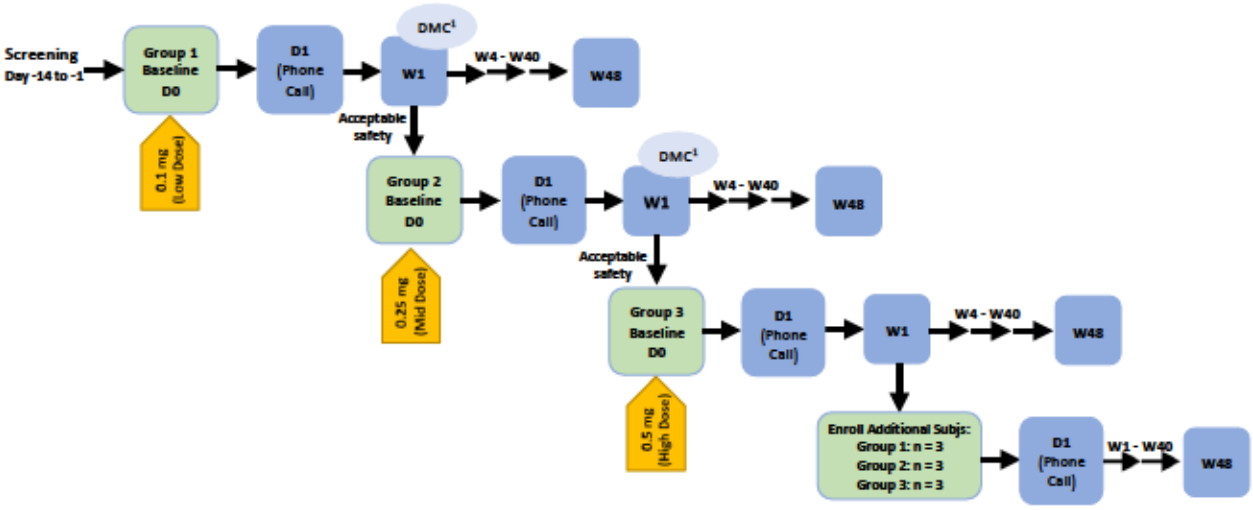
5.1 Overall Study Design

This is an open-label, dose-escalating, 48-week study assessing the safety, tolerability, bioactivity and duration of action of a single intravitreal injection of 0.1 mg (low dose), 0.25 mg (mid dose), or 0.5 mg (high dose) AXT107 in approximately 18 subjects (6 subjects per dose) with DME.

Upon providing written informed consent, subjects will be enrolled into the study with the dose-escalation strategy as depicted in Figure 1. A total of 16 visits are planned in the study, including Screening (Day -14 to -1), Baseline (Day 0), and follow-up visits on Day 1 (Phone call), Week 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48. Table I-1 in Appendix I provides a summary of the study visit and the procedures to be performed at each visit.

The study drug will be administered by the study Investigator at Baseline (Day 0), after completion of the Baseline assessments, including BCVA, IOP measurement, slit lamp biomicroscopy, and SD-OCT. IOP will be repeated and DFE will be completed after administration of the study drug at the Baseline visit. Post-baseline assessments will be completed as specified in Section 7 and as described in the Manual of Procedures (MOP).

Figure 1 **Study Schematic**



[1] DMC review of safety data at Week 1. Three subsequent subjects are to be enrolled to receive the next higher treatment dose only upon confirmation from the DMC of acceptable safety profile of the previous group.

5.1.1 Study Measures

The Safety measures are as follows:

- Adverse Events
- ETDRS BCVA
- IOP
- Slit lamp Biomicroscopy
- DFE
- Optos (at selected sites only)
- SD-OCT
- OCT-A (at selected sites only)
- Fundus Photography
- Fluorescein Angiography
- Diabetic Retinopathy Severity Scale (DRSS)
- Clinical Labs
- Vital signs
- Physical examination
- Pregnancy testing

The efficacy measures are as follows:

- Change in CST from Baseline (Day 0)
- BCVA (Mean change in ETDRS letters)
- BCVA (Proportion improving ≥5, ≥10, and ≥15 letters from Baseline (Day 0)

Refer to Table I-1 in Appendix I for a schedule of study visits and Procedures.

5.1.2 Measures to Minimize Bias

This is an open label first-in-human and dose-finding study. Randomization or masking is not employed in this study.

5.1.3 Treatment Assignment and Dose Escalation Criteria

Subjects will be sequentially assigned to receive either the low, mid, or high dose of study medication, in multiples of 3. Decision regarding dose escalation will be based upon the recommendation from the Data Monitoring Committee (DMC).

