A Phase 2, Prospective, Multicenter, Randomized, Double-Masked, Active-Controlled Study to Assess the Safety, Tolerability, and Evidence of Activity of a Repeat Intravitreal Injection of UBX1325 in Patients with Neovascular Age-Related Macular Degeneration (ENVISION)

Investigational Product(s)	UBX1325
Protocol Number	UBX1325-03
Version Number	4.0
Version Date	13 January 2023
IND Number	145348
Sponsor	UNITY Biotechnology, Inc.
Sponsor's Legal Representative	Sharon Klier, MD, MPH VP and Medical Director, Ophthalmology UNITY Biotechnology, Inc. 285 East Grand Avenue South San Francisco, CA 94080

	Date
Original Protocol:	26 August 2021, Version 1.0
Protocol Amendment 1:	15 December 2021, Version 2.0
Protocol Amendment 2:	31 August 2022, Version 3.0
Protocol Amendment 3:	13 January 2023, Version 4.0

SUMMARY OF CHANGES: AMENDMENT 1

The following summarizes the principal elements requiring that change be made to the protocol. Other minor modifications for administrative purposes have been made to provide clarity and are captured in the redlined document.

The principal components of change to the study are described in the table below.

Area of change	Rationale
Repeat dose arm added and instead of a sham control there is an active control [Synopsis] and [Section 4.2 Design Rationale] [Section 6.0 Study Conduct] and [Section 7.6 Administration of aflibercept]	Repeat dose arm was incorporated after additional data from the First-in-Human study suggested that a single injection may not be sufficient to all patients. A repeat dose of UBX1325 can potentially be beneficial clinically with elimination of additional senescent cells. Active control arm replaced the sham control in order to make the standard of care consistent
Increased duration of follow-up from 16 weeks to 24 weeks Increased overall study duration from 20 to 22 months [Synopsis] and [Section 6.0 Study Conduct]	To assess longer term effect of study drug through repeat IVT injection of UBX1325. The number of study visits aligns with standard of care to see wet AMD patients every 4 weeks.
Added Aflibercept run-in: Once patients meet inclusion/exclusion criteria, they will receive a single run-in injection of aflibercept approximately -8 to -4 weeks prior to Day 1 [Synopsis] and [Section 6.0 Study Conduct]	To homogenize the patient population
Updated primary objective to include biological activity and primary endpoints to include changes in BCVA from Baseline within group at any or all visits Secondary and exploratory objectives and endpoints were also updated [Synopsis] and [Section 3.0 Objectives and Endpoints]	To align with current objectives following the interim results of the UBX1325-01 study
Sample size increased and order of efficacy endpoints was shifted putting BCVA changes at the top. [Synopsis] and [Section 3 Objectives and Endpoints] and [Section 9.2 Determination of Sample Size]	Sample size was recalculated based on the new primary efficacy endpoint and overall list of endpoints better aligns with key endpoints in future wet AMD studies

Area of change	Rationale
Increased number of sites from 20 to 25 [Synopsis]	To align with the sample size
Inclusion 2: applied to Screening and Day 1 Inclusion 3: required 2-anti-VEGF in previous 6 months with the last injection within 4-8 weeks prior to Screening Inclusion 4: advised that Investigator discretion be utilized Removed original Exclusion 13 and listed cataract surgery in Exclusion 5 Reworded Exclusion 8 to emphasize poorly controlled glaucoma Exclusion 11: History of topical steroid use for the SE or systemic steroid use for 6 months prior to Screening. The use of intravitreal steroids is prohibited. Inhaled and locally administered steroids are acceptable Reverted Exclusion for history of malignancy within the last 3 years to within the last 5 years [Section 5.3 Inclusion Criteria] and [Section 5.4 Exclusion Criteria]	Eligibility criteria revised to address 1 or more issues: - remove redundancies - remove specific criteria put in place before additional safety data was ascertained in the First-in-Human study - clarify requirements - better align with patient population
Safety updates based on available data from the First-in-Human study, UBX1325-01. [Section 2.4.4 Supportive Nonclinical Data] and [Section 2.4.5 Benefit:Risk Assessment]	The summary of safety data was revised to reflect additional non-serious, non-drug related adverse events
Added section on exploratory substudies [Section 3.1 Exploratory Substudies]	Added flexibility for future potential substudies
Clarified collection of historical medical and medication data, including all imaging and ophthalmological assessments [6.1.3 Medical History and Concomitant Medication Review]	To obtain the retrospective view of the patient's anti-VEGF response
Revisions to schedule of events table [Schedule of Events] and [Section 6.0 Study Conduct]	To align with new endpoints and revised study schematic

Area of change	Rationale
Unmasked injector will need to be available for IVT injections (or sham procedures if applicable) at Visits 1, 3, 4 and 6. [Section 7.8 Masked and Unmasked Study Staff]	This accounts for additional days when IVT injections/sham procedures would be conducted per revised study schematic
Updated Statistical Methods [Statistical Methods]	To align with revised objectives, sample size, and study design

SUMMARY OF CHANGES: AMENDMENT 2

The following summarizes the principal elements requiring that change be made to the protocol. Other minor modifications for administrative purposes have been made to provide clarity and are captured in the redlined document.

The principal components of change to the study are described in the table below.

Area of change	Rationale
Clarifications include: • Post-dose anterior and posterior segment evaluations and intraocular pressure are to be assessed in only the SE, not OU • Data collection of anti-VEGF in the preceding 6 months from Screening should be in OU. • Data collection in the preceding 6 months from Screening of SD-OCT and visual acuity assessments should be in OU and supports BCVA and CST entry into EDC • OCT-A/FA/FP should be assessed at Screening instead of Day 1 • Sham procedure is utilized to maintain double-masking, and masked team members are specified • Therapies that would preclude an IVT injection or can potentially exhibit retinal toxicity such as tamoxifen, hydroxychloroquine and trastuzumab are prohibited • Numbing of the eye should be per standard of care and utilized consistently for sham and IVT injections. Medications used for numbing should be documented as concomitant medication • Fluorescein used for IOP and IVFA/OCT-A should be documented as concomitant medication • Treatment for the fellow eye should be completed at least 7 days from treatment of the SE. Treatment of the fellow eye during Screening is permitted since aflibercept run-in is open label.	Incorporate Protocol Clarification Memo #1 dated 17Feb2022 and Protocol Clarification Memo #2 dated 25May2022.

Area of change	Rationale
• Exceptions to taking temperatures orally are acceptable when COVID protocols are in place. Method for taking temperature should be consistent throughout the study. • AEs and SAEs are collected after aflibercept run-in during Screening [Section 6.0 Study Conduct] and [Section 7.7 Administration of Sham Procedure] and [Section 7.10 Permitted and Prohibited Concomitant Treatments] and [Section 8.2.1 Timeframe for Collection]	
Extended the duration from 24 weeks to 48 weeks Added 2 additional injections of UBX1325 at Weeks 24 and 28 in the UBX1325 arm Added coadministration of UBX1325 with aflibercept at Week 24 and 32 in the aflibercept arm [Synopsis] and [Section 3 Objectives and Endpoints] and [Section 6.0 Study Conduct] and [7.7 Coadministration of Aflibercept and UBX1325 or Sham]	To study the safety, tolerability, and biological activity of 2 additional UBX1325 injections through 48 weeks, as well as coadministration of UBX1325 with aflibercept through 48 weeks. Efficacy parameters and retinal structure for the 2 additional UBX1325 injections through 48 weeks and coadministration of UBX1325 with aflibercept will also be studied.
Elaborated on the dosing interval and schedule as well as findings of IVT administration of UBX1325 in combination with aflibercept from the GLP toxicology study in cynomolgus monkeys. [Section 2.4.4.3 Toxicology]	To support coadministration of UBX1325 with aflibercept
Clarified that for Unscheduled Visit, tests/procedures can be performed as PI discretion whereas all tests/procedures should be performed. [Section 1.2 Schedule of Events] and [Section 6.1.1.16 Unscheduled Visit/Early Termination (ET)]	To distinguish between tests/procedures required between UnscheduledVisit and Early Termination Visit.

Area of change	Rationale
Removed “more than 2” from the exploratory endpoint looking at proportion of UBX1325 treated patients who require anti-VEGF therapy [Synopsis] and [Section 3 Objectives and Endpoints]	Details of the analysis will be outlined in the Statistical Analysis Plan.
Added interim analysis may be performed at 24 weeks and removed at 8 weeks [Section 9.8 Planned Interim Analysis]	To align with extension of the study

SUMMARY OF CHANGES: AMENDMENT 3

The following summarizes the principal elements requiring that change be made to the protocol. Other minor modifications for administrative purposes have been made to provide clarity and are captured in the redlined document.

The principal components of change to the study are described in the table below.

Area of change	Rationale
Clarified the Primary Objective and Endpoint by removing “Primary Safety” references and added that the endpoint is assessed following a repeat IVT injection of UBX1325 compared to active control (aflibercept) through Week 24 Secondary Objectives and Endpoints, added “safety” in the Objectives description, removed duplicative BCVA endpoint and clarified that safety is assessed through Week 48 [Synopsis] and [Section 3 Objectives and Endpoints]	Correct typographical errors and clarify endpoint assessments
Clarifications include: • The protocol SOE is correct that a complete PE is required at Screening, Visit 8/Week 24, Visit 14/Week 48 and Early Termination. Sites should conduct this complete PE and enter any abnormalities or changes in EDC • Per previous protocol, "For visits with masked study drug, FE treatment is to be completed 7 days from SE treatment (e.g., D1, Week 4, 8, 16, 24, 28, 32, and 40)." This restriction is being removed from the protocol in the latter 24 weeks of the study to allow Investigators greater clinical discretion of when it is appropriate to treat the fellow eye. At Visit 8/Week 24, Visit 9/Week 28, Visit 10/Week 32 and Visit 12/Week 40, the SE treatment and FE treatment no longer require a separation window of 7 days. Please ensure however that the FE treatment is done after SE treatment. • Per protocol, AE collection begins after	Incorporate Protocol Clarification Memo #3 dated 11Oct2022

Area of change	Rationale
the aflibercept run-in, however, this should include the run-in injection. The "Relationship to Aflibercept Administration" AE field in EDC corresponds to this run-in dose of aflibercept at Screening only. Please ensure that this relationship is assessed accordingly. [Section 1.2 Schedule of Events] and [Section 7.10.1 Permitted Treatments] and [Section 8.2.1 Timeframe for Collection]	

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCPs) as outlined by International Conference on Harmonisation (ICH) E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the IRB or Ethics Committee of Record (ECR) for the protocol and all materials provided to potential patients. Screening at a site may not begin prior to approval from the IRB/IEC and the Sponsor.

Any amendments to the protocol or changes to the consent document will be approved by the IRB/IEC before implementation of that amendment. Reconsent of previously enrolled patients may be necessary, depending on the nature of the amendment.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP training, as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	A Phase 2, Prospective, Multicenter, Randomized, Double-Masked, Active-Controlled Study to Assess the Safety, Tolerability, and Evidence of Activity of a Repeat Intravitreal Injection of UBX1325 in Patients with Neovascular Age-Related Macular Degeneration
Protocol Number	UBX1325-03
Version Number	4.0
Version Date	13 January 2023

The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature table below.

Sponsor's Legal Representative			
Name:	**Title:**	**Signature:**	**Date:**
Sharon Klier, MD, MPH	VP and Medical Director, Ophthalmology	DocuSigned by: Sharon Klier BE897EA10F0D4FC...	2/6/2023

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study UBX1325-03 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all Study Drug provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each patient's participation and all data required by the protocol

Name	**Title**	**Institution**

Signature	**Date**

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AMD	age-related macular degeneration
A/C IOL	Aphakia or Anterior Chamber Intraocular Lens
AE	adverse event
ADL	activities of daily living
ANOVA	analysis of variance
AR	adverse reaction
Bcl-2	B-cell lymphoma 2
Bcl-xL	B-cell lymphoma-extra large
BCVA	best corrected visual acuity
CFP	color fundus photography
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNV	choroidal neovascularization
COVID-19	Coronavirus Disease 2019
CST	central subfield thickness
CV	coefficient of variation
DAPI	4’,6-diamidino2-phenylindole
DME	diabetic macular edema
DNA	Deoxyribonucleic acid
DR	diabetic retinopathy
ECG	electrocardiogram
eCRF	electronic case report form
ECR	Ethics Committee of Record
EDC	electronic data capture
ERG	electroretinography
ERM	epiretinal membrane
ET	early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FDA	Food and Drug Administration
GA	Geographic atrophy
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hERG	human ether-à-go-go-related gene
HRMEC	human retinal microvascular endothelial cells
IB	Investigator’s Brochure
ICF	Informed Consent Form

Abbreviation	Definition
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IND	Investigational New Drug (application)
IOP	intraocular pressure
IRB	Institutional Review Board
IRF	Intraretinal fluid
IV	Intravenous
IVT	intravitreal
LLVA	Low-luminance visual acuity
MedDRA	Medical Dictionary for Regulatory Activities
mfERG	multifocal electroretinography
MMRM	mixed model for repeating measures
mRNA	messenger ribonucleic acid
N	number of patients
wet AMD	neovascular age-related macular degeneration
NCI CTCAE v4.03	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03
NOAEL	no-observed-adverse-effect-level
NOEL	No-observed-effect-level
NSnC	non-senescent cells
NV	neovascularization
NZW	New Zealand White
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
OIR	oxygen-induced retinopathy
OU	both eyes
p16	p16 cellular biomarker
p21	p21 cellular biomarker
PDGF	platelet-derived growth factor
PDT	Photodynamic therapy
PK	pharmacokinetic
POC	Proof-of-Concept
PS 80	polysorbate 80
RBC	red blood cell
RPE	retinal pigment epithelium
SAC	Safety Assessment Committee
SAD	single-ascending dose

Abbreviation	Definition
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	suspected adverse reaction
SASP	senescence-associated secretory phenotype
SD-OCT	spectral domain optical coherence tomography
SE	study eye
SnCs	senescent cells
SRF	Subretinal fluid
SOE	Schedule of Events
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TNF	tumor necrosis factor
US	United States
VEGF	vascular endothelial growth factor
WBC	white blood cell
WHO	World Health Organization

1 SYNOPSIS

Title	A Phase 2, Prospective, Multicenter, Randomized, Double-Masked, Active-Controlled Study to Assess the Safety, Tolerability and Evidence of Activity of a Repeat Intravitreal Injection of UBX1325 in Patients with Neovascular Age-Related Macular Degeneration (wet AMD)
Phase	Phase 2
Study Design	This is a Phase 2 Proof-of-Concept (POC) study. Approximately 46 patients will be enrolled and randomized 1:1 into the repeat IVT injections of UBX1325 or active-control (aflibercept) and coadministration of UBX1325 study arms, in order to assess the primary and secondary objectives. All patients will be followed for approximately 48 weeks. The injector will be unmasked. The evaluator, patient, and sponsor clinical study personnel remains masked throughout the study.
Rationale	This study is intended to assess safety, tolerability and biological activity of repeat IVT injections of UBX1325 in patients with wet AMD.
Target Population	This study will enroll patients ≥ 50 years of age with wet AMD with best corrected visual acuity (BCVA) between 70 to 20 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (equivalent to 20/40 to 20/400 on the Snellen chart) at Screening
Number of Patients	Approximately 46 patients
Length of Participation	**Run-in:** Once patients meet inclusion/exclusion criteria, they will receive a single run-in injection of aflibercept approximately -8 to -4 weeks prior to Day 1 **On treatment:** On Day 1, patients will be randomized to either the UBX1325 arm or the aflibercept arm. Patients randomized to the UBX1325 arm will receive UBX1325 on Day 1, Weeks 4, 24, and 28; and sham procedure on Weeks 8, 16, 24, 32, and 40. Patients randomized to the active-control aflibercept arm will receive aflibercept per active-control every 8 weeks starting from day 1 until Week 40. In addition, these patients will receive UBX1325 on Week 24 and Week 32; and a sham procedure at Week 4 and Week 28. **On study:** Up to a total of approximately 56 weeks (8-week screening period + IVT of aflibercept at -8 to -4 weeks + 48-week follow-up period)

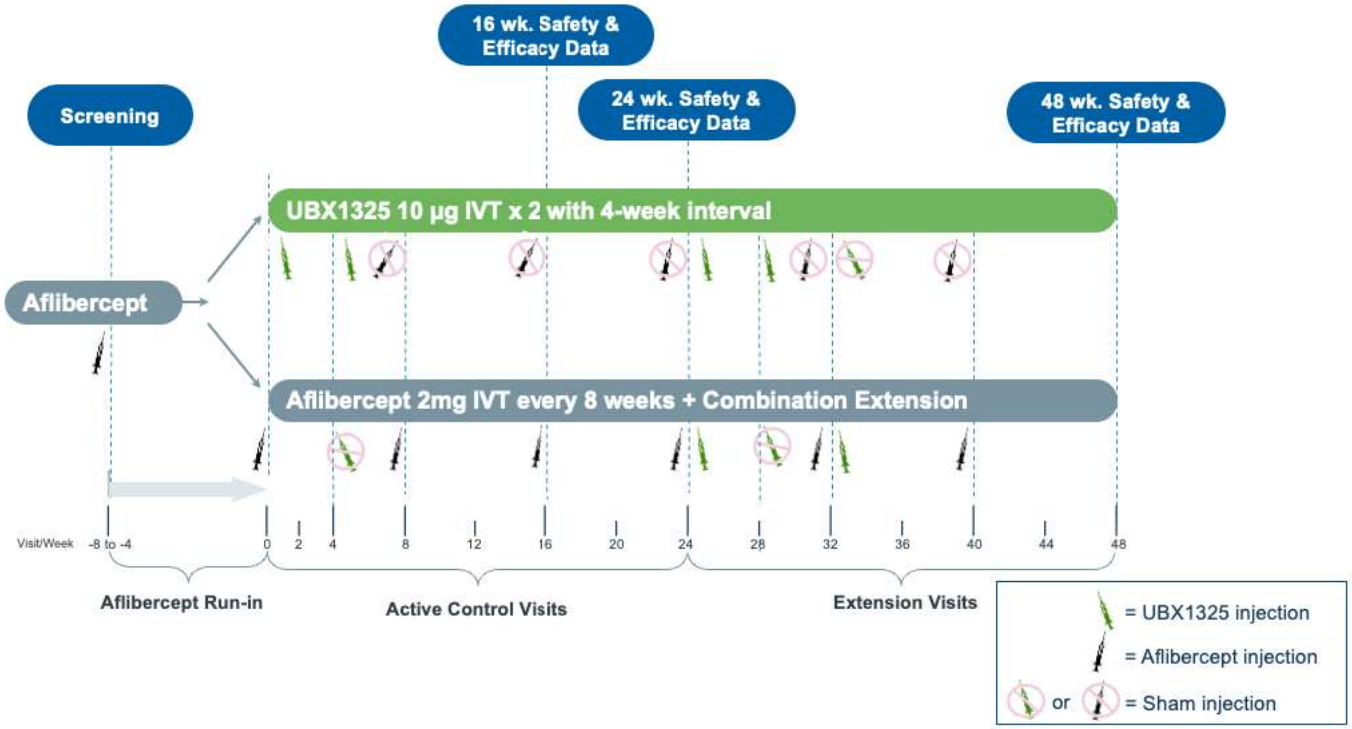
Intervention	Patients will be administered 50 µL of 0.2 µg/µl solution UBX1325 IVT injection at Day 1, Week 4, 24, and 28 (total injection of 10 µg x 4 injections in a 48-week period), active-control (aflibercept) per label, same day administration of aflibercept followed by UBX1325 approximately 30 minutes later at Week 24 & Week 32, or sham procedure(s).
Primary Objective and Endpoint	**Objective:** Assess the local and systemic safety, tolerability and biological activity following a repeat IVT injection of UBX1325 compared to active control (aflibercept) through Week 24 **Endpoint:** Ocular and systemic safety and tolerability of a repeat IVT injection of UBX1325 compared to active-control (aflibercept) evaluated by treatment emergent adverse events (TEAEs) through Week 24.
Secondary Objectives and Endpoints	**Objectives:** Assess safety, efficacy parameters, and retinal structure of patients following: • 2 IVT injections (Cycle 1) of UBX1325 compared to active control (aflibercept) every 8 weeks through Week 24. • 2 additional IVT injections (Cycle 2) of UBX1325 through Week 48 compared to Cycle 1 through Week 24 • Coadministration of UBX1325 with aflibercept through Week 48 compared to aflibercept alone through Week 24 **Endpoints**: o Change in BCVA from Baseline over time o Change in CST from Baseline over time as assessed by SD-OCT and read by a Central Reading Center o Safety through Week 48

Exploratory Objectives and Corresponding Endpoints	**Objective:** Explore anatomical and physiological responses of a repeat IVT injections of UBX1325 compared to active-control and/or coadministration with aflibercept. **Endpoints:** o Proportion of UBX1325 treated patients who require anti-VEGF rescue treatments over time o Time to rescue injection(s) o Change in retinal fluid from Baseline over time as assessed by SD-OCT and read by a Central Reading Center o Proportion of patients with absence of exudation (subretinal fluid [SRF]/intraretinal fluid [IRF]/cystoid edema) at any or all visits o Change in choroidal neovascularization (CNV) leakage and lesion size from Baseline on FA o Change in CNV lesion size from Baseline on OCT-A o Changes in choroidal blood flow on OCT-A
Number of Sites	Approximately 25 sites in the US
Study Duration	Approximately 31 months including start up
Safety Assessment Committee	A Safety Assessment Committee (SAC) will be established for adjudication of adverse events (AEs) or possible safety signals. The committee will meet on an ad hoc basis.

1.1 Study Schematic

The study schematic is presented in Figure 1.

Figure 1 Schematic of Phase 2 Proof-of-Concept Study



1.2 Schedule of Events

The Schedule of Events (SOE) is presented in Table 1.

Table 1 Schedule of Events

Test/Procedure	Screening Day -56 to Day -28	Visit 1 Week 0 Day 1	Visit 2 Week 2 Day 15 ± 7	Visit 3 Week 4 Day 29 ± 7	Visit 4 Week 8 Day 57 ± 7	Visit 5 Week 12 Day 85 ± 7	Visit 6 Week 16 Day 113 ± 7	Visit 7 Week 20 Day 141 ± 7	Visit 8 Week 24 Day 169 ± 7	Visit 9 Week 28 Day 197 ± 7	Visit 10 Week 32 Day 225 ± 7	Visit 11 Week 36 Day 253 ± 7	Visit 12 Week 40 Day 281 ± 7	Visit 13 Week 44 Day 309 ± 7	Visit 14 Week 48 Day 337 ± 7	Unscheduled Visit/ET[k]
Informed Consent	X															
Demographics	X															
Medical / Ophthalmic History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication History/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[L]	X								X						X	X
Vital Signs and Weight	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests: Hematology and Chemistry	X[b]								X						X	X
Pregnancy Test	X (serum)[b]	X (urine)[c]		X (urine)[c]	X (urine)[c]				X (urine)[c]						X (urine)	X (urine)
12-Lead ECG	X[b]								X						X	X
BCVA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anterior Segment Evaluation	X[d]	X[d]	X	X[d]	X[d]	X	X[d]	X	X[d]	X[d]	X[d]	X	X[d]	X	X	X
Posterior Segment Evaluation	X[d]	X[d]	X	X[d]	X[d]	X	X[d]	X	X[d]	X[d]	X[d]	X	X[d]	X	X	X
IOP	X[d]	X[d]	X	X[d]	X[d]	X	X[d]	X	X[d]	X[d]	X[d]	X	X[d]	X	X	X
SD-OCT[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT-A[e]	X			X	X		X		X			X			X	X
FA[e]	X			X	X		X		X			X			X	X[f]
CFP[e]	X			X	X		X		X			X			X	X

Test/Procedure	Screening Day -56 to Day -28	Visit 1 Week 0 Day 1	Visit 2 Week 2 Day 15 ± 7	Visit 3 Week 4 Day 29 ± 7	Visit 4 Week 8 Day 57 ± 7	Visit 5 Week 12 Day 85 ± 7	Visit 6 Week 16 Day 113 ± 7	Visit 7 Week 20 Day 141 ± 7	Visit 8 Week 24 Day 169 ± 7	Visit 9 Week 28 Day 197 ± 7	Visit 10 Week 32 Day 225 ± 7	Visit 11 Week 36 Day 253 ± 7	Visit 12 Week 40 Day 281 ± 7	Visit 13 Week 44 Day 309 ± 7	Visit 14 Week 48 Day 337 ± 7	Unscheduled Visit/ET[k]
mfERG[e]		X		X	X				X			X			X	
Low-luminance visual acuity[i]	X			X	X		X		X			X			X	X
Eligibility Criteria	X	X														
Aflibercept Administration	X[g]															
IVT Injection and/or Sham Procedure[h]		X		X	X		X		X[j]	X	X[j]		X			
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; BCVA = best corrected visual acuity; CFP = color fundus photography; ECG = electrocardiogram; ET = early termination; FA = fluorescein angiography; IOP = intraocular pressure; mfERG = multifocal electroretinography; OCT-A = optical coherence tomography angiography; SD-OCT = spectral domain optical coherence tomography

[a] Height should also be measured at Screening

[b] Serum pregnancy test, labs and ECG results are not required prior to aflibercept administration during Screening. The results must be verified prior to Day 1 randomization.

[c] Pre-dose urine dipstick.

[d] Procedure to be performed pre-dose OU and post-dose SE only. On coadministration days, these assessments should be done pre and at each post IVT injection or sham procedure.

[e] CFP, FA, SD-OCT, and OCT-A and mfERG images should be transmitted to the Central Reading Center at each applicable visit. mfERG to be conducted as the first ocular evaluation at sites with the proper equipment available and completed prior to IVT injection

[f] To be completed only if assessment has not been done within the last 30 days.

[g] All patients will receive aflibercept as a run-in injection prior to being randomized on Day 1

[h] IVT injection is either UBX1325 study drug/sham and/or aflibercept/sham, depending on the arm the patient is randomized to. Refer to Study Schematic Figure 1 and Pharmacy Manual. Sham procedure should be administered to maintain the integrity of double-mask. NOTE: After all IVT injections or sham procedures have completed, sites should follow their standard practice with administration of prophylactic antibiotics and document all medication given.

[i] LLVA to be conducted at sites with the proper equipment

[j] Refer to section 7.7, before coadministration, IOP must be ≤ 30 mmHg. Administration of UBX1325 or sham needs to be no less than 15 minutes apart and no longer than 2 hours unless there are safety concerns, in which case the site should contact the unmasked medical monitor.

[k] For Unscheduled Visit, tests/procedures can be performed as PI discretion. For ET all tests/procedures need to be performed.

[l] Complete physical examinations will be performed by a licensed physician (or a physician's assistant or nurse practitioner) at Screening, Visit 8 (Day 169), Visit 14 (Day 337) or ET. Aside from those timepoints, symptom-directed physical examinations are required to be performed as clinically indicated

2 INTRODUCTION

UBX1325 is a new molecular entity that is being investigated by UNITY Biotechnology, Inc. (the Sponsor) for the treatment of neovascular Age-Related Macular Degeneration (wet AMD) and other retinovascular diseases.

Age-related macular degeneration (AMD) is a leading cause of severe, irreversible vision loss in people age 60 and over. The neovascular form (wet AMD) is an advanced stage, which is responsible for the most severe vision loss (Schlottmann et al., 2017). It is an acquired disease of the macula characterized by progressive visual impairment due to late-onset neurodegeneration of the photoreceptor-retinal pigment epithelial complex (Al-Zamil and Yassin 2017).

As many as 11 million people in the US have some form of AMD. This number is expected to double to nearly 22 million by 2050. Age is a prominent risk factor for AMD. The risk of developing advanced AMD increases from 2% for those ages 50-59, to nearly 30% for those over the age of 75 (Bright Focus Foundation 2020).

Despite success of anti-VEGF therapy, patients experience an increased burden of treatment due to frequent injections and multiple office visits to assess treatment response. This presents a burden on patients and providers and ultimately results in reduced patient adherence and an inconsistent response (Holz et al., 2016). Additionally, several retrospective studies have reported suboptimal responder rates for anti-VEGF agents to be as high as 10-15% (Otsuji et al., 2013; Suzuki et al., 2014).

2.1 Overview of Age-Related Macular Degeneration

There are 2 forms of macular degeneration. All AMD starts as the dry form, also called nonexudative or atrophic AMD. The dry form is the most common type; about 90% of people with AMD have dry AMD. The wet form, known as exudative or neovascular, occurs in about 10% of those with AMD. Neovascular AMD is the cause of 80 to 90% of the severe vision loss cause by AMD (Cheung and Easton 2013).

Early stages of AMD usually are asymptomatic and are characterized by the presence of drusen and pigmentary alterations within 2 disc diameters of the fovea (Ferris et al., 2012). Advanced AMD includes geographic atrophy (GA) and wet AMD. While early and intermediate AMD cause only minimal visual acuity impairment, advanced AMD is the leading cause of blindness worldwide (van Lookeren Campagne et al., 2014).

AMD is a multifactorial blinding disease. It has been previously demonstrated that oxidative stress, aging, DNA damage and ultraviolet radiation can lead to AMD by influencing the autophagy function of retinal pigment epithelial (RPE) cells, cellular senescence, and the immune-inflammatory response (Wang et al., 2019).

wet AMD is typically diagnosed using a fundus photo by the presence of the following: RPE and/or retinal detachment, exudates (lipid degradation products), fibrovascular scars, and hemorrhage. FA and OCT can be used to further characterize the vascular lesions based on location (subfoveal, juxtafoveal, or extrafoveal) and presenting features of drusen, atrophy, and neovascularization (van Lookeren Campagne et al., 2014; Al-Zamil and Yassin 2017; Ferris et al., 2012).

Choroidal neovascularization (CNV) in wet AMD is likely a secondary reaction. Stress or damage in the RPE and the associated immune responses are believed to promote the production of pro-angiogenic factors, thereby driving CNV. In addition, degenerative changes

within the choridal vasculature are another plausible cause of pathological angiogenesis (van Lookeren Campagne et al., 2014).

Examination of early AMD lesions indicated that loss of vessels and/or reduction of perfusion in the choriocapillaris precedes the formation of pathological vessels. Vascular loss is often accompanied by the accumulation of macrophages and giant cells as well as early signs of angiogenesis such as endothelial cell and pericyte activation. These asymptomatic vascular changes may result in hypoxia and upregulate angiogenic factors in the choroid, leading to the formation of pathological vessels. Among the angiogenic factors investigated, VEGF-A is found to be a key factor in animal models and patients. Indeed, VEGF-A inhibitors have proven to be safe and effective in treating wet AMD (van Lookeren Campagne et al., 2014).

2.2 Standard of Care

Macular photocoagulation was studied extensively in the 1970s. Laser photocoagulation showed efficacy with positive visual outcomes in certain lesions. However, the adoption of laser photocoagulation in the treatment of wet AMD is hampered by several issues, including a high recurrence rate; a risk of producing vision loss, especially with subfoveal membranes; and a limited visual improvement potential. In the era of anti-VEGF therapies, the role of direct photocoagulation as a major treatment approach for wet AMD is waning. If used, this treatment should be limited to treat very small lesions outside the central macula (Al-Zamil and Yassin 2017).

Photodynamic therapy (PDT) was introduced in the late 1990s. It was used with a photosensitizer verteporfin administered intravenously to form reactive-free radicals that damage the vascular endothelium and induce occlusion of new vessels. The use of PDT has declined because of inadequate and unpredictable effects of PDT on CNV. Nowadays, the use of PDT is usually considered in combination with an anti-VEGF or steroid as a second line of therapy to nonresponders (Al-Zamil and Yassin 2017).

There are 3 available anti-VEGF therapies in the US that are considered standard of care for wet AMD. However, not all patients benefit from the effect of these drugs and many respond sub-optimally. It has been hypothesized that this high rate of suboptimal responders is largely due to angiogenic factors and pathways other than VEGF playing a role in the disease progression. Long-term studies evaluating the efficacy of anti-VEGF agents have demonstrated that initial improvements in vision over the first 2 years are not always sustained over longer periods of time. This may be the result of under treatment in the real world setting or potentially the development of macular atrophy in these patients (Gahn and Khanani 2018).

2.3 Target Indication and Population

This study will enroll patients ≥ 50 years of age with wet AMD with BCVA of 70 TO 20 ETDRS letters (equivalent to 20/40 to 20/400 on the Snellen chart).

2.4 Scientific Rationale for UBX1325 as a Treatment for wet AMD

The Sponsor hypothesizes that the accumulation of senescent cells (SnCs) in the retina contributes to retinal disease. UBX1325 is a phosphate pro-drug of the active parent molecule, UBX0601, an inhibitor of the anti-apoptotic protein Bcl-xL in the retina. Inhibition of Bcl-xL leads to induction of apoptosis, ultimately leading to cell death. IVT administration of UBX1325 in mouse oxygen-induced retinopathy (OIR) model decreased neovascular retinal area and avascular area, presumably due to restoration of healthy vasculature after elimination of

pathological SnCs. The effect of UBX1325 on mouse OIR model provides support for the treatment of neovascular diseases such as proliferative diabetic retinopathy and wet AMD.

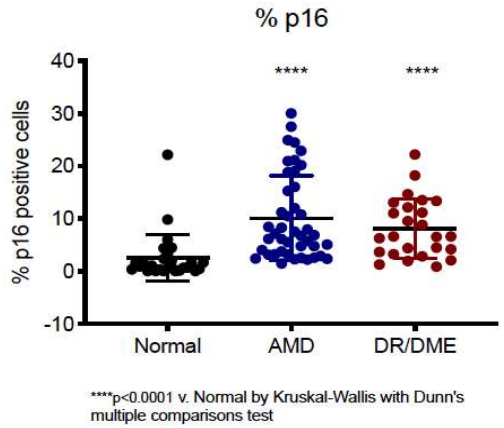
2.4.1 Role of Senescence in Retinal Disease

The principal feature of senescence, a regulated cellular program, is to induce a cell to enter a permanent state of cell cycle arrest. The first observation that human cells do not divide indefinitely was proposed in 1961 by the seminal work by Leonard Hayflick (Hayflick and Moorhead 1961). Several important features of the senescence program have since been elucidated. Exposure to damage-inducing stimuli such as oxidative stress, radiation, and ischemia are among factors associated with the induction of senescence. Several studies (Marazita et al., 2016; Lamoke et al., 2015; Ma and Wong 2016) have confirmed the correlation between these stressors and angiogenic retinal disease. SnCs produce a set of proinflammatory factors, cytokines, chemokines, and others that are called senescence-associated secretory phenotype (SASP). Although many factors of SASP have been identified in wet AMD and diabetic retinopathy (DR), a list of the most relevant ones associated with each disease have been studied and identified with many of them having a proinflammatory role (Funk et al., 2009; Sato et al., 2018; Schori et al., 2018).

Blasiak et al., 2017 demonstrated the role of SASP in RPE cells, photoreceptors, and choriocapillaris and postulated that in the central retina, RPE cells cannot be easily replaced by peripheral RPE cells leading to DNA damage response, autophagy, photoreceptor degeneration, and eventually, vision loss.

Evidence of SnCs in human retinopathies has focused on SASP and in vitro culture systems but reports of $p16^{+}$ immunohistochemistry (IHC) and cell-type identification are limited. Literature reports suggest presence of SnCs in aged primates (Mishima et al., 1999), and the proliferation potential of human RPE cells in vitro is suggested to be influenced by donor age (Flood et al. 1980). Recently, Lopez-Luppo et al., 2017 reported the presence of $p16^{+}$ cells in the retinal vasculature of aged human donors and vessels associated with microaneurysms.

Figure 2 Immunohistochemical Staining of $p16^{+}$ Cells in Human Donors



AMD = age-related macular degeneration; DAPI = 4',6-diamidino2-phenylindole; DME = diabetic macular edema; DR = diabetic retinopathy; N = number of patients; p16 = p16 cellular biomarker.

Retinal sections from human donor tissue were subject to immunohistochemical staining for p16. Cell nuclei were stained with DAPI, and % cells positive for p16 were calculated for each donor globe.

N = 27-43 per group.

Immunohistochemical staining performed by the Sponsor, of retinal sections from patients with DR/diabetic macular edema (DME) and AMD indicates the presence of $p16^{+}$ cells (Figure 2). When quantified and compared to age-matched normal tissue, a significant SnC burden was observed in both DR/DME and AMD globes.

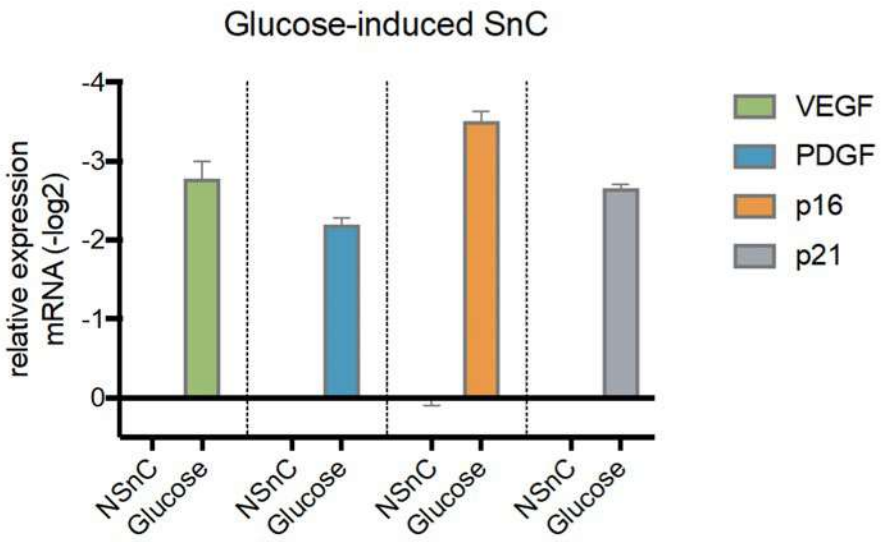
The Sponsor hypothesizes that there is a close relationship between senescence burden, measured by p16 IHC in the retina, the presence of SASP in the tissue, and clinical progression in patients with DR and DME. UBX1325 has the potential to remove SnCs from a tissue without altering the healthy resident cells in the eye and slow down the progression of the disease or even provide structural and functional recovery by addressing not just one target factor like VEGF, but a set of proinflammatory or growth factors present in the SASP. This approach would address more effectively the multifactorial character of the disease and may decrease the proportion of patients that respond either poorly or partially to anti-VEGF, the need for repeated treatments, and the long-term complications like fibrosis and macular atrophy.

2.4.2 Disease-Relevant Senescence-Associated Secretory Phenotype from Senescent Retinal Cells

In addition to the cellular marker of senescence, elevated expression of several secreted factors has been associated with retinal diseases, which have been detected in the vitreous humor and aqueous humor from patients with ocular disease. Levels of mediators such as VEGF, tumor necrosis factor (TNF), IL-1β, platelet-derived growth factor (PDGF), and IL-6 are significantly increased in the ocular fluids of DR and AMD globes (Bromberg-White et al., 2013; Boss et al., 2017; Ghodasra et al., 2016; Sato et al., 2018). In addition to p16, the Sponsor is focused on the association of disease-relevant SASP to our senescent cellular and in vivo animal models. Elimination of SnCs by UBX1325 may lead to a reduction in SASP by targeting the source, resulting in the restoration of homeostasis and retinal function.

Human ocular cell types can be cultured and rendered senescent by a variety of different insults, including DNA-damaging treatment (e.g., irradiation) and disease relevant- conditions such as incubation in elevated glucose media. Human retinal microvascular endothelial cells (HRMEC) upregulate the production of important mediators such as VEGF and PDGF upon induction of senescence by glucose (Figure 3). As these molecules have been shown to be elevated in DR patients (Ghodasra et al., 2016; Klaassen et al., 2017), it stands to reason that senescent HRMEC in the retinas of patients may be the source of the elevated VEGF/PDGF that contribute to disease pathogenesis.

Figure 3 Induction of Senescence and DR-Relevant Genes After Glucose Treatment



DR = diabetic retinopathy; HRMEC = human retinal microvascular endothelial cells; mRNA = messenger ribonucleic acid; NSnC = non-senescent cells; SnC = senescent cells; PDGF = platelet-derived growth factor; p16 = p16 cellular biomarker; p21 = p21 cellular biomarker; VEGF = vascular endothelial growth factor.

Increased expression of several genes was observed by qRT-PCR in non-senescent HRMEC (NsnC) or HRMEC treated with elevated glucose (200 mM) in culture media for 2 weeks.

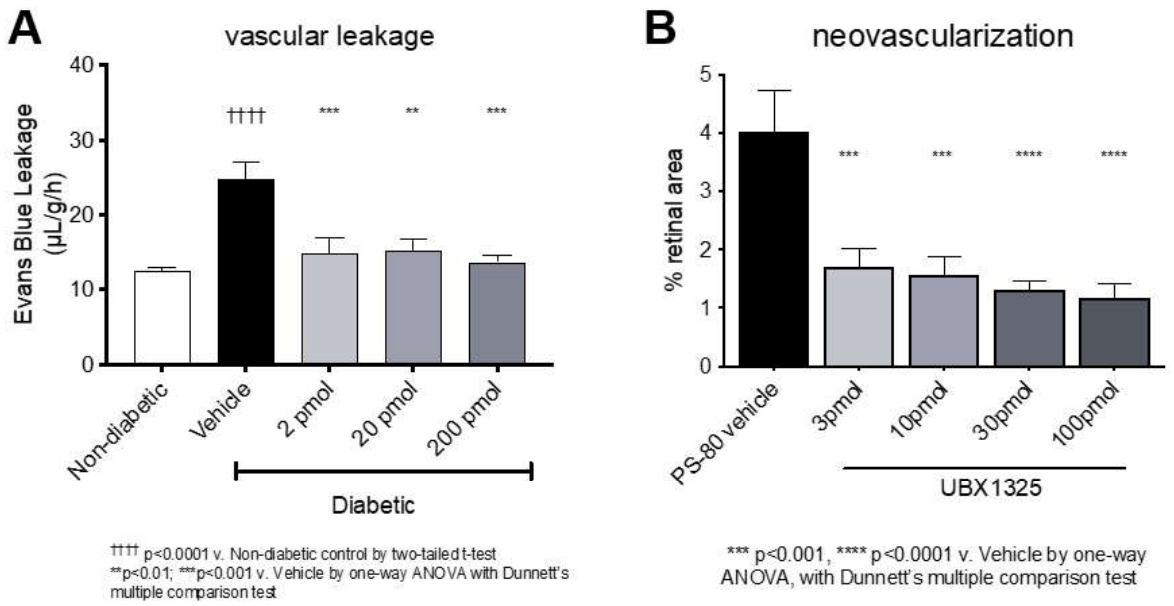
2.4.3 Description of UBX1325

UBX1325 is a phosphate pro-drug of the active parent molecule, UBX0601, which is cleaved rapidly in tissues by a ubiquitously present enzyme, a phosphatase. UBX1325 was designed to aid in solubility of UBX0601 as an ophthalmic formulation. In all nonclinical studies conducted, UBX1325, as a pro-drug, is administered in an appropriate formulation, then converted *in vivo* rapidly to UBX0601 in vivo for its potent inhibition of Bcl-xL in the retina. In this protocol, Study Drug refers to UBX1325.

The Bcl-2 gene family encodes more than 20 proteins that regulate the intrinsic apoptosis pathway and are fundamental to the balance between cell survival and death. Inhibition of particular members of the Bcl-2 family of apoptosis regulatory proteins disrupts the interactions with pro-apoptotic activators and effectors, resulting in cell death. SnCs utilize pro-survival mechanisms to remain viable and rely on particular members of the Bcl-2 family of apoptosis regulatory proteins members to persist and accumulate in tissues (Yosef et al., 2016). Binding of retinal Bcl-xL by UBX0601 in senescent HRMEC acts to promote caspase activation and the apoptotic cascade, ultimately leading to cell death (manuscript in preparation).

In streptozotocin-induced DR mouse model, IVT administration of UBX1325 resulted in decreased vascular leakage at all doses tested (2 to 200 pmol) (Figure 4). Similarly, IVT administration of UBX1325 in the mouse OIR model resulted in decreased neovascularization (Figure 4). Refer to the Investigator's Brochure (IB) for additional details.

Figure 4 Improved Vascular Leakage and Neovascularization by UBX1325



ANOVA = analysis of variance; IVT = intravitreal; PS-80 = polysorbate 80

A) Increased retinal vascular leakage was measured by Evans Blue extravasation in diabetic mice (Vehicle) as compared to non-diabetic animals. All 3 dose levels of UBX1325 (2-200 pmol, IVT) significantly reduced vascular leakage. B) Neovascular area was determined from isolectin B4-stained images of OIR retinas. All 4 dose levels of UBX1325 (3-100 pmol, IVT) significantly reduced retinal neovascularization as compared to vehicle control animals.

2.4.4 Supportive Nonclinical Data

All nonclinical pharmacology, pharmacokinetic (PK), and toxicology, studies briefly described in this section were conducted by or for the Sponsor. More detailed information is provided in the current version of the IB.

2.4.4.1 Pharmacology

UBX1325 (pro-drug) and UBX0601 (active parent molecule), where appropriate, were studied in cellular and animal models of ocular disease to demonstrate activity in the retina. UBX1325 is a potent inhibitor of Bcl-2 family of apoptosis regulatory proteins, which results in initiation of apoptosis in HRMEC, in vitro. In 2 different mouse models of retinal dysfunction, UBX1325 demonstrated inhibition of disease-relevant endpoints such as neovascularization (NV) and vascular leakage. UBX1325 is a pro-drug of UBX0601, which is cleaved rapidly in tissues by a ubiquitously present enzyme, phosphatase.

2.4.4.2 Pharmacokinetics

Ocular tissue exposures of UBX1325 and UBX0601 following a single IVT injection of 50 µg of UBX1325 were well-characterized in rabbits following serial necropsy at 2, 24, 72, 168, 240, and 336 hours, post-dose. UBX0601 half-lives in the vitreous humor, retina, choroid, and iris-ciliary body of rabbits were 48 hours, 34 hours, 47 hours, and 80 hours, respectively. The concentration of UBX0601 in the lens showed a slower rate of decline with an estimated half-life of 173 hours. Aqueous humor concentrations, which did not allow for PK estimates, appeared to

remain at a very low level of 0.02 µg/mL. Systemic exposure to UBX1325/UBX0601 following intraocular dose was minimal, usually below the lower limit of quantification in the assay (1 ng/mL), suggesting rapid clearance once UBX0601 reaches systemic circulation.

2.4.4.3 Toxicology

UBX1325 has been evaluated in Good Laboratory Practice (GLP) ocular toxicity studies in New Zealand White (NZW) rabbits and monkeys with observation periods of up to 2 months following a single IVT dose. In addition, a GLP 6-week IVT cynomolgus monkey combination study with UBX1325 and aflibercept with a 4-week recovery period was completed. Also, in order to evaluate the potential for systemic toxicity, one-month GLP studies were conducted in which UBX1325 was given as a once weekly IV dose to rats and dogs. The no-observed-effect-level (NOEL) following IVT injection in rabbits at which there were no findings was 5 µg/eye; the no-observable adverse effect level (NOAEL) in monkeys was 25 µg/eye. In the systemic toxicity studies, NOAELs were 0.3 mg/kg and 0.1 mg/kg for rats and dogs, respectively. The systemic levels noted at these NOAELs are not anticipated to be observed following IVT dosing. Cardiovascular, respiratory, and neurobehavioral safety pharmacology studies following IV dosing of UBX1325 did not show any impact on these parameters. Specifically, in the CV dog study, there were no effects on QTc. This result was consistent with UBX1325 and UBX0601 not having clinically relevant effects on the human ether-à-go-go-related gene (hERG) channel. The combination of UBX1325 with aflibercept was well tolerated with no effects on IOP, ERGs, or clinical and anatomic pathology endpoints with the NOAEL being the high dose combination of 25/500 ug/eye UBX1325/aflibercept. Findings were generally similar to single agent studies in the cynomolgus monkey. There was no apparent impact of UBX1325/UBX0601 on systemic aflibercept concentrations. In addition, UBX1325 and UBX0601 were not genotoxic in in vitro and in vivo studies. Further development of UBX1325 is supported by the available data.

In the GLP 6-week IVT cynomolgus combination study, UBX1325 and aflibercept were dosed at a 2-week interval with no apparent signs of toxicity.

Intravitreal administration of UBX1325 (on Study Day 15) in combination with aflibercept (on Study Days 1 and 29), was well tolerated. There was no mortality and no UBX1325/aflibercept or aflibercept-related clinical observations or changes in food consumption or body weight; no UBX1325/aflibercept or aflibercept-related IOP changes or effects on ffERG or VEP; and no clinical or anatomic pathology effects. UBX1325/aflibercept-related findings were limited to non-adverse and reversible findings noted ophthalmoscopically and on OCT.

2.4.5 Benefit:Risk Assessment

2.4.5.1 Previous Human Experience with Bcl-2 Inhibitors

UBX1325 is in a class of agents known to inhibit certain members of the Bcl-2 family that are apoptosis regulatory proteins. Targeting this pathway has been extensively studied in connection with the search for new oncology medicines. Some tumor cells can become dependent on Bcl-2 for survival, which allows for specific targeting with inhibitors of Bcl-2. Bcl-2 inhibitors have been investigated in the oncology setting indicating safety and tolerability when administered systemically in humans (Tse et al., 2008; Touzeau et al., 2014; Souers et al., 2013). To the best of the Sponsor's knowledge, Bcl-2 inhibitors have not previously been investigated in an ocular setting.

UBX1325 was administered to patients with advanced DME and wet AMD in the Phase 1 single ascending dose (SAD) study, UBX1325-01. UBX1325 was well tolerated with favorable safety

profile supporting further development. As of November 9, 2021 there were a total of 14 adverse events unrelated to study drug. Of those 14, 4 were non-ocular, non-serious, non-drug related adverse events in 2 wet AMD patients (1 patient contracted COVID-19 and 1 patient had a tooth extraction, blister on gums and constipation). The remaining 10 ocular, non-serious, non-drug related adverse events occurred in 9 patients (2 DME and 7 wet AMD). Nine were study eye related (progression of disease in 8 patients, 1 DME and 7 wet AMD) and 1 was non-study eye related (retinal detachment in 1 DME patient). There were no serious adverse events, dose-limiting toxicities, inflammation, or AEs that would preclude advancement into later-stage clinical development.

The Sponsor is aware of the systemic toxicities associated with venetoclax, an FDA-approved oral Bcl-2 selective inhibitor for chronic lymphocytic leukemia/small lymphocytic lymphoma and acute myeloid leukemia. As a consequence of being in the same class of molecules, and in view of similar systemic toxicities noted in UBX1325 IV nonclinical studies, the Sponsor is planning to monitor for potential Bcl-2 inhibitor related toxicities (e.g., cytopenia) that may emerge from UBX1325 IVT treatment (Section 8). However, based on currently available exposure data from nonclinical studies following IVT dosing (Section 2.4.4.2) and the lack of measurable systemic exposure of UBX1325 and UBX0601 after a single IVT dose at all doses tested in patients in the Phase 1 SAD study, the Sponsor expects systemic exposure of UBX1325 following IVT treatment to be low in patients and, therefore, the potential to observe such systemic events is also low.

3 OBJECTIVES AND ENDPOINTS

Tier		
Primary Objective and Endpoint	Assess the local and systemic safety, tolerability and biological activity following a repeat IVT injection of UBX1325 compared to active control (aflibercept) through Week 24	Ocular and systemic safety and tolerability of a repeat IVT injection of UBX1325 compared to active-control (aflibercept) evaluated by treatment emergent adverse events (TEAEs) through Week 24
Secondary Objectives and Endpoints	Assess efficacy parameters and retinal structure of patients following: • 2 IVT injections (Cycle 1) of UBX1325 compared to active-control (aflibercept) every 8 weeks through Week 24. • 2 additional IVT injections (Cycle 2) of UBX1325 through Week 48 compared to Cycle 1 through Week 24 • Coadministration of UBX1325 with aflibercept through Week 48 compared to aflibercept alone through Week 24	○ Change in BCVA from Baseline over time ○ Change in CST from Baseline over time as assessed by SD-OCT and read by a Central Reading Center ○ Safety through Week 48

Exploratory Objectives and Corresponding Endpoints	Explore anatomical and physiological responses of a repeat IVT injections of UBX1325 compared to active-control and/or coadministration with aflibercept.	○ Proportion of UBX1325 treated patients who require anti-VEGF rescue treatments over time ○ Time to rescue injection(s) ○ Change in retinal fluid from Baseline over time as assessed by SD-OCT and read by a Central Reading Center ○ Proportion of patients with absence of exudation (subretinal fluid [SRF]/intraretinal fluid [IRF]/cystoid edema) at any or all visits ○ Change in choroidal neovascularization (CNV) leakage and lesion size from Baseline on FA ○ Change in CNV lesion size from Baseline on OCT-A ○ Changes in choroidal blood flow on OCT-A

3.1 Exploratory Substudies

At select sites, the Sponsor may propose exploratory substudies associated with this Protocol. If so, each substudy will be documented in a separate substudy protocol and will utilize separate Informed Consent Form(s).

4 STUDY PLAN

4.1 Study Design

This is a Phase 2, prospective, multicenter, randomized, double-masked, active-controlled study to assess the safety, tolerability and evidence of activity of repeat IVT injections of UBX1325 in patients with wet AMD. Approximately 46 patients will be enrolled 1:1 to the repeat doses of UBX1325 or active-controlled (aflibercept) study arms, in order to assess the primary objective. All patients will be followed for approximately 48 weeks.

See Section 7.8 for details on double-masking and site requirements. A schematic representation of the study design is presented in Figure 1.

4.2 Design Rationale

4.2.1 Patient Population Selection

Based on the in vitro and in vivo pharmacology and toxicology data (refer to the UBX1325 IB) and scientific rationale (see Section 2.4), the Sponsor asserts that UBX1325 can be tested for safety, tolerability and evidence of activity in wet AMD patients.

Patients will be those who are 50 years of age or older and diagnosed as having wet AMD with BCVA in the SE of 70 to 20 ETDRS letters (equivalent to 20/40 to 20/400 on the Snellen chart).

4.2.2 Dose Rationale

As of November 9, 2021, in patients with advanced DME and wet AMD in the SAD Phase 1 study, UBX1325 was well tolerated with favorable acute safety profile supporting development; no dose-limiting toxicities in any of the dose cohorts, including the high dose of 10 µg. The planned dose is 10 µg based on favorable safety data in the Phase 1 SAD study.

In terms of mechanism of action, of the drug and based on preclinical models, a single injection of UBX1325 is proposed to induce the selective elimination of SnCs. However, it is conceivable that a single injection is insufficient in eliminating all SnCs in the tissue, therefore elimination of additional SnCs with a repeat dose of UBX1325 can potentially be clinically beneficial.

For patients with wet AMD, in whom choroidal vasculature is affected, optimum efficacy and durability may require a repeat dose so this Phase 2 aims to determine if the repeat will be clinically beneficial.

5 POPULATION

5.1 Recruitment

Approximately 46 patients are planned to enroll in this study.

5.2 Definitions

Patients officially enter the Screening Period following provision of informed consent.

A screen failure is a consented patient who has been deemed ineligible on the basis of 1 or more eligibility criteria or who has withdrawn consent prior to randomization. Screen failures may be rescreened. Patients will be permitted to re-screen once and in consultation with the Sponsor's Medical Monitor.

An enrolled patient is one who has been deemed eligible and has been randomized.

5.3 Inclusion Criteria

To be included in this study, each individual must satisfy all of the following criteria:

1. Patients aged ≥ 50 years.
2. Active CNV associated with age-related macular degeneration as evidenced on FA and SD-OCT with presence of intraretinal or subretinal fluid at Screening and Day 1 with either the CNV or fluid involving the center of the fovea
3. Wet AMD patients who have had at least 2 anti-VEGF treatments in the SE in the preceding 6 months prior to Screening, with the last injection within 4-8 weeks of Screening
4. BCVA in the SE (most affected) of 70 to 20 ETDRS letters (equivalent to 20/40 to 20/400 on the Snellen chart) at Screening. On Day 1, BCVA cannot be an improvement of 10 or more letters from Screening

   Note: if both eyes are eligible, Investigator discretion should be utilized.
5. IOP ≤ 23 mmHg in the SE.
6. Clear ocular media and adequate pupillary dilation to permit CFP, SD-OCT, and adequate BCVA evaluation.
7. Patients who have the capacity to give informed consent and who are willing and able to comply with all study-related procedures and assessments.

5.4 Exclusion Criteria

If an individual meets any of the following criteria, he or she is ineligible for this study:

8. Concurrent disease in the SE or structural damage, other than wet AMD, that could compromise BCVA, prevent BCVA improvement, require medical or surgical intervention during the study period, confound interpretation of the results, or interfere with assessment of toxicity or CFP in the SE. This includes, but is not limited to, the following:
   - Clinically significant subretinal fibrosis

- Subfoveal lipid with atrophy involving center of fovea
- Cataract requiring surgery during the study period
- RPE atrophy or tear or rips involving the macula
- Presence of macular hole
- History of uveitis
- Vitreomacular traction
- Clinically significant epiretinal membrane (ERM)
- Aphakia or Anterior Chamber Intraocular Lens (A/C IOL)
- Other retinovascular disease (e.g., macular telangectasia)

9. Any ocular/intraocular/periocular infection or inflammation in either eye in the past 12 weeks prior to Screening (mild blepharitis is acceptable)
10. Subretinal hemorrhage with bleeding area ≥ 4 disc area in the SE
11. History of vitrectomy in the SE
12. History of intraocular, periocular, or corneal surgery (including cataract surgery), in the SE within 3 months prior to Screening, or anticipated need for such surgery during the study
13. History of panretinal photocoagulation or macular laser photocoagulation in the SE
14. History of corneal transplant in the SE
15. Patients with glaucoma who are poorly controlled in the opinion of the investigator or on 3 or more medications (whether administered as single agents or in combination formulations)
16. Any condition, including laboratory findings and findings in the medical history or in screening or Day 1 assessments, that, in the opinion of the Investigator, constitutes a risk or contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation or prevent the patient from fully participating in all aspects of the study
17. Presence of severe myopia (-8 diopters or greater) in the SE
18. History of topical steroid use for the SE or systemic steroid use for 6 months prior to Screening. The use of intravitreal steroids is prohibited. Inhaled and locally administered steroids are acceptable
19. History of Visudyne® photodynamic therapy in the SE
20. Significant media opacities, including cataract, which might interfere with visual acuity, assessment of toxicity, or fundus imaging
21. Known allergy to any component (phosphate buffered saline and polysorbate 80) of the Study Drug or to any component of aflibercept, or a clinically relevant sensitivity to fluorescein dye
22. Female patients who are pregnant, lactating, or of childbearing potential who do not agree to use highly effective methods of birth control (e.g., progesterone-only hormonal contraception, double barrier, or intrauterine device) during the study and for 3 months following the last dose of Study Drug. Postmenopausal females (> 45 years old and without

menses for more than 1 year) and surgically sterilized females are exempt from these requirements.

23. Male patients who do not agree to use a highly effective method of contraception during the study and for 3 months following the last dose of Study Drug, if sexually active with a female partner of childbearing potential.

24. Patients who within 3 months of screening received or are concurrently on another investigational drug or vaccine study, including patients who previously received treatment in a UBX1325 study. Coronavirus Disease 2019 (COVID-19) vaccinations are permitted prior to or during the course of the study.

25. Any uncontrolled medical condition, in the opinion of the Investigator, would preclude participation in this study, including, but not limited to, history of malignancy within the last 5 years, history of myocardial infarction within the last 6 months, or concomitant therapy that, in the opinion of the Investigator, would preclude participation in this study.

6 STUDY CONDUCT

The expected duration of study participation for patients will be approximately 56 weeks, which includes a 8-week screening period and 48 weeks of follow-up.

The procedures outlined below and in the Schedule of Events (Table 1) will take place for all patients.

6.1 Study Procedures

6.1.1 Study Screening and Treatment Periods

6.1.1.1 Screening Period (Day -56 to Day -28)

- Informed Consent
- Demographics
- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Historical anti-VEGF, BVCA, and CST for OU in the 6 months preceding Screening, where available
- Physical Examination (Complete)
- Vital Signs and Weight
- Height
- Laboratory Tests: Hematology and Chemistry*
- Pregnancy Test (serum)*
- 12-lead ECG*
- BCVA
- Anterior Segment Evaluation (pre-dose in OU and post-dose in SE of aflibercept)
- Posterior Segment Evaluation (pre-dose in OU and post-dose in SE of aflibercept)
- IOP (pre-dose in OU and post-dose in SE of aflibercept)
- SD-OCT
- OCT-A (to be conducted at sites with proper equipment available)
- FA
- CFP
- Low-luminance visual acuity (to be conducted at sites with the proper equipment)

- Eligibility Criteria
- Aflibercept Administration
  - For patients currently receiving aflibercept, they will be maintained on that therapy; for patients on other anti-VEGF agents, they will all be switched to aflibercept at Screening
- AE assessment

*NOTE: the results must be verified on Day 1 and are not required prior to aflibercept administration during Screening

6.1.1.2 Visit 1 (Day 1)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Vital Signs and Weight
- Pregnancy Test (pre-dose urine dipstick)
- BCVA
- Anterior Segment Evaluation (pre-IVT injection in OU and post IVT injection in SE)
- Posterior Segment Evaluation (pre-IVT injection in OU and post IVT injection in SE)
- IOP (pre-IVT injection in OU and post IVT injection in SE)
- SD-OCT
- mfERG (to be conducted at sites with proper equipment available and done prior to IVT injection)
- Eligibility Criteria
- IVT injection of UBX1325 or aflibercept
- Prophylactic Antibiotics Post IVT Injection (optional)
- AE assessment

6.1.1.3 Visit 2 (Day 15)

The following procedures will be done:

- Medical and Ophthalmic History

- Medication History/Concomitant Medications
- Vital Signs and Weight
- BCVA
- Anterior Segment Evaluation
- Posterior Segment Evaluation
- IOP
- SD-OCT
- AE Assessment

6.1.1.4 Visit 3 (Day 29)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Vital Signs and Weight
- Pregnancy Test (pre-dose urine dipstick)
- BCVA
- Anterior Segment Evaluation (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- Posterior Segment Evaluation (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- IOP (both pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- SD-OCT
- OCT-A (to be conducted at sites with proper equipment available)
- FA
- CFP
- mfERG (to be conducted at sites with proper equipment available and done prior to IVT injection or sham procedure)
- Low-luminance visual acuity (to be conducted at sites with proper equipment available)
- IVT injection of UBX1325 or sham procedure

- Prophylactic Antibiotics Post IVT Injection or sham procedure (optional)
- AE assessment

6.1.1.5 Visit 4 (Day 57)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Vital Signs and Weight
- Pregnancy Test (pre-dose urine dipstick)
- BCVA
- Anterior Segment Evaluation (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- Posterior Segment Evaluation (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- IOP (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- SD-OCT
- OCT-A (to be conducted at sites with proper equipment available)
- FA
- CFP
- mfERG (to be conducted at sites with proper equipment available and done prior to IVT injection or sham procedure)
- Low-luminance visual acuity (to be conducted at sites with proper equipment available)
- IVT injection of aflibercept or sham procedure
- Prophylactic Antibiotics Post IVT Injection or sham procedure (optional)
- AE assessment

6.1.1.6 Visit 5 (Day 85)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications

- Vital Signs and Weight
- BCVA
- Anterior Segment Evaluation
- Posterior Segment Evaluation
- IOP
- SD-OCT
- AE Assessment

6.1.1.7 Visit 6 (Day 113)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Vital Signs and Weight
- BCVA
- Anterior Segment Evaluation (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- Posterior Segment Evaluation (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- IOP (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- SD-OCT
- OCT-A (to be conducted at sites with proper equipment available)
- FA
- CFP
- Low-luminance visual acuity (to be conducted at sites with proper equipment available)
- IVT injection of aflibercept or sham procedure
- Prophylactic Antibiotics Post IVT Injection or sham procedure (optional)
- AE assessment

6.1.1.8 Visit 7 (Day 141)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Vital Signs and Weight
- BCVA
- Anterior Segment Evaluation
- Posterior Segment Evaluation
- IOP
- SD-OCT
- AE Assessment

6.1.1.9 Visit 8 (Day 169)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Vital Signs and Weight
- Physical Examination (Complete)
- Laboratory Tests: Hematology and Chemistry
- Pregnancy Test (urine dipstick)
- 12-lead ECG
- BCVA
- Anterior Segment Evaluation (pre-IVT injection in OU and post IVT injections and/or sham procedure in SE)
- Posterior Segment Evaluation (pre-IVT injection in OU and post IVT injections and/or sham procedure in SE)
- IOP (pre-IVT injection in OU and post IVT injections and/or sham procedure in SE). Before coadministration, IOP must be ≤ 30 mmHg.
- SD-OCT
- OCT-A (to be conducted at sites with proper equipment available)
- FA

- CFP
- mfERG (to be conducted at sites with proper equipment available)
- Low-luminance visual acuity (to be conducted at sites with proper equipment available)
- IVT injection of UBX1325 and aflibercept or sham. Administration of UBX1325 or sham needs to be no less than 15 minutes apart and no longer than 2 hours unless there are safety concerns, in which case the site should contact the unmasked medical monitor.
- Prophylactic Antibiotics Post IVT Injection or sham procedure (optional)
- AE assessment

6.1.1.10 Visit 9 (Day 197)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Vital Signs and Weight
- BCVA
- Anterior Segment Evaluation (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- Posterior Segment Evaluation (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- IOP (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- SD-OCT
- IVT injection of UBX1325 or sham procedure
- Prophylactic Antibiotics Post IVT Injection or sham procedure (optional)
- AE assessment

6.1.1.11 Visit 10 (Day 225)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Vital Signs and Weight
- BCVA

- Anterior Segment Evaluation (pre-IVT injection in OU and post IVT injections and/or sham procedures in SE)
- Posterior Segment Evaluation (pre-IVT injection in OU and post IVT injections and/or sham procedures in SE)
- IOP (pre-IVT injection in OU and post IVT injections and/or sham procedures in SE). Before coadministration, IOP must be ≤ 30 mmHg.
- SD-OCT
- IVT injection of UBX1325 or sham and aflibercept or sham. Administration of UBX1325 or sham needs to be no less than 15 minutes apart and no longer than 2 hours unless there are safety concerns, in which case the site should contact the unmasked medical monitor.
- Prophylactic Antibiotics Post IVT Injection or sham procedure (optional)
- AE assessment

6.1.1.12 Visit 11 (Day 253)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Vital Signs and Weight
- BCVA
- Anterior Segment Evaluation
- Posterior Segment Evaluation
- IOP
- SD-OCT
- OCT-A (to be conducted at sites with proper equipment available)
- FA
- CFP
- mfERG (to be conducted at sites with proper equipment available)
- Low-luminance visual acuity (to be conducted at sites with proper equipment available)
- AE assessment

6.1.1.13 Visit 12 (Day 281)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Vital Signs and Weight
- BCVA
- Anterior Segment Evaluation (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- Posterior Segment Evaluation (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- IOP (pre-IVT injection in OU and post IVT injection or sham procedure in SE)
- SD-OCT
- IVT injection of aflibercept or sham procedure
- Prophylactic Antibiotics Post IVT Injection or sham procedure (optional)
- AE assessment

6.1.1.14 Visit 13 (Day 309)

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Vital Signs and Weight
- BCVA
- Anterior Segment Evaluation
- Posterior Segment Evaluation
- IOP
- SD-OCT
- AE assessment

6.1.1.15 Visit 14 (Day 337)

- Medical and Ophthalmic History

- Medication History/Concomitant Medications
- Vital Signs and Weight
- Physical Examination (Complete)
- Laboratory Tests: Hematology and Chemistry
- Pregnancy Test (urine dipstick)
- 12-lead ECG
- BCVA
- Anterior Segment Evaluation
- Posterior Segment Evaluation
- IOP
- SD-OCT
- OCT-A (to be conducted at sites with proper equipment available)
- FA
- CFP
- mfERG (to be conducted at sites with proper equipment available)
- Low-luminance visual acuity (to be conducted at sites with proper equipment available)
- AE assessment

6.1.1.16 Unscheduled Visit/Early Termination (ET)

For Unscheduled Visit, tests/procedures can be performed as PI discretion. For ET, all tests/procedures need to be performed.

- Medical and Ophthalmic History
- Medication History/Concomitant Medications
- Complete Phyisical Examination for ET & Symptom Directed Physical Examination for Unscheduled Visit
- Vital Signs and Weight
- Laboratory Tests: Hematology and Chemistry
- Pregnancy Test (urine dipstick)

- 12-lead ECG
- BCVA
- Anterior Segment Evaluation
- Posterior Segment Evaluation
- IOP
- