A MULTICENTER, OPEN-LABELED, PHASE 2A STUDY EVALUATING THE SAFETY, TOLERABILITY, AND EFFICACY OF INTRAVITREAL AG-73305 IN PATIENTS WITH DIABETIC MACULAR EDEMA

Protocol Number:	P2-73305-001
Sponsor:	Allgenesis Biotherapeutics Inc. 9F-3, No.760, Sec. 4, Bade Rd., Songshan Dist., Taipei City 105, Taiwan (R.O.C.) Tel: +886-2-8787-1232 Fax: +882-2-8787-1239
Clinical Research Organization:	Lexitas Pharma Services Address: 313 Foster St., Durham, NC 27701
IND Number:	152032
Clinical Phase:	2a
Date:	05 July 2022
Protocol Version Number:	4.0
Version History:	2.0 submitted to IND; 22 February 2022 3.0 Amendment 1; 05 July 2022 4.0 Amendment 2; 27 December 2022

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

SPONSOR APPROVAL AND SIGNATURE PAGE

The following individuals approve this protocol V4.0 dated 27 December 2022

Sunil Patel, MD, PhD Chief Medical Officer Allgenesis Biotherapeutics Inc.	Date
George Magrath, MD Medical Monitor Lexitas Pharma Services	Date

INVESTIGATOR SIGNATURE PAGE

I agree to:

a) Implement and conduct this clinical study diligently and in strict compliance with the protocol, Good Clinical Practice (GCP), and all applicable laws and regulations.
b) Maintain all information supplied by Allgenesis Biotherapeutics Inc. and Lexitas Pharma Services in confidence and when this information is submitted to an Institutional Review Board (IRB), Human Research Ethics Committee (HREC), Independent Ethics Committee (IEC), or other review board, it will be submitted with a designation that the material is confidential.

I have read this protocol, P2-73305-001, Version 4.0. dated 27 December 2022, in its entirety and agree to all aspects.

Signature of Investigator	Date

Investigator Name (print or type)

Name of Facility

Location of Facility (city, state)

Please return to Lexitas Pharma Services

STUDY TITLE

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

SHORT NAME

AG-73305 Single Ascending Dose Cohort Study in DME

PROTOCOL NUMBER

P2-73305-001

STUDY PERSONNEL

Allgenesis Biotherapeutics Inc.		
Chief Medical Officer	Sunil Patel MD, PhD	sunil.patel@allgenesis.com
Lexitas Pharma Services		
Medical Monitor	George Magrath, MD	George.magrath@lexitas.com
Trial Statistician	Richard Zink, PhD	Richard.zink@lexitas.com

Serious Adverse Events Reporting:

Drug Safety Navigator (DSN)

2605 Meridian Pkwy, Suite 115

Durham, NC 27713

EMAIL ADDRESS FOR SAE QUESTIONS:

pvg@drugsafetynavigator.com

TABLE OF CONTENTS

Statement of Compliance

This study is to be conducted in accordance with Institutional Review Board (IRB) regulations (United States [US] 21 Code of Federal Regulations [CFR] Part 56.103) or applicable Human Research Ethics Committee (HREC), or Independent Ethics Committee (IEC) regulations. The investigator must obtain approval from a properly constituted HREC/IRB/IEC prior to initiating the study and re-approval or review at least annually. Allgenesis is to be notified immediately if the responsible HREC/IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all HREC/IRB/IEC correspondence with the investigator should be provided to Allgenesis.

The investigator should not implement any deviation from or changes to the protocol without approval by Allgenesis and prior review and documented approval/favorable opinion from the HREC/IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

1 PROTOCOL SUMMARY

1.1 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 (see Figure 1).