The first 3 eligible subjects will receive the low dose of AXT107 injection (Group 1). After Group 1 has completed a 7-day follow-up, the DMC will review their safety data. If an acceptable safety profile is determined by the DMC, 3 additional subjects will be enrolled to receive the mid dose of AXT107 injection (Group 2). Upon completion of a 7-day follow-up, review of the safety data, and determination of an acceptable safety profile by the DMC for Group 2, 3 additional subjects will be enrolled to receive the high dose of AXT107 injection (Group 3). After the 9 initial subjects have completed the 7-day follow-up, 9 additional subjects (3 each in each treatment group) may be enrolled. If the maximum tolerated dose (MTD) is not reached after the 0.5 mg group, a higher dose up to 1.0 mg may be tested.

5.1.4 Criteria for Termination of the Study (Stopping Rules)

The DMC will conduct ongoing reviews of collected safety data to determine the need for early termination of the study. Stopping rules will be incorporated if any of the following events are identified:

- Decrease in Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) of ≥ 15 letters (3-line decrease) unrelated to the natural progression of the disease and determined by the Investigator to be related to the study drug in ≥ 2 subjects
- Intraocular inflammation (anterior or posterior) grade +2 or more in ≥ 2 subjects (using SUN Grading Working Group and Nussenblatt et al grading)
- Increase in intraocular pressure (IOP) to ≥ 30mmHg for more than 24 hours post-injection in ≥ 2 subjects despite IOP lowering medication treatment
- Any other serious ocular or systemic adverse event (AE) that, in the opinion of the Investigator, is related to the study drug in ≥ 1 subject

Upon DMC's recommendation for study termination, further enrollment of study subjects in the study will be discontinued. Subject withdrawal procedures must be followed for all active subjects to ensure the safety of the subjects at the conclusion of the study.

5.2 Selection and Withdrawal of Study Subjects

Approximately 18 subjects may be enrolled into the study, with 6 subjects in each of the low (Group 1), mid (Group 2), and high (Group 3) treatment dose arms. The first 9 sequential subjects MUST NOT be treatment naïve. The additional 9 subjects can be previously treated or treatment naïve.

5.2.1 Subject Inclusion Criteria

1. 18 years of age or older
2. Type 1 or 2 diabetes mellitus with study eye center-involved DME and with central subfield thickness ≥ 305 µm (females) or 320 µm (males) on Spectralis® Spectral Domain Optical Coherence Tomography (SD-OCT) device or 290 µm (females) or 305 µm (males) on Cirrus® SD-OCT device and intraretinal or subretinal fluid as evidenced by Spectral Domain Optical Coherence Tomography (SD-OCT) at Screening, as confirmed by the Investigator
3. BCVA in the study eye at Baseline (Day 0) between 65 and 23 ETDRS letters (20/40 and 20/320 Snellen equivalent) with BCVA decrement determined by the Investigator primarily attributable to DME
4. BCVA of 34 ETDRS letters or better (20/200 or better Snellen equivalent) in the non-study eye at Baseline (Day 0)
5. Able and willing to give signed informed consent and follow study instructions

5.2.2 Subject Exclusion Criteria

1. Any signs of high risk proliferative diabetic retinopathy in the study eye and related complications, as determined by the Investigator
2. Previously treated patients who are non-responders to anti-VEGF determined by the Investigator
3. Panretinal photocoagulation within 6 months or macular laser photocoagulation within 3 months from Screening in the study eye

4. Use of intraocular or periocular corticosteroids within 4 months (with the exception of fluocinolone acetonide intravitreal implant which is excluded), Aflibercept within 8 weeks, Ranibizumab and Bevacizumab within 6 weeks from Baseline (Day 0) in the study eye
5. Any concurrent disease that would require medical or surgical intervention during the study in the study eye (e.g. retinal detachment, significant cataract, uncontrolled glaucoma)
6. Any condition that may preclude improvement in visual acuity or affect the evaluation of the study eye after resolution of DME (e.g. vitreous hemorrhage, macular ischemia, pre-retinal fibrosis involving the macula, pre-retinal macular hemorrhage, visually significant vitreomacular traction, or media clarity insufficient to obtain quality images)
7. Chronic uveitis or ongoing clinically significant infection or inflammation (e.g. keratitis, scleritis) in either eye
8. Previous vitreoretinal surgery, previous filtration surgery, cataract surgery within 3 months or YAG laser capsulotomy within 1 month of Screening in the study eye
9. History of cataract surgery complications (vitreous loss) or aphakia in the study eye
10. History of penetrating ocular trauma in the study eye
11. History of allergy to fluorescein or povidone iodine
12. History or current systemic condition that preclude the safe administration of the study treatment or confound results (e.g. HbA1c > 12% at Screening, uncontrolled hypertension [≥ 180/100] on optimal medical regimen at Screening, systemic anti-VEGF treatment, renal failure requiring dialysis, or renal transplant)
13. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control
14. Participation in an interventional clinical study at Screening

5.2.3 Subject Withdrawal Criteria

Subjects may withdraw from participation (withdraw consent) at any time during the study, without cause, and regardless of circumstances. In addition, the Principal Investigator or the Medical Monitor may terminate a subject's participation in the study for reasons related to safety and/or to protect the rights and interest of the subject. Subjects may be discontinued from the study due to any of the following reasons:

- Non-compliance
- Lost to follow-up
- Protocol violation
- Withdrawal by subject
- AEs
- Death
- Clinical judgment of the Investigator or the Medical Monitor
- Other

If a subject is discontinued from the study before completing the Week 48 visit, all safety and performance assessments scheduled at the final visit should be performed on the day of discontinuation, to the extent possible. The final assessments and the reason for discontinuation should be documented in the subject's records and the appropriate early termination Case Report Forms (CRF).

