Statistical Analysis Plan for A Multicenter, Open-Labeled, Phase 2a Study Evaluating the Safety, Tolerability, and Efficacy of Intravitreal AG-73305 in Patients with Diabetic Macular Edema

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine Amino Transferase
AREDS	Age-related Eye Disease Study
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BCVA	Best Corrected Visual Acuity
BPM	Beats per Minute
CD	Capillary Density
CRC	Central Reading Center
CRF	Case report form
CST	Central Subfield Thickness
DFE	Dilated Fundus Exam
DLT	Dose-limiting Toxicities
DME	Diabetic Macular Edema
DRSS	Diabetic Retinopathy Severity Score
ECG	Electrocardiogram
eCRF	Electronic case report form
ELM	External Limiting Membrane
ETDRS	Early Treatment Diabetic Retinopathy Study
EZ	Ellipsoid Zone
FAS	Full Analysis Set
FAZ	Foveal Avascular Zone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbA1c	Hemoglobin A1c
ICH	International Conference on Harmonisation
IgG1 Fc	The Crystallizable Fragment of the Immunoglobulin G1

IOP	Intraocular Pressure
IP	Investigational product
IVT	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
OCT-A	Optical Coherence Tomography-Angiography
OD	Oculus dexter (right eye)
OS	Oculus sinister (left eye)
OU	Oculus uterque (both eyes)
PK	Pharmacokinetic
PR interval	The Time between the Onset of the P-wave to the Onset of the QRS Complex on the Electrocardiogram
PT	Preferred term
QC	Quality control
QRS	A Combination of the Q Wave, R Wave and S Wave on the Electrocardiogram
QT	The Time between the Start of the Q Wave and the End of the T Wave on the Electrocardiogram
RBC	Red blood cell count
RR interval	The Time Elapsed between Two Successive R-waves of the QRS Signal on the Electrocardiogram
SAE	Serious adverse event
SD	Standard deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Study eye
SOC	System organ class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
ST	The Plateau Phase of the Action Potential
TEAE	Treatment emergent adverse event
VEGF	Vascular Endothelial Growth Factor

WBC	White blood cell count
WHODrug	World Health Organization Drug Dictionary

PROTOCOL SYNOPSIS

Title: A Multicenter, Open-Labeled, Phase 2a Study Evaluating the Safety, Tolerability, and Efficacy of Intravitreal AG-73305 in Patients with Diabetic Macular Edema.

Study Objectives:

- Evaluate the safety, tolerability, duration of effect, systemic pharmacokinetic (PK) and immunogenicity profile of ascending doses of AG-73305 administered by intravitreal (IVT) injection in patients with diabetic macular edema (DME).
- Evaluate pharmacodynamic endpoints (e.g., best-corrected visual acuity [BCVA], spectral domain optical coherence tomography [SD-OCT] and OCT-angiography [OCT-A]).
- Determine the maximum tolerated dose or the highest administered dose for evaluation in future studies.

Study Description: This is a multi-centered, open-labeled, single ascending-dose-cohort study with a sentinel patient at each dose level. Cohort management will be overseen by a Safety Review Committee (SRC). The following hypotheses will be evaluated:

- AG-73305 has an acceptable safety profile, as measured by the incidence and severity of adverse events (AEs).
- At least 1 dose of AG-73305 demonstrates some clinical beneficial effects as measured by SD-OCT, BCVA and OCT-A findings.

Response Measures:

Safety assessments:

- Adverse Events (AEs)
- ETDRS BCVA
- Intraocular pressure (IOP)
- Slit lamp biomicroscopy
- Dilated fundus exam (DFE)
- Crystalline lens assessment using AREDS scale
- Post-injection assessment
- Laboratory evaluation (hematology, serum chemistry and urinalysis)
- Electrocardiogram (ECG)
- Vital signs
- Physical examination
- Pregnancy test

Efficacy assessments:

- Improvements in ETDRS BCVA
- SD-OCT (Heidelberg Spectralis, dense scan) as measured by Central Reading Center (CRC)
    - Central subfield thickness (CST)
    - Ellipsoid zone (EZ)
    - External limiting membrane (ELM)
    - Intraretinal and subretinal fluid
    - Posterior vitreous detachment
- OCT-A as measured by CRC
    - Foveal avascular zone (FAZ)
    - Foveal capillary density (CD) (superficial and deep capillary plexuses)
- Diabetic retinopathy severity score (DRSS) assessed via color fundus photography
- Time to rescue medication

Pharmacokinetics: Plasma concentrations of AG-73305.

Immunogenicity: Serum levels of anti-AG-73305 antibodies (using binding and neutralizing antibody assays, if available).

Study Population: Approximately 25, adult male or female patients with center involving DME in the study eye will participate in the study, including a sentinel patient in each of 4 dose cohorts.

Phase: 2a

Description of Sites: Approximately 8 sites in the United States will enroll patients.

Description of Study Treatment: AG-73305 is a humanized IgG1 Fc-fusion protein that targets vascular endothelial growth factors, placental growth factors and integrins. AG-73305 is a clear solution formulated in a 40 mg/mL concentration for intravitreal injection. Ascending doses of a single injection of AG-73305 will be assigned by cohort to 0.5, 1, 2, and 4 mg or until the maximally tolerated (or maximum administered) dose has been reached (see Table 1).

Rescue Medication will be standard-of-care anti-vascular endothelial growth factor (VEGF) administered by IVT in the study eye. Rescue medication is allowed at the Week 4 visit or later in patients meeting any of the following criteria:

- Loss of > 10 ETDRS letters from a previous best study visit with worsening of intraretinal or subretinal fluid observed by SD-OCT and judged by the Investigator to be the cause of the BCVA loss.
- Loss of > 5 ETDRS letters at 2 consecutive visits (one can be unscheduled) from a previous best study visit due to worsening of DME.
- An increase in CST > 75 μm from a previous best study visit which remains consistently > 75 μm from the previous best study in two consecutive visits, as assessed by SD-OCT.

The later visit can be an unscheduled visit if determined to be necessary by the Investigator.