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

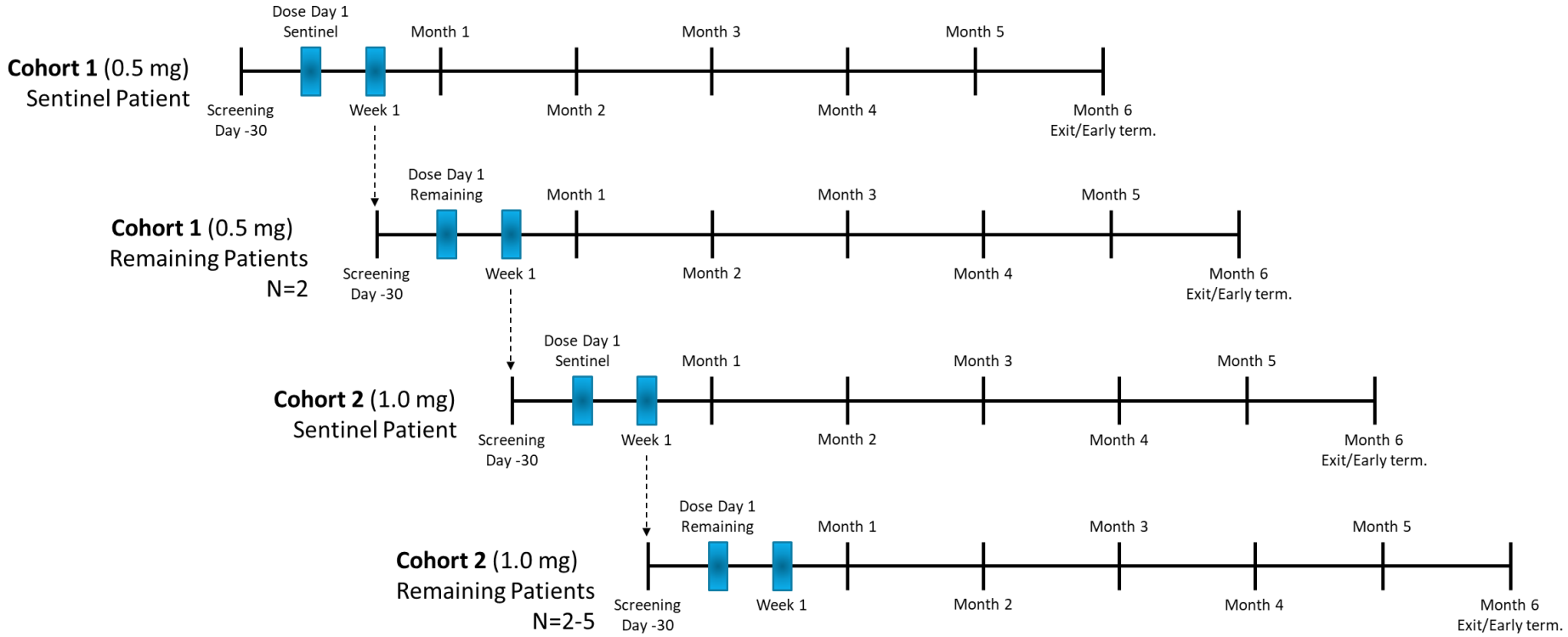
Randomization: none

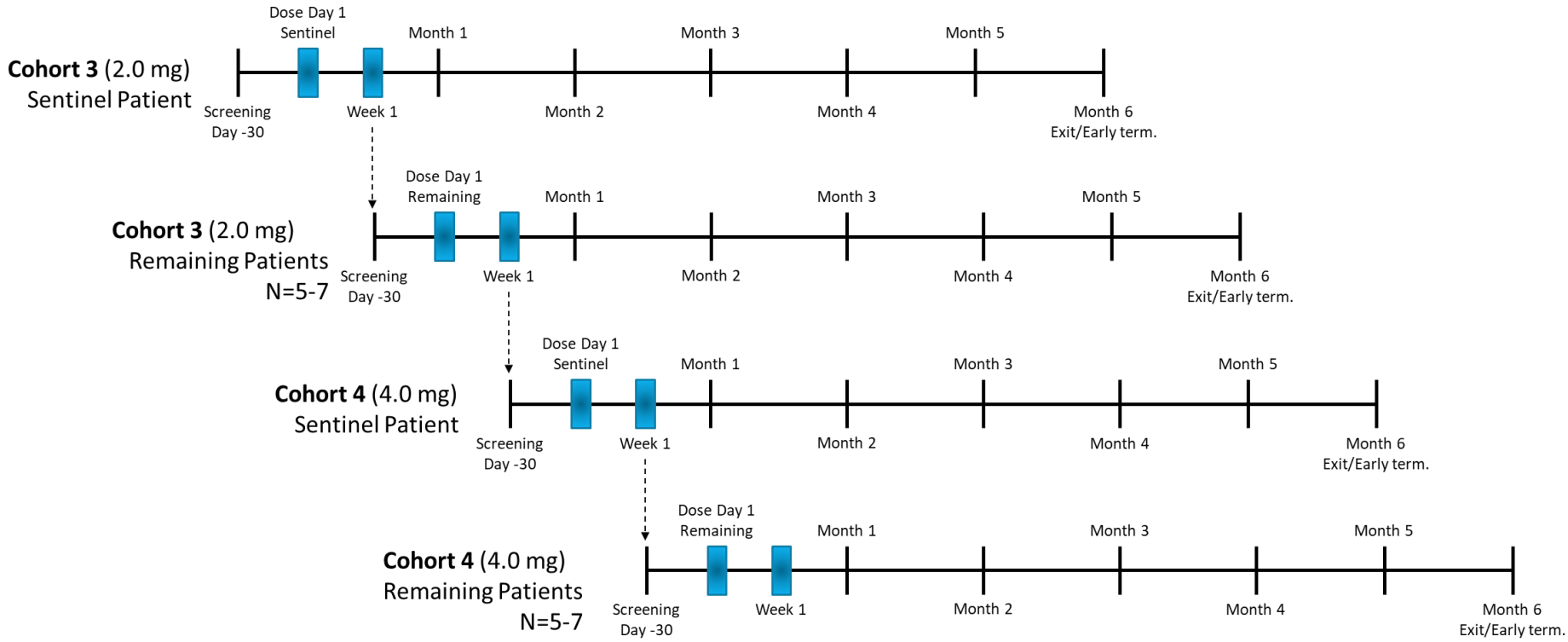
Study Duration: The anticipated study duration is approximately 52 weeks, including 24 weeks for recruitment, up to 4 weeks for screening and 24 weeks of follow-up after administration of a single intravitreal injection of AG-73305. In certain cases, screening may be increased to 6 weeks, for a total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

1.2 STUDY SCHEMA

Figure 1 **Single Ascending Dose Design in DME Patients**




Cohort 3 (2.0 mg)
Sentinel Patient
Dose Day 1
Sentinel
Screening
Day -30
Week 1
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Exit/Early term.
Cohort 3 (2.0 mg)
Remaining Patients
N=5-7
Dose Day 1
Remaining
Screening
Day -30
Week 1
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Exit/Early term.
Cohort 4 (4.0 mg)
Sentinel Patient
Dose Day 1
Sentinel
Screening
Day -30
Week 1
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Exit/Early term.
Cohort 4 (4.0 mg)
Remaining Patients
N=5-7
Dose Day 1
Remaining
Screening
Day -30
Week 1
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Exit/Early term.

1.3 SCHEDULE OF ACTIVITIES

	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								
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.