Subjects who prematurely discontinue from the study may be replaced only with approval obtained from the Sponsor.

5.3 Treatment of Subjects

5.3.1 Study Drug Administration

Study medication will be administered via IVT injection by a qualified physician. Subjects will receive a single dose of AXT107 (based on assigned dosage) in the study eye on Day 0 (Baseline). Refer to the Pharmacy Manual for instructions on the preparation of the study drug.

5.3.2 Determination of the Study Eye

Study eye will be defined as the eye that meets all of the inclusion and none of the exclusion criteria. If both eyes meet criteria, study eye will be defined as the eye with the worse vision on Day 0 (Baseline). If both eyes have the same vision, the right eye (OD) will be determined as the study eye. Refer to the MOP for study eye preparation prior to administration of study drug.

5.3.3 Rescue Therapy

Rescue therapy with the Investigator's preferred treatment will be allowed starting at Week 12, for any subject who has received injection of AXT107 and for whom there is ≥ 7 letter ETDRS BCVA decrease from Baseline (Day 0) or ≥ 75 µm increase in CST compared to the lowest measurement at any previous visit. It is recommended that rescued subjects complete all study follow up visits through Week 48/Exit.

5.3.4 Concomitant Medication

There are no prohibited concomitant medications in the study. When possible, concomitant medications should be used with a consistent dose throughout the study. The use of concomitant medications (prescription or over-the-counter) will be recorded in the source documents during the study, using the generic name, indication, route of administration, frequency, dose, start date and stop date (if applicable).

5.3.5 Treatment Compliance

The treatment in this study includes a single dose injection administered by the study Investigator. Measurement of treatment compliance is not applicable to this study.

5.3.6 Restrictions

Subjects will be instructed to remain seated for approximately 30 minutes following the AXT107 IVT. Subjects should be advised that they should avoid vigorous exercise such as jumping jacks, aerobics, yoga, lifting weights, etc. within a month after the AXT107 IVT.

5.4 Study Drug Management and Handling

5.4.1 Investigational Drug

Study medication will be tested in 3 concentrations in this study; the 0.1 mg solution is considered the "low dose", the 0.25 mg solution is considered the "mid dose", and the 0.5 mg

solution is considered the "high dose". Syringes and needles will be utilized to administer the study medication (See the MOP and Pharmacy Manual for administration instructions).

5.4.2 Study Drug Packaging and Labeling

AXT107 will be provided as a lyophilized powder in a vial. The study drug will be reconstituted, as described in the Pharmacy Manual, for injection to provide the appropriate dose. The label will include the name of the study drug, the protocol number, kit number, and storage conditions. The Carton will include a statement that indicates the product is for investigational use only.

5.4.3 Study Drug Storage

AXT107 is to be stored at 2-8ºC, in a securely locked area with access given only to appropriate study personnel.

5.4.4 Additional Clinical Supplies

Urine pregnancy test kits and clinical laboratory supplies for obtaining blood and urine specimens will be provided by the central laboratory.

5.4.5 Study Drug Accountability

It is the responsibility of the Principal Investigator (or designee) to ensure the receipt, accountability, proper storage, and dispensing of study drug. Inventory procedures should be in place and conducted upon receipt of study drug and supplemental supplies (e.g., syringes), and any discrepancy is to be communicated to the Sponsor immediately upon awareness by the Principal Investigator. The clinical supplies shipment form must be completed and a copy must be returned to the Sponsor as directed, while the original record is retained in the clinical trial files. A current record of the inventory, storage conditions, and dispensing must be kept by the investigative site staff, and will be provided to the Sponsor representatives (Study monitor) when necessary for the purpose of accounting for all clinical supplies. Any discrepancy and/or deficiency must be recorded with provided explanation.

5.4.6 Return of Unused Supplies

All unused supplies are to be returned to the Sponsor upon completion of the study. It is the responsibility of the Principal Investigator to ensure the proper packaging and shipment of clinical supplies when returning to the Sponsor. The site's standard practice will be followed for the disposal of used study drug supplies.