- An increase in CST > 50 μm from a previous best study visit, as assessed by SD-OCT and a loss of > 5 ETDRS letters, which remains consistently > 50 μm and loss > 5 ETDRS letters from the previous best study in two consecutive visits. The later visit can be an unscheduled visit if determined to be necessary by the Investigator.
- Progression of or worsening of proliferative diabetic retinopathy.

Patients will be followed for at least 4 weeks after Rescue medication administration or through Week 12, whichever is greater.

Table 1: Summary of Open-label Cohorts and Dosing

Dose (mg)	Stock Vial Concentration (mg/mL)	Dilution Requirement	Volume to be Injected (mL)
0.5	40	1:1 with diluent	0.025
1	40	None	0.025
2	40	None	0.050
4	40	None	0.100

Randomization: none

Study Duration: The anticipated study duration is approximately 52 weeks, including 24 weeks for recruitment, up to 4 weeks for screening and 24 weeks of follow-up after administration of a single intravitreal injection of AG-73305. In certain cases, screening may be increased to 6 weeks, for a total of 54 weeks for the study duration.

Patient Duration: 28 weeks participation for patients from Screening to Exit. For patients where screening is increased to 6 weeks, then a total of 30 weeks of participation is expected.

9.5. EFFICACY AND SAFETY VARIABLES

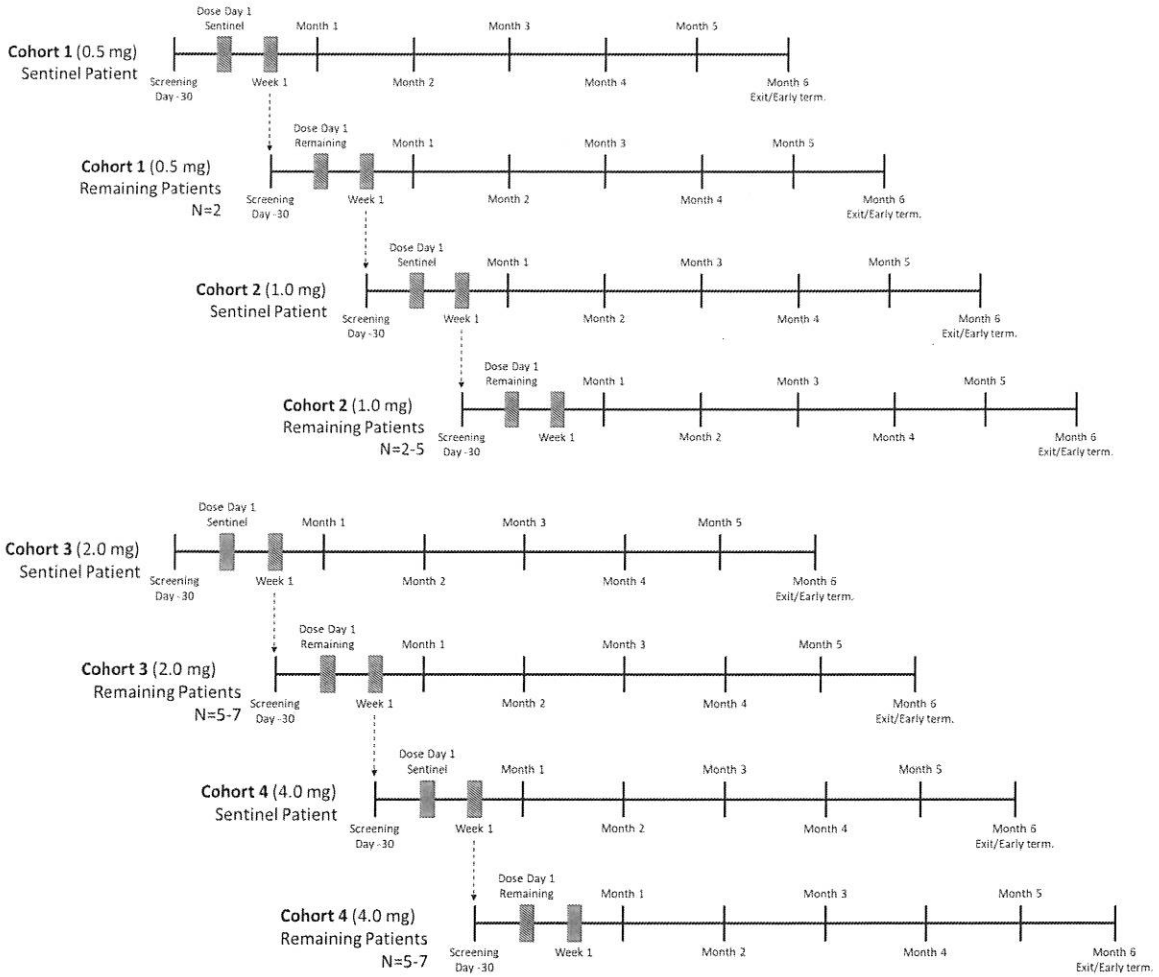
9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

The objectives of this study are to:

- Evaluate the safety, tolerability, duration of effect, systemic pharmacokinetic (PK) and immunogenicity profile of ascending doses of AG-73305 administered by intravitreal (IVT) injection in patients with diabetic macular edema (DME).
- Evaluate pharmacodynamic endpoints (e.g., best-corrected visual acuity [BCVA], spectral domain optical coherence tomography [SD-OCT] and OCT-angiography [OCT-A]).
- Determine the maximum tolerated dose or the highest administered dose for evaluation in future studies.

Figure 1 summarizes the design of the study.

Figure 1: Study Schematic



9.5.1.1. Visit and Procedure Schedule

See Table 3 in Appendix I for a complete visit and procedure schedule.

9.5.1.2. Demographics and Baseline Characteristics

9.5.1.2.1. Demographics

Demographic characteristics including age (years), sex, race, ethnicity, and eye color will be collected at the Screening Visit.

9.5.1.2.2. Medical and Surgical History

9.5.1.2.3. Ocular and non-ocular medical and surgical history will be collected at the Screening Visit. Prior and Concomitant Medications

Previous history of anti-VEGF IVT treatment for DME should be collected as detailed as possible, minimally for the last three years from baseline.

Details of all medications (other than those intended to treat the study patient's DME), therapies and supplements administered within 3 months prior to Screening Visit until the end of the study will be recorded in the electronic case report form (eCRF).

Permissible, prohibited, and rescue medications are outlined in the protocol Sections 6.5.1 – 6.5.3.

9.5.1.3. Efficacy Assessments

9.5.1.3.1. Primary Efficacy Assessment(s)

Best Corrected Visual Acuity (BCVA) measures will be used to determine vision improvement or maintenance of vision over time. ETDRS letters will be assessed in each eye at each in-clinic visit.

9.5.1.3.2. Secondary Efficacy Assessments

Dilated color fundus photography will be performed OU at the Baseline Visit, in the SE at Week 4, and OU at Week 24 to assess diabetic retinopathy severity score (DRSS).

Spectral Domain Optical Coherence Tomography (SD-OCT) will be performed OU at each in-clinic visit (Heidelberg Spectralis, dense scan). SD-OCT will assess central subfield thickness (CST), ellipsoid zone (EZ), external limiting membrane (ELM), intraretinal and subretinal fluid volume, and posterior vitreous detachment.

OCT Angiography (OCT-A) will be performed OU at the Baseline Visit, in the SE at Weeks 4 and 24, and OU at the visit when Rescue treatment is given. OCT-A will assess foveal avascular zone (FAZ) and foveal capillary density (CD) (superficial and deep capillary plexuses).

Color fundus photos and SD-OCT and OCT-A images will be submitted to a central reading center for grading.

Time to rescue medication will be assessed. Rescue medication will be standard-of-care anti-vascular endothelial growth factor (VEGF) administered by intravitreal injection (IVT) in the

study eye. Rescue medication is allowed at the Week 4 visit or later in patients meeting any of the criteria outlined in the protocol Section 6.5.3.

9.5.1.3.3. Exploratory Efficacy Assessments

Not applicable.

9.5.1.4. Safety Assessments

The safety of AG-73305 ophthalmic solution will be evaluated using the following assessments, conducted at each in-clinic visit unless otherwise noted.

1. Adverse event (AE) monitoring
2. ETDRS BCVA
3. Intraocular pressure (IOP)
4. Slit lamp biomicroscopy, including crystalline lens assessment using AREDS scale
5. Dilated fundus exam (DFE)
6. Post-injection assessment – Baseline Visit
7. Laboratory evaluation (hematology, serum chemistry and urinalysis) – Screening Visit and Weeks 4, 12, 24
8. Electrocardiogram (ECG) – Screening Visit and Weeks 4, 24
9. Vital signs
10. Pregnancy test – Baseline Visit and Week 24

A brief physical examination will also be conducted by the Principal Investigator or designee at Screening including review of systems.

9.5.1.4.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to that product. Worsening of the DME is not an AE, unless the worsening is greater than expected.

An AE 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 disability/incapacity, or substantial disruption of the ability to conduct normal life function.
- A congenital anomaly/birth defect

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

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity, as assessed by the Investigator:

- **Mild**: Event requires minimal or no treatment, and do not interfere with the patient's daily activities.
- **Moderate**: Event results in a low level of inconvenience or concern, no or minimal medical intervention/therapy is required. Moderate events may cause some interference with daily activities.
- **Severe**: Event interrupts a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

All AEs must have their relationship to study intervention assessed by the Investigator who examines and evaluates the patient based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical study, the investigational product (IP) must always be suspect.

- **Unrelated**: no reasonable possibility that the administration of the IP caused the event, no temporal relationship between the IP and event onset, or an alternate etiology has been established.
- **Related**: is known to occur with the IP, is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.

9.5.1.4.2. ETDRS BCVA

BCVA measures will be used as safety measures to determine vision loss over time. ETDRS letters will be assessed in each eye at each in-clinic visit.

9.5.1.4.3. Intraocular Pressure (IOP)

IOP will be measured in each eye with a tonometer per study site's standard operating procedures. A Baseline IOP will be measured before AG-73305 administration and after; the IOP measurement after IP administration should be performed using site specific SOPs. Pre-dose IOP must be measured prior to pupil dilation. The same type of equipment should be used for each IOP assessment per patient.

At the Baseline visit, IOP measurement will be performed prior to and after AG-73305 injection. After injection, IOP will be measured within 15 minutes using a non-contact method. If IOP >30mmHg, IOP measurement will be repeated at 15±5 minutes post injection until pressure is reduced.

9.5.1.4.4. Slit Lamp Biomicroscopy

Biomicroscopy will be performed in each eye by slit-lamp examination of the lids, conjunctiva, cornea, and iris with clinically significant abnormal findings reported. The status of the crystalline lens will be assessed using the Age-Related Eye Disease Study (AREDS) scale.

9.5.1.4.5. Dilated Fundus Exam (DFE)

Dilated ophthalmoscopy will be performed in each eye with an indirect ophthalmoscope to evaluate any posterior segment abnormalities. When possible, for consistency purposes, the same lens should be used for all assessments throughout the study. Clinically significant abnormal findings will be reported on the eCRF.

9.5.1.4.6. Post-Injection Assessment

Post-injection assessment is to be performed within 15 minutes after the injection checking for finger counts or hand motion and measuring IOP using site specific SOPs; if needed, the patient can be requested to do additional examinations (i.e., additional IOP or ophthalmoscopy), per discretion of the Investigator prior to completing the study visit.

In addition, a next-day post-injection on-site safety visit will be conducted in all patients which will comprise of assessments such as adverse events, BCVA, IOP, slit lamp biomicroscopy and dilated fundus exam.

9.5.1.4.7. Laboratory Evaluation (Hematology, Serum Chemistry and Urinalysis)

Hematology. Includes hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelets, red blood cell (RBC) count, RBC morphology, total white blood cell (WBC) count, and differential (neutrophils, bands, lymphocytes, monocytes, basophils, and eosinophils).

Non-fasting serum chemistry. Includes albumin, alkaline phosphatase, Alanine amino Transferase (ALT), Aspartate amino Transferase (AST), bicarbonate, calcium, chloride, creatinine, direct bilirubin, gamma-glutamyl transferase, indirect bilirubin, magnesium, non-fasting glucose, (HbA1C), phosphorous, potassium, sodium, total bilirubin, total cholesterol, total protein, urea nitrogen, and uric acid.

Urinalysis. Includes clarity, color, bilirubin, creatinine, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen, microscopic sediment (WBCs, RBCs, casts, bacteria, crystals, and epithelial cells), and screen for drug use.

Approximately 13.5 mL of blood will be drawn for clinical laboratory evaluations at the required visits. A qualified central laboratory will receive all blood and urine samples from the site(s) and will analyze and report the results. Data will be transferred to Allgenesis or their designee on a periodic basis throughout the duration of the study.

9.5.1.4.8. Electrocardiogram (ECG)

Electrocardiograms will be obtained using a 12-lead standard equipment. The investigator will be responsible for the initial review of the ECG to assess whether the ECG is within the reference limits. All ECGs will be sent to a central reader for interpretation, including confirmation of eligibility and ongoing safety assessments, and assessed for the following measures: P wave, QRS complex, U wave, QRS duration, QT interval, T wave, ST segment, RR interval, PR interval, and qualitative results. Blood draws, vital signs, and other procedures should be delayed until after each ECG.

9.5.1.4.9. Vital Signs

Systolic and diastolic blood pressure (mmHg), heart rate (BPM), body temperature (°F) and respiratory rate (breaths per minute) will be measured after patients have been at rest (seated) for at least 5 minutes.

9.5.1.4.10. Pregnancy Test

Pregnancy testing will be performed using a human chorionic gonadotropin pregnancy urine dipstick test for female patients of childbearing potential only.

9.5.1.5. Other Assessments

9.5.1.5.1. Pharmacokinetics

In a subset of at least 2-4 patients per study group (at selected study sites), blood samples (approximately 10 mL per sample) will be collected for monitoring the plasma concentrations of AG-73305. In cohorts 1 and 2 on plasma monitoring samples will be collected on Day 1 at pre-dose and at 1, 3, and 8 after the intravitreal injection, and at the Week 1 and 4 visits. In cohorts 3 and 4, samples will be collected on Day 1 at pre-dose and at 3, 8 and 24 hours after the intravitreal injection, and at the Week 1 and 4 visits. Plasma drug concentrations will be measured using a validated enzyme-linked immunosorbent assay, with a target lower limit of quantitation of ~1 ng/mL. Allgenesis shall have full ownership rights to any biological samples derived from the study.

9.5.1.5.2. Immunogenicity

Blood samples (approximately 20 mL per sample) will be collected for the assessment of anti-drug antibodies towards AG-73305 at pre-dose, Week 1, 4, 8 and 24.

9.5.2. Appropriateness of Measurements

All assessments used in this study are widely used and generally recognized as reliable, accurate, and relevant.

9.5.3. Primary Efficacy Variable(s)

The key efficacy measure is best-corrected visual acuity score of the study eye using the ETDRS as assessed by certified Investigator or designee. The endpoint is the change from baseline in overall BCVA score at Week 4.

9.5.4. Drug Concentration Measurements

The measurement of plasma drug concentration will be conducted at B2S Life Sciences and transferred to Lexitas. Plasma drug concentrations will be measured using a validated enzyme-linked immunosorbent assay, with a target lower limit of quantitation of ~1 ng/mL.

9.6. DATA QUALITY ASSURANCE

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures, the monitors will verify that the clinical trial is conducted, and data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH-GCP, and applicable regulatory requirements (e.g., GLP, Good Manufacturing Practice).

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.6.1. Training and Education of Investigators and Study Site Personnel

An Investigator Meeting will be held before study initiation and attended by the Investigators and/or Sub-Investigators from each study site, study coordinators from each study site, if possible, and personnel from the sponsor and the Contract Research Organization (Lexitas Pharma Services, Inc., hereafter referred to as Lexitas). The purpose of this meeting is to train and instruct the Investigators and the study coordinators on the proper conduct of the clinical trial and ensure that all patients are aware of their obligations set out by the protocol, ICH guidelines, GCP guidelines, and other applicable regulatory requirements.

9.6.2. Monitoring of Study Sites

Clinical site monitoring is conducted to ensure that the rights and well-being of the trial patients are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH Good Clinical Practice (GCP), and with applicable regulatory requirement(s).

- A representative of Allgenesis will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations, such as the objective, purpose, design, complexity, masking, size, and endpoints of the study.
- Authorized representatives of Allgenesis or regulatory authority representatives will conduct on-site visits to review, audit, and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

9.6.3. Data Entry and Verification of Database Used for Analysis and Reporting

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site's Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Lexitas will review the eCRFs entered by investigational site staff for completeness and accuracy and instruct the investigational site staff to make any required corrections or additions. After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Queries will be sent to the investigational site and designated investigational site staff are required to respond to the query and edit data, as necessary. All changes to the study database will be documented.

It is the responsibility of the monitor to make certain that all data are completed on the eCRFs. At the end of each study period, the Investigator will sign and date the eCRF to attest to the authenticity of the collected data and coherence between the data in the eCRF and the data in the source documents.

Collection of SD-OCT, OCT-A, and color fundus imaging will be done at sites with the requisite equipment and certified by an independent imaging reading center. The grading of images will be completed by the reading center.

BCVA measures will be performed by qualified technicians who have recent or current certification to minimize bias. Appropriate and relevant documentation of certification of the technicians at each investigative site will be provided prior to screening any study patients.

9.6.4. Clinical Study Report

The final clinical study report will be reviewed, audited, and approved by medical, clinical, statistical, and regulatory staff from the sponsor, and key study contributors from Lexitas.

9.6.5. Inter-Laboratory Standardization Methods

Not applicable. A single, qualified, and certified central clinical laboratory will be used to analyze and report clinical laboratory data.

9.7. STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

This section of the analysis plan describes the analyses explicitly mentioned in the protocol as well as additional analyses not explicitly mentioned in the protocol but planned prior to breaking the treatment mask. Section 9.8 describes any changes to analyses that were explicitly mentioned in the protocol or statistical analysis plan.

9.7.1. Statistical and Analytical Plans

General Conventions

Summary statistics for the data collected during this study will be presented to give a general description of the patients studied. Data from all sites will be combined in the computation of these descriptive summaries. Categorical variables will be summarized by the frequency and percentage of patients in each category. Continuous variables will be summarized using N, mean, standard deviation (SD), median, minimum, and maximum values.

Number of patients, minimums, and maximums will be calculated to the same number of decimal places as the source data. Means, medians, standard deviations, and quartiles will be calculated to one more decimal place than the source data. Percentages will be calculated to the nearest one decimal place. Zero count cells will be displayed as "0" with percentage of (0%). Unless otherwise noted, summaries will be performed by the treatment group and presented in the order of: AG-73305, 0.5 mg; AG-73305, 1 mg; AG-73305, 2 mg; AG-73305, 4 mg.

Baseline values will be defined as the last measurement prior to dosing of study medication. Ocular measurements will use the most recent measurement for each eye.

Numeric laboratory, pharmacokinetic, and immunogenicity data may be recorded at limits of detection (with a '<' or '>' sign, e.g., < 0.1 or > 0.1). To summarize laboratory data, the original value will be converted to one unit less or more at the level of measured precision (e.g. 0.4 in the case of < 0.5 and to 0.6 in the case of > 0.5). For pharmacokinetic data, for Time = 0 (predose), any result that is below the level of quantitation (BLQ) is set to zero; all other timepoints are set to missing for any computations. For immunogenicity, any titer < Value (a negative result) is set to zero. Summary tables for immunogenicity titer will not include these negative results.

The actual values will be presented in the data listings.

All data collected in this study will be presented in individual patient data listings for all patients.

Computations for all results will be performed using SAS (Version 9.4, SAS/STAT 15.2) computer software package (SAS Institute, Inc, 2013, 2020), unless otherwise specified.

Strata and Covariates

Not applicable.

Subgroups

Not applicable.

Multiplicity

Not applicable.

Missing Data and Outliers

Every attempt will be made to capture all study data. All analyses will utilize observed data only.

Visit Windows

The nominal visits listed in the eCRF will be used in the summaries. In general, unscheduled visits will not be summarized in tables unless otherwise noted.

Missing Dates

Missing dates that occur for prior or concomitant medications or adverse events will be queried for a date. If no date is obtained, the following imputation rules will apply:

- For start dates, if the given year (or year-month) is the same as study drug administration, the start date will be imputed as study drug administration date; otherwise, missing month-day (or day) will be imputed as '01-01' (or '01').
- For stop dates, missing months will be imputed as '12' and missing days will be imputed as the last day of the month. If this creates a date after discontinuation/completion, the date of discontinuation/completion will be used.

Imputed dates will only be used to classify events or medications, such as occurring before or after the start of treatment. Imputed dates will only be used in tables. Listings will display the available date data.

Interim Analysis

No formal interim analysis is planned. However, as the study is open-label, safety and efficacy data will be periodically reviewed and summarized for assisting the Safety Review Committee with their assessments.

9.7.1.1. Analysis Populations

9.7.1.1.1. Populations

The Full Analysis Set will include all patients who received at least one dose of investigational product as indicated on the dosing record. Patients will be analyzed in the group according to the treatment received. All efficacy and safety variables will be analyzed using the Full Analysis Set and only observed data will be included.

9.7.1.1.2. Analysis Eyes

Patients in the FAS will have at least one eye that qualifies based on the criteria in the protocol. Both eyes may qualify based on the criteria.

Efficacy analyses will be performed for the study eye; safety analyses will be presented for both eyes, by study eye and non-study eye.

The study eye is defined as the eye meeting all inclusion criteria and no exclusion criteria, and with the worse BCVA assessed at screening and confirmed at the Baseline (Day 1) visit. If both eyes meet all of the inclusion/exclusion criteria and BCVA values are identical for both eyes, the patient may choose the eye for study enrollment, or else the right eye will be selected as the study eye.

9.7.1.2. Analysis of Patient Disposition

The number of patients enrolled at each site will be summarized by treatment cohort and overall using the FAS.

Patients' enrollment and disposition during the study will be summarized by treatment cohort and overall using the FAS. The reasons for discontinuation will be displayed in the order as they appear on the eCRF, and percentages will be calculated based on the number of patients who discontinued the study.

Summary tables will include the following. The percentages will be calculated based on the number of patients in the FAS.

- Number of patients screened
- Number and percentage of patients treated
- Number and percentage of patients treated who completed the study
- Number and percentage of patients treated who discontinued from the study
- The reasons for study discontinuation
- Number and percentage of patients attending each scheduled study visit

A listing of patients who do not meet all inclusion criteria or meet exclusion criteria will be provided. A table of major protocol deviations will be presented using the FAS.

9.7.1.3. Analysis of Demographic and Baseline Characteristics

9.7.1.3.1. Demographics and Disease Characteristics

Demographic and disease characteristics including age (years), age group (<65 years, ≥65 years), sex, race, ethnicity, study eye (OD/OS), eye color, duration of DME, duration of diabetes, type of diabetes (type 1 or type 2), DME in the non-study eye, and prior laser photocoagulation in the study eye, will be summarized descriptively by treatment group and overall using the FAS. For categorical parameters, the percentages will be calculated overall and based on the number of patients in each treatment group based on non-missing observations.

Duration of diabetes and DME will be determined from the medical history page compared to date of consent. Presence of DME in the non-study eye, laser photocoagulation, and type of diabetes will be determined from medical history page.

9.7.1.3.2. Medical and Surgical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 25.0, Mozzicato, 2009). The frequency and percentage of patients with any medical history will be summarized by treatment group using the FAS. System organ class (SOC) will be sorted alphabetically and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

1. Descending frequency within AG-73305, 0.5 mg;
2. Descending frequency within AG-73305, 1 mg;
3. Descending frequency within AG-73305, 2 mg;
4. Descending frequency within AG-73305, 4 mg;
5. PT in alphabetical order.

The medical history will include both the ocular and the general (non-ocular) history. Ocular medical history and general (non-ocular) medical history will be summarized separately. Ocular and non-ocular medical histories are identified according to which CRF the event is recorded. Ocular medical history will be summarized separately for study eye and non-study eye.

9.7.1.3.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) (Version 2022-03, Lagerlund et al., 2020) for anatomical therapeutic chemical (ATC) classification and preferred drug name.

The frequency and percentage of patients with coded medications will be summarized by treatment group using the FAS. A patient who used multiple medications will be counted only once for each ATC and preferred drug name. Therapeutic Subgroup is sorted alphabetically, and preferred term is sorted by descending frequency overall within each Level 3 term according to:

1. Descending frequency within AG-73305, 0.5 mg;
2. Descending frequency within AG-73305, 1 mg;
3. Descending frequency within AG-73305, 2 mg;
4. Descending frequency within AG-73305, 4 mg;
5. PT in alphabetical order.

Prior and concomitant medications will be summarized separately. Ocular medications are defined as those medications for which an eye has been specified (OD, OS, or OU). Ocular and non-ocular medications will be summarized separately. Ocular medications will be summarized separately for study eye, non-study eye, and either eye.

Prior medications are defined as any medications that started and stopped prior to the first dose of study drug. Concomitant medications are defined as any medications that (1) start prior to the first dose of study drug and stop or are ongoing at or after the date of first dose of study drug; or (2) start at or after the first dose of study drug. Medications taken after Visit 9 or withdrawal from the study are not considered concomitant.

9.7.1.4. Analysis of Study Medication Compliance and Exposure

Not applicable as this is a single dose study.

9.7.1.5. Analysis of Efficacy

Summary descriptive statistics will be presented for all study visits at which efficacy data are collected. Efficacy analyses will be presented by cohort for the study eye using the FAS population. Data for efficacy assessments for the non-study eye will be provided in listings.

All efficacy data will be censored (set to missing) on or after the earliest instance of rescue therapy when summarized in tables. All data will be presented in listings.

9.7.1.5.1. Primary Efficacy Analysis

The key efficacy measure is best-corrected visual acuity score of the study eye using the ETDRS as assessed by certified Investigator or designee. The endpoint is the change from baseline in ETDRS letters at Week 4, so scores from Day 1 and Week 4 will be analyzed. Final scores will be calculated as Week 4 minus Day 1 BCVA letter counts. A positive result will indicate more letters gained following AG-73305 injection, while a negative score indicates worsening of vision. Observed and change from baseline in BCVA letter count at other visits will be summarized in a similar fashion to the key efficacy measure.

In addition, change from baseline in BCVA letter count as measured by ETDRS at each visit and the proportion of study eyes with ≥ 5, ≥ 10, and ≥ 15 BCVA letter increase from baseline will be analyzed.

9.7.1.5.2. Secondary Efficacy Analyses

Observed and change from baseline in CST as measured by SD-OCT at Week 1, 4, 8, 12, 16, 20 and 24 will be presented. A change from baseline in CST will indicate a positive response if the treatment difference is < 0. Observed and change in intraretinal and subretinal fluid volumes, ELM and EZ by SD-OCT at each visit will also be presented. The presence of posterior vitreous detachment will be summarized by frequency and percentage.

Observed and change from baseline in FAZ and CD of the superficial and the deep capillary plexuses will be presented, as measured by OCT-A at the Baseline Visit, Week 4, and Week 24.

Observed and change from baseline in DRSS will be presented, assessed via color fundus photography at the Baseline Visit, Week 4, and Week 24.

Time from Day 1/Baseline to receipt of rescue medication in the study eye will be analyzed using Kaplan-Meier time-to-event analyses. Follow-up is measured to the earliest instance of receipt of rescue therapy in the study eye for patients receiving rescue therapy. Otherwise, patients are censored at the date they complete or discontinue the study. In addition, reasons for rescue and use of rescue medication by visit will be summarized by frequency and percentage. Rescue will be included at Visit X if the date rescue is provided is on or after Visit X and before Visit X + 1.

9.7.1.5.3. Exploratory Efficacy Analysis

Not applicable.

9.7.1.6. Analysis of Safety

Safety will be evaluated by:

1. Adverse event (AE) monitoring (study eye and fellow eye)
2. ETDRS BCVA
3. Intraocular pressure (IOP)
4. Slit lamp biomicroscopy, including crystalline lens assessment using AREDS scale
5. Dilated fundus exam (DFE)
6. Post-injection assessment
7. Laboratory evaluation (hematology, serum chemistry and urinalysis)
8. Electrocardiogram (ECG)
9. Vital signs
10. Pregnancy test

The FAS will be used for all safety analyses. All data will be summarized as observed and no data imputation will be performed. No statistical treatment group comparisons will be performed, unless otherwise specified. Analyses will be presented by cohort and by study eye and non-study eye, if applicable.

Results from the physical examination performed at Screening will be presented in a listing.

All safety data will be censored (set to missing) on or after the earliest instance of rescue therapy when summarized in tables. All data will be presented in listings. This will impact the definition of TEAE.

9.7.1.6.1. Adverse Events

AEs are coded using MedDRA Version 25.0. Treatment-emergent adverse events (TEAE) are defined as events that start on or after the administration of study medication and up to the earliest instance of rescue therapy. Pretreatment adverse events are events that begin prior to administration of study medication. Ocular AEs are defined as those events for which an eye has been specified (OD, OS, or OU).

Ocular and non-ocular treatment-emergent AEs will be summarized separately. Ocular AEs will be presented by study eye and non-study eye and overall (OU) if an event occurs in either eye.

In all summaries of AEs, percentages are calculated based on the number of patients in each treatment group of the Safety Analysis Set.

Overall summaries of AEs by treatment will include:

- the number of AEs and SAEs reported;
- the number and percentage of patients who experienced any AE;

- the number and percentage of patients who experienced any serious adverse event (SAE) and the reason for seriousness;
- the number and percentage of patients with any AE by worst severity and worst relationship.

The overall summaries of TEAEs will also include the number and percentage of patients with any TEAEs leading to study termination.

Summaries of the frequency and percentage of patients with AEs by SOC and preferred term by treatment group will include:

- All AEs by SOC and preferred term;
- All AEs by SOC, preferred term, and maximum severity;
- All AEs by SOC, preferred term, and maximum relationship.

System organ class (SOC) will be sorted alphabetically, and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

1. Descending frequency within AG-73305, 0.5 mg;
2. Descending frequency within AG-73305, 1 mg;
3. Descending frequency within AG-73305, 2 mg;
4. Descending frequency within AG-73305, 4 mg;
5. PT in alphabetical order.

Patients are counted only once for each SOC and PT. In summaries of maximum severity and maximum relationship, patients with multiple occurrences of events will only be counted once at the maximum severity/relationship per SOC and PT.

Any treatment-emergent AEs that have a missing severity will be presented as severe in the summary table but will be presented with a missing severity in the data listing. Any treatment-emergent AEs that have a missing relationship will be presented as "Related" in the summary table but will be presented with a missing relationship in the data listing.

All AEs are displayed in listings. In addition, separate listings will be provided for:

- Patients with any treatment-emergent adverse event leading to study termination;
- Patients with any serious adverse event (treatment-emergent or otherwise);
- Patient deaths.

9.7.1.6.2. ETDRS BCVA

Descriptive summaries of the observed values at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented for both eyes. Patients with a loss of ≥ 5, ≥ 10, and ≥ 15 letters in BCVA will be summarized by frequency and percentage.

9.7.1.6.3. Intraocular Pressure (IOP)

Descriptive summaries of the observed values at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented for both eyes. Patients with an increase of ≥ 10 mmHg in IOP will be summarized by frequency and percentage.

9.7.1.6.4. Slit Lamp Biomicroscopy

The frequency and percentage of patients with observed values of each categorical response or grade as well as the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit for both eyes. The percentages of patients with observed values of each categorical response will be calculated based on the number of patients at each visit in each treatment group of the FAS. Percentages for categorical shifts from baseline will be based on the number of patients with baseline and post-baseline values at each visit in each treatment group.

9.7.1.6.5. Dilated Fundus Exam

The frequency and percentage of patients with observed values of each categorical response as well as the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit for both eyes. The percentages of patients with observed values of each categorical response will be calculated based on the number of patients at each visit in each treatment group of the FAS; percentages for vitreous hemorrhage severity and localization will be calculated based on the number of patients with vitreous hemorrhage present. Percentages for categorical shifts from baseline will be based on the number of patients with baseline and post-baseline values at each visit in each treatment group.

9.7.1.6.6. Post-Injection Assessment

The frequency and percentage of patients able to see hand motion or count fingers with the study eye will be presented.

9.7.1.6.7. Laboratory Evaluation (Hematology, Serum Chemistry and Urinalysis)

Descriptive summaries of the observed test results at Screening and Weeks 4, 12, and 24, as well as the change from baseline at Weeks 4, 12, and 24, will be presented for hematology, serum chemistry, and a subset of urinalysis labs. The frequency and percentage of patients with observed values of Low, Normal, High as well as the categorical shifts from baseline will be tabulated for hematology and serum chemistry labs. The percentages will be calculated based on the number of patients with baseline and post-baseline values at each visit in each treatment group. The frequency and percentage of patients with observed values for categorical urinalysis laboratory measurements will also be tabulated, with percentages calculated based on the number of patients with values at each visit in each treatment group.

It is expected that all samples will be analyzed by a central laboratory. If a local laboratory is used (such as for an unscheduled visit), the results will be included in the listings of laboratory data, but will not be included in descriptive summaries.

9.7.1.6.8. Electrocardiogram (ECG)

Descriptive summaries of the observed values at the Screening Visit, Visit 4, and Visit 12, as well as the change from baseline at each post-baseline visit will be presented. The frequency and percentage of patients with observed values of each categorical response as well as the categorical shift from baseline at each post-baseline visit will also be tabulated.

9.7.1.6.9. Vital Signs

Descriptive summaries of the observed values at each scheduled visit as well as the change from baseline at each post-baseline visit will be presented.

9.7.1.6.10. Pregnancy Test

The results of pregnancy tests for women of childbearing potential will be presented in a listing.

9.7.1.7. Analysis of Other Measurements

9.7.1.7.1. Pharmacokinetic Analyses

Observed AG-73305 plasma concentrations will be summarized for each cohort for the Day 1, 24hr post-dose (if available), Week 1, and Week 4 visits. Mean plasma-concentration profiles will be graphed for each cohort.

A model-independent non-compartmental approach will be used to calculate plasma PK parameters for AG-73305, where appropriate, including AUC_{0-t}, C_{max}, and T_{max}, and summary statistics will be presented.

9.7.1.7.2. Anti-Drug Antibody Analyses

The immunogenicity (anti-AG-73305 antibody) results (reactive [positive], negative, or inconclusive) will be summarized. The titer value for positive samples will also be summarized. Quantitative relationships between immunogenicity findings and AG-73305 PK, efficacy, and/or safety variables may be explored.

9.7.2. Determination of Sample Size

A sample size of 3-8 patients for each cohort is not based on formal power considerations. The table below defines the probability of observing at least one patient with a DLT or SAE among 3, 6, or 8 patients for assumed probabilities of a DLT or SAE (see Table 2).

Table 2: Probabilities of DLT or SAE

Probability of a DLT/SAE	Probability of Observing ≥ 1 Patient with DLT/SAE		
	Cohort of 3 Patients	Cohort of 6 Patients	Cohort of 8 Patients
0.05	0.143	0.265	0.337
0.1	0.271	0.469	0.57
0.15	0.386	0.623	0.728
0.2	0.488	0.738	0.832
0.25	0.578	0.822	0.9
0.3	0.657	0.882	0.942
0.35	0.725	0.925	0.968

0.4	0.784	0.953	0.983

9.8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1. Protocol Amendments

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Amendment 1 made the following changes:

- Sponsor address;
- Exclusion criteria 19f.

Amendment 2 made the following changes:

- The additional collection of safety assessments the next day after dosing;
- The addition of a 24-hour post-dose PK sample for Cohorts 3 and 4;
- Clarification on timing and specificity of some assessments.

Amendment 3 made the following changes:

- Changed the dose of Cohort 4 to 4mg (0.1 mL);
- Updated CST trigger for rescue medication;
- Added 14-day extension to screening window;
- Updated safety data and margin;
- Updated inclusion criteria;
- Updated schedule of activities;
- Updated prohibited medications;
- Updated storage conditions.

9.8.2. Changes from Protocol-Specified Analyses

Not applicable.

REFERENCES

1. Mozzicato P. (2009). MedDRA: An overview of the medical dictionary for regulatory activities. Pharmaceutical Medicine 23: 65-75.
2. Lagerlund O, Strese S, Fladvad M & Lindquist M. (2020). WHODrug: A global, validated and updated dictionary for medicinal information. Therapeutic Innovation & Regulatory Science 54: 1116–1122.
3. SAS Institute Inc. What's New in Base SAS® 9.4 and SAS® Viya®. (2013). SAS Institute Inc., Cary, NC, USA.
4. SAS Institute Inc. (2020). SAS/STAT User's Guide. SAS Institute Inc., Cary, NC, USA.

APPENDIX I: SCHEDULE OF ASSESSMENTS

Table 3: Schedule of Assessments

	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Activity/Assessment	Screening	Baseline[a]	Next Day Follow-up[b]	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24 or Early Term
Visit Day ± Window	Day -30 to -2[c]	Day 1	Day 2	Day 8 ± 2	Day 28± 5	Day 56± 5	Day 84± 5	Day 112 ± 5	Day 140 ± 5	Day 168 ± 5
Informed Consent	X									
Inclusion/Exclusion Review	X									
Demographics	X									
Medical and Drug History	X									
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Concurrent Procedures	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG) (12-lead)	X				X					X
Vital Signs[d]	X	X		X	X	X	X	X	X	X
Physical Examination	X									
Clinical Lab Tests[e]	X				X		X			X
Pregnancy test[f]		X								X
BCVA (ETDRS)[g]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
IOP[h]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Color Fundus Photos (7-field)[i]		OU			SE					OU
SD-OCT[i]	OU	OU		OU	OU	OU	OU	OU	OU	OU
OCT-A[i,j]		OU			SE					SE
Biomicroscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Ophthalmoscopy[k]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Prednisolone acetate 1% Dispense[l]	X									
AG-73305 Dosing[m]		SE								

	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Activity/Assessment	**Screening**	**Baseline[a]**	**Next Day Follow-up[b]**	**Week 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 or Early Term**
Adverse Events		X	X	X	X	X	X	X	X	X
Plasma Drug Monitoring [n]		X	X	X	X					
Immunogenicity [o]		X		X	X	X				X

Abbreviations: BCVA = best-corrected visual acuity; ECG = electrocardiogram; ETDRS = Early Treatment of Diabetic Retinopathy Study; IOP = intraocular pressure; OU = both eyes; SD-OCT = spectral domain optical coherence tomography; OCT-A = OCT angiography; SE = study eye

a. Preferably within Monday-Thursday to ensure next day safety assessment and timely collection of 24-hour post dose plasma drug monitoring sample. Any Baseline planned on a Friday needs to be pre-approved by Allgenesis
b. Patients who do not provide PK sample may complete the safety follow-up within 1-3 days post dose
c. An additional 14-day extension to the 30-day screening window is allowed, upon approval from Sponsor and Medical Monitor, on a case-by-case basis
d. Blood pressure, heart rate, body temperature, and respiratory rate
e. Blood chemistries, hematology and urinalysis and drugs of abuse screen (Screening only)
f. Urine pregnancy test, females of childbearing potential only
g. BCVA will use the ETDRS method and chart
h. IOP measurement will be performed prior to and after AG-73305 injection at Baseline/Day1. After injection, IOP will be measured within 15 minutes using a tono-pen or tono-pen like device. If IOP >30mmHg, repeat IOP measurement at 15±5 minutes post injection until pressure is reduced
i. Color fundus photos, OCT-A and SD-OCT images will be submitted to a reading center for grading; not required for eligibility
j. OCT-A is to be performed at baseline and at the visit (OU) when **Rescue** treatment is given. OCT-A is to be performed prior to the rescue treatment
k. Dilated fundus exam
l. Prednisolone acetate 1% ophthalmic suspension will be provided to patients, who will be instructed to prophylactically treat the study eye QID 2 days prior to the Baseline visit. Patients will be instructed to taper based on the Day 2 follow-up visit
m. Within 15 minutes following intravitreal injection, a post-injection assessment will be done, including checking for count fingers or hand motion vision
n. At selected sites, blood (~10 mL) will be collected for plasma drug monitoring on Day 1 pre-dose (all Cohorts), 1 hour (Cohort 1 and 2 only), 3 hours (all Cohorts), 8 hours (all Cohorts) and 24 hours post dose (Cohort 3 and 4 only), Week 1 (all Cohorts), and Week 4 (all Cohorts) in approximately 2-4 patients.
o. ~20 mL of blood will be collected on Day 1 pre-dose and Weeks 1, 4, 8 and 24 from all patients for anti-drug antibody assessments.

Additional examinations and unscheduled visits can be included as safety concerns arise.

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Allgenesis P2-73305-001 SAP Final V2.0 2023-05-02

Final Audit Report 2023-05-02

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