5.5 Assessment of Safety

5.5.1 Definitions and classification of Adverse Events

An adverse event (AE) is considered as any untoward medical occurrence associated with the use of a drug product in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

- Death
- a life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

5.5.2 Collection and Assessment of Adverse Events

In this study, AEs are to be collected from the time of informed consent. Therefore, any undesirable medical condition occurring at any time, including Baseline or pre-treatment period

(even if no study drug has been administered), must be evaluated for an AE. Any clinically significant change from baseline in a subject's condition or pre-existing condition must be evaluated as an AE, unless the change is determined to be a continuation of a pre-existing condition that is documented in the subject's medical history. However, a clinically significant worsening in severity, intensity, or frequency of a pre-existing condition may indicate an AE.

All conditions that lead to hospitalizations, defined as an overnight hospital stay, are to be considered as SAEs. Elective surgical procedures scheduled or planned prior to study entry that do not require overnight hospital stay, and the underlying diagnosis for which surgery is to be performed is captured in the medical history as a pre-existing condition are not considered AEs. The surgical procedure should still be documented in the subject records with an explanation of circumstances.

Lack of efficacy of AXT107 for the condition being investigated is not considered an AE unless a clinically significant change is assessed by the Principal Investigator.

Adverse events in this study will be collected by way of seeking information (direct questioning and physical examination) by the Investigator at each subject contact, or upon information that is provided voluntarily by the subject, and are to be followed to resolution, or until the condition is determined to be irreversible, chronic, or stable, for up to 30 days after the subject's exit from the study. Unresolved AEs beyond 30 days of the subject's exit from the study should be evaluated on a case-by-case basis, depending upon the condition and based on the clinical judgement of the Investigator or at the direction of the Sponsor.

Adverse events will be assessed by the Investigator for seriousness (see CFR 21 part 312 criteria in Section 6.5.1) and severity according to the following criteria:

> **Mild:** No interference with the subject's daily activities; no medical intervention/therapy required
>
> **Moderate:** Possible interference with the subject's daily activities; no or minimal medical intervention/therapy required
>
> **Severe:** Considerable interference with the subject's daily activities; medical intervention/therapy required

The Investigator must also make a determination of relatedness to the study drug (related or not related), based on the Investigator's clinical judgment, facts (product information or Investigator's Brochure), evidence, and scientific rationales as to whether there is a causal relationship between the AE and AXT107.

- An AE must be reported as **Related** to AXT107 if there is a reasonable possibility that the experience may have been caused by AXT107, and the AE cannot be readily explained by the subject's clinical state, concurrent illness, or concomitant therapies.
- An AE may be considered as **Not Related** to AXT107 if evidence that the AE has an etiology other than the AXT107 (e.g., pre-existing medical condition, underlying disease, concurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the AXT107 (e.g., newly diagnosed condition after administration of AXT107).

The Investigator will be required to assess the outcome of the AE as one of the following:

- Resolved
- Resolved with sequelae
- Resolving
- Not Resolved
- Fatal
- Unknown

An event that is assessed as resolved with sequelae or resolving indicates that the subject has stabilized to a level acceptable to the Investigator and has concurrence by the Sponsor.

5.5.3 Reporting of Adverse Events

All AEs reported after the subjects has provided written informed consent and within 30 days following the last visit will be recorded in the subject's medical records and the appropriate CRF.

Recognized medical terms should be used when recording the AE, avoiding colloquialisms and/or abbreviations when possible. Separate AEs should be reported for events that are observed simultaneously but are deemed to be unrelated based on the clinical judgement of the Investigator. If a diagnosis cannot be established, the prominent sign, symptom, or finding should be documented as the AE description. Intermittent events should be reported with the date of the first episode as the onset date, and with maximum severity as observed among the collective episodes. Intermittent hospitalizations as a result of a primary event should be documented with the primary event and not as separate events.

5.5.3.1 Serious Events Reporting Criteria

Serious AEs must be reported to the Sponsor or Sponsor representative within 24 hours of the Investigator's knowledge of the event. An SAE report form, including at minimum subject identification, AE description, and onset date must be forwarded to the Sponsor or Sponsor representative at the following number/email:

Email: safetygroup@clinipace.com
SAE Fax : 1-919-573-0332

Upon availability of any new information, the subject's medical records and CRFs must be updated, and the information is to be provided to the Sponsor when applicable.

5.5.4 Additional Safety Assessments

Refer to the MOP for a description of the following procedures to be performed in the study.

5.5.4.1 Best Corrected Visual Acuity

BCVA will be measured in both eyes starting at Screening (Day -14 to Day -1) and at all attended visits, using an ETDRS chart, with the use of standardized manifest refraction and testing protocol as described in the Manual of Procedure. BCVA evaluation should precede any

study procedure that requires contact with the eye. All examiners must be certified prior to the Screening visit.

5.5.4.2 Intraocular Pressure

IOP will be measured in each eye at Screening (Day -14 to Day -1), before and after injection at Baseline (Day 0), and at all other attended visits prior to pupil dilation. The same type of tonometer should be used throughout the study for the same subject. At the Baseline visit, tonometry will be performed prior to administration of AXT107 and will be repeated at 30 (± 10) minutes post-injection of AXT107. Elevated IOP of ≥ 30 mmHg will be re-measured at 60 (± 10) minutes post injection of AXT107.

5.5.4.3 Slit Lamp Biomicroscopy

Slit lamp biomicroscopy will be performed on each eye starting at Screening (Day -14 to Day -1) and at all attended visits. Assessment of the eyelids, conjunctiva, cornea, anterior chamber, iris, and lens will be documented. At the Baseline visit, the biomicroscopy examination will be performed prior to administration of AXT107.

5.5.4.4 Dilated Fundus Examination

DFE will be performed on each eye at Screening (Day -14 to Day -1), before and after study drug injection at Baseline (Day 0), and at all other attended visits to assess change from baseline and the visibility of AXT107. Assessments of the vitreous, retina, macula, choroid, optic nerve, and cup/disc ratio will be documented.. Additional follow-up visits may be required to evaluate the AXT107 visibility if AXT107 is still visible at Visit 15/Exit (Week 48).

5.5.4.5 Spectral Domain Optical Coherence Tomography

SD-OCT images will be captured for each eye starting at Screening (Day -14 to Day -1) and at all attended visits, following the standardized procedures detailed in the Reading Center Manual. The approved equipment is also listed in the Reading Center Manual.

5.5.4.6 Fundus Photography

Fundus photography of each eye is to be obtained at Screening (Day -14 to Day -1), Visit 6 (Week 12), Visit 9 (Week 24), and Visit 15/Exit (Week 48). Refer to the Reading Center Manual for the procedure to obtain color FP.

5.5.4.7 Fluorescein Angiography

Fluorescein angiography of each eye will be obtained at Screening (Day -14 to Day -1), Visit 6 (Week 12), Visit 9 (Week 24) and Visit 15/Exit (Week 48). Sodium fluorescein will be injected into systemic circulation and digital images of the retina will be taken with blue light illumination at 490 nm of wavelength. Refer to the Reading Center Manual for the procedure.

5.5.4.8 Optical Coherence Tomography Angiography

OCT-A images will be captured at selected sites only. Images will be taken for each eye starting at Screening (Day -14 to Day -1) and at all attended visits, and will follow standardized procedures as detailed in the Reading Center Manual.

5.5.4.9 Widefield Retinal Imaging (Optos)

Widefield retinal image will be used to capture the AXT107 visibility in the study eye at Baseline (Day 0) after AXT107 injection, Week 8, and Week 36 at selected sites.

5.5.4.10 AC Tap

Anterior chamber paracentesis will be performed at selected sites at Baseline (Day 0), Visit 4 (Week 4), Visit 6 (Week 12), Visit 9 (Week 24), and Visit 14 (Week 44).

5.5.4.11 Optical Coherence Tomography Imaging at Home

Home OCT imaging will be performed weekly for each eye using the Notal Vision Home OCT device by study subjects, after enrollment at selected sites.

5.5.4.12 Visual Acuity Measurement at Home

Visual acuity measurement will be performed weekly for each eye, utilizing the M&S Technology visual acuity system at home by study subjects, after enrollment at selected sites.

5.5.4.13 Laboratory Evaluation

Laboratory tests (fasting for diabetic subjects) will include a complete blood count (hematology and differential), chemistry panel, and urinalysis at Screening (Day -14 to Day -1), Visit 9 (Week 24), and Visit 15 (Week 48). The Screening clinical laboratory results must be reviewed prior to enrollment to identify any clinically significant disease that in the opinion of the Investigator may preclude the subject from participation in the study. An anti-drug antibody (ADA) assay will be completed at Screening, Visit 4 (Week 4), Visit 6 (Week 12), and Visit 15 (Week 48/Exit).

5.5.4.14 Vital Signs

Heart rate and blood pressure will be measured starting at Screening (Day -14 to Day -1) and at all attended visits, using an automated or manual blood pressure monitor. Systolic and diastolic blood pressures will be recorded in millimeters of mercury (mmHg), and heart rate will be recorded in beats per minute (bpm).

5.5.4.15 Physical Examination

A complete physical examination will be conducted by the Principal Investigator or designee at Screening (Day -14 to Day -1).

5.5.4.16 Pregnancy

Women of childbearing potential are not excluded from the study as long as it can be determined at Baseline that they are not pregnant, nursing, or planning a pregnancy, and are using effective methods of contraception. Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before Baseline. In case of oophorectomy alone, only when

the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to Baseline). For female subjects in the study, the vasectomized male partner should be the sole partner for that subject
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

Pregnancy is not considered an AE, but must be reported if occurred during a clinical study. Female subjects must be instructed to contact the Investigator immediately if pregnancy is suspected during their participation in the study. Every attempt will be made to collect data on the pregnancy of female subjects and/or pregnant partners of male subjects. Decision regarding continuation of the subject in the study will be made based upon the circumstances surrounding the pregnancy. Pregnancy must be followed to term to assess for potential complications. Complications may be reportable based on clinical judgement.

5.6 Assessment of Efficacy

5.6.1 Central Subfield Thickness

SD-OCT will be performed for both eyes starting at Screening (Day -14 to Day-1) and at all attended visits. Mean change in CST from Baseline (Day 0) will be assessed.

5.6.2 Best Corrected Visual Acuity

Mean change in ETDRS letters from Baseline (Day 0) and percentages improving at least 5, 10, and 15 letters will be assessed.

5.7 Contingency Measures in Case of a Global Emergency

In case of global or regional emergencies, such as the Covid-19 public health emergency, the investigational site may implement contingency plans to minimize the impact of the emergency on trial integrity and to reduce missing data, while ensuring the safety of study participants and the investigational site staff. In the event that study participants are unable or unwilling to attend in person study visits, telephone and virtual visits may be conducted for completion of assessments that can be conducted without requiring an in-person evaluation by the study investigator (eg, in-home assessments of OCT and VA, subject reported symptomology and AEs). Virtual or telephone visits should be clearly documented as such in the case report forms to account for missing safety and efficacy assessment when summarized.

Deviations from the protocol may be unavoidable during the current Covid-19 public health emergency. Delayed or missed visits due COVID-19 illness and/or COVID-19 control measures should be documented as such in an effort to assess the potential impact of Covid-19 on study conduct and the collection of data.

6. STATISTICAL ANALYSIS PLAN

6.1 Analysis Populations

Intent-to-Treat (ITT) Population:

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

Safety Population:

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

6.2 Statistical Hypotheses

No statistical hypotheses are defined for this study.

6.3 Statistical Methods

Age, sex, race, ethnicity, and baseline assessments will be summarized and listed by dose level. Medical history, history of ocular surgery and procedures, and concomitant medication will also be summarized and listed.

Changes from baseline in BCVA and retinal thickness (CST) will be summarized by dose level using continuous summary statistics. BCVA change will be summarized using categorical summaries as well, including frequency counts and percentages improving at least 5, 10, and 15 letters.

Verbatim descriptions of AEs will be mapped to MedDRA thesaurus terms and be presented in a data listing. Treatment emergent AEs, those that occur after the first dose of study medication, will be summarized by dose level using frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. Summaries will be presented separately for ocular and non-ocular AEs. TEAEs will be summarized by severity and study drug relatedness.

BCVA will be summarized at each time point using both continuous summaries (ETDRS letter score), including change from Baseline (Day 0), and categorical summaries, including change from Baseline (Day 0) on an ETDRS chart in the number of lines.

IOP will be summarized at each time point using both continuous summaries, including change from Baseline (Day 0), and categorical summaries for pre-stated categories of change in IOP.

Slit lamp biomicroscopy and ophthalmoscopy measures will be summarized at each measured time point using categorical summary statistics.

FA will be summarized by visit.

DRSS will be summarized by visit and change from Baseline (Day 0) to each visit.

Vital signs will be summarized at each visit and for change from Baseline (Day 0) to each visit using continuous summary statistics by treatment group and visit.

Clinical laboratory results will be summarized using both continuous summaries, including change from Baseline (Day 0), and discrete summaries, including frequency and percent of subjects with an abnormal value and shift tables from Baseline (Day 0). Additionally, laboratory data will be presented in data listings.

Exploratory analyses will be performed to summarize the results obtained from the Notal Vision Home OCT device and home M&S® Technology visual acuity measurement.

6.4 Sample Size Determination

Approximately 18 subjects will be enrolled, with 6 subjects in each treatment group. The final number of subjects enrolled may be adjusted based on the presence of dose limiting toxicities. This sample size is not planned based on statistical considerations.

6.5 Handling of Missing Data

For safety measures, missing scores will not be imputed for data summaries.
Completely or partially missing onset and resolution dates for AEs and completely or partially missing start and end dates of concomitant medications will be imputed in a conservative fashion. For bioactivity endpoints, missing post-treatment values will be imputed using the last-observation-carried-forward (LOCF) approach.

6.6 Interim Analyses

Interim analyses will be performed after all subjects complete the Week 12, Week 24, and Week 36 visits to evaluate the overall safety and preliminary bioactivity.

7. DATA MANAGEMENT AND ADMINISTRATIVE REQUIREMENTS

7.1 Completion of Source Document and Case Report Forms

The nature and location of source documentation in this study will be identified to ensure that original data required to complete the CRFs exist, are accessible, and verifiable by the Sponsor or its representatives (e.g., study monitor). Authors of the source documents and CRFs must be identifiable via the study personnel log, and the identity of study personnel implementing any modifications to the source documents and CRFs must be documented (ie, by initials or signature and date). Any discrepancies between the source documents and CRFs will be examined, corrected, and an explanation will be provided in writing. All modifications to source data and CRFs will be completed in a manner that does not obscure the original entry.

Deviations from the protocol, including but not limited to adherence to eligibility criteria, study conduct, completion of safety and efficacy procedures, visit windows, study drug administration, and data collection, must be documented and explained in the source documents, including the visit/date of deviation, nature of deviation, and any corrective action taken by the site if necessary.

7.2 Quality Control and Quality Assurance

Instructions on the conduct of the protocol, the completion of source documents and CRFs, and performance of the study procedures will be provided to the Investigator. Study progress will be monitored (via monitoring visits) by on-site, written, remote review, or telephone communications between the Investigator's site study staff and the study monitor (or other Sponsor representatives). Source data verification of the CRFs against original source documentation and the subject's medical records and other records relevant to the study will be performed during the on-site and/or telephone monitoring visits. All study related data including CRFs, medical records (source documents), signed consent forms, study related correspondence and regulatory files, as well as, records of study medication storage, preparation, and disposition will be inspected during monitoring visits.

Data received via CRFs will be reviewed by the Sponsor for accuracy and completion, and any discrepancies or suspected error in the data will be queried by the monitor and/or Sponsor (or designee).

Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results, will instigate a root cause analysis and appropriate corrective and preventive actions will be implemented by the Sponsor. Serious and/or persistent noncompliance on the part of an Investigator/institution, may lead to termination of the Investigator's/institution's participation in the trial.

7.3 Data Handling and Record Keeping

A data management plan detailing the relevant aspects of data processing, including storage, validation, reconciliation, and releasing methods, will be maintained by AsclepiX. Coding of the safety parameters (e.g., AEs, examination findings, medication, medical history) will be implemented using a current accepted medical dictionary.

8. ETHICS

8.1 Ethics Review

Prior to initiation of the study, the protocol, ICF, any materials used to recruit subjects, and all documents that are provided to subjects must undergo review by a local or central IRB, and documented approval or favorable opinion of the IRB/IEC must be present. Only the current IRB/IEC approved protocol and study materials must be use during the conduct of the study. Deviations from, or changes to the protocol are prohibited without agreement by the Sponsor and without documented written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)). It is the responsibility of the Principal Investigator to adhere to IRB/IEC requirements with respect to progress reports and notifications of any reportable serious adverse drug reactions product.

8.2 Ethical Conduct of Study

This clinical study must be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH guidelines outlining GCP, and the IRB/IEC and applicable regulatory requirements.

8.3 Informed Consent and Subject Confidentiality

Voluntary written informed consent must be obtained from every subject prior to the initiation of any study-related activities. The Investigator must have a defined process for obtaining consent. Subjects must be given ample time to read, understand, and ask questions, in order to consider voluntary participation. The subject must indicate voluntary consent by providing a written signed and dated informed consent form (ICF). A copy of the signed and dated ICF must be provided to the subject, and the original document must be filed in the subject's study records.

The ICF must meet all applicable local laws and be written in language that the subject understands. Subjects must be informed that their participation in the study is voluntary and that their decision to withdraw from participation at any time during the study will not impact any aspect of their standard care. Subjects will be provided with contact information for the appropriate individuals should questions or concerns arise after signing the ICF during the clinical study.

Subjects must also be informed that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must ensure all procedures and practices are in place to protect the privacy and the best interest of the subject.

9. INVESTIGATOR OBLIGATIONS

The Principal Investigator is responsible to ensure that all study personnel are qualified and properly trained to perform their assigned tasks during the course of the study. A record of all study personnel and their responsibilities must be retained with the study regulatory files, and must be kept updated to reflect the roles of study staff during the entire course of the study.

9.1 Direct Access to Source Data/Documents

The Investigator must agree to provide direct access to all source data and clinical documents pertaining to the study, to the Sponsor and its representative (i.e., study monitor) and to all regulatory bodies (i.e., IRB/IEC, FDA).

9.2 Financing and Insurance

The Principal Investigator and all sub-Investigators will provide financial disclosure information prior to participation in the study, and must agree to notify the Sponsor promptly of any required revision to their financial disclosure status during the term of this study, annually, or at the end of the study (if applicable). Updated financial disclosure information must be provided upon the Sponsor's written request following completion of the study.

9.3 Record Retention

All essential records relating to the conduct of this study must be retained by the Principal Investigator until notified by the Sponsor of procedures to destroy the records.

9.4 Confidentiality Disclosure and Publication Policy

Information related to this study or other AsclepiX products, any potential trade secrets or commercially sensitive information residing within this document must not be disclosed to any unauthorized individuals, unless when required by law, or called upon by a regulatory body.

All data and discoveries arising out of the study, patentable or non-patentable, are the sole property of AsclepiX Therapeutics, Inc. Any publication or presentations related to the study that are prepared by the Principal Investigator or other study staff must be approved by the Sponsor.

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APPENDICES

APPENDIX I. Schedule of Visits and Procedures

Table I-1 Schedule of Visits and Procedures

Visit Procedures	Screening	Visit 1/ Baseline	Visit 2/ Day 1 (Phone Call)	Visit 3/ Week 1	Visit 4/ Week 4	Visit 5/ Week 8	Visit 6/ Week 12	Visit 7/ Week 16 Visit 8/ Week 20	Visit 9/ Week 24	Visit 10/ Week 28 Visit 11/ Week 32 Visit 12/ Week 36 Visit 13/ Week 40 Visit 14/ Week 44	Visit 15/ Week 48/ Exit
Visit Windows (Days)	-14 to -1	0	2	±2	±3	±7	± 7	± 7	± 7	± 7	± 7
Informed Consent[1]	X										
Inclusion/Exclusion	X	X									
Demographics	X										
Medical/Ophthalmic History	X										
Concomitant Medications	X	X		X	X	X	X	X	X	X	X
Vital signs	X	X		X	X	X	X	X	X	X	X
Physical Exam	X										
Urine Pregnancy Test[2]	X										X
Clinical Labs	X								X		X
ADA Assay[3]	X				X		X				X
Adverse Events[4]	X	X	X	X	X	X	X	X	X	X	X
ETDRS BCVA	OU	OU		OU	OU	OU	OU	OU	OU	OU	OU
IOP	OU	OU		OU	OU	OU	OU	OU	OU	OU	OU
AC Tap[5]		SE			SE		SE		SE	SE[6]	
Slit lamp Biomicroscopy	OU	OU		OU	OU	OU	OU	OU	OU	OU	OU
Dilated Fundus Exam[8]	OU	OU[9]		OU	OU	OU	OU	OU	OU	OU	OU
AXT107 visibility[7]		SE		SE	SE	SE	SE	SE	SE	SE	SE
SD-OCT	OU	OU		OU	OU	OU	OU	OU	OU	OU	OU
OCT-A[5]	OU	OU		OU	OU	OU	OU	OU	OU	OU	OU
Fundus Photography[8]	OU						OU		OU		OU
Fluorescein Angiography	OU						OU		OU		OU
DRSS Evaluation	OU						OU		OU		OU
Treatment assignment		X									
Study drug (AXT107) administration		SE[9]									
Home OCT[5]	OU	OU		OU	OU	OU	OU	OU	OU	OU	OU
Home VA[5]	OU	OU		OU	OU	OU	OU	OU	OU	OU	OU

[1] The informed consent form must be signed/dated prior to performing any study procedures, including screening procedures.
[2] Required for all female subjects of childbearing potential. Urine pregnancy tests will be performed unless local regulations/IRBs require a serum pregnancy test.
[3] Additional blood samples will be obtained during clinical laboratory collection at the Screening, Week 4, Week 12, and Week 48 visits for ADA assay.
[4] AEs reported after screening and before randomization will be reported as pre-injection AEs.
[5] Procedure to be performed at selected sites only.
[6] At Week 44 only.
[7] AXT107 visibility will be assessed via fundus exam for all subjects. Optos will be used at selected sites to evaluate AXT107 visibility at Baseline (after IVT), Week 8, and Week 36.
[8] Stereoscopic 7-field or 4-widefield color fundus photography will be taken.
[9] IOP measurement must be performed prior to and after the AXT107 injection at Visit 1/Baseline. After injection, IOP will be measured 30±10 minutes. If IOP ≥30mmHg, repeat IOP measurement at 60±10 minutes post-injection. Fundus exam will be performed before and after injection at the Baseline visit.

APPENDIX II. Approval Signatures

ASCLEPiX THERAPEUTICS	Form	Doc. No.: FRM-CR-001A.00
Clinical Protocol Approval Form		Effective Date: 4 Aug 2020

Protocol Number and Title:

AXT107-CS101

Phase 1/2a Study of the Safety and Bioactivity of AXT107 in Subjects with Diabetic Macular Edema (DME) – CONGO study

Version Number and Version Date: Version 1.0, 31 Aug 2020

Protocol Amendment(s) (if applicable): N/A

Approval Date: 31 Aug 2020

Protocol Approver	Print Name	Signature	Date dd-mmm-yyyy
Medical Monitor	Quan Dong Nguyen	DocuSigned by: Quan Dong Nguyen Signer Name: Quan Dong Nguyen Signing Reason: I approve this document Signing Time: 9/1/2020 | 8:39:59 AM PDT 4689C4AC4E8E45B28E56E0D31A218BA5	9/1/2020
Clinical Research	Huan Sheng	DocuSigned by: Huan Sheng, MD Signer Name: Huan Sheng, MD Signing Reason: I approve this document Signing Time: 8/31/2020 | 9:31:56 PM PDT	8/31/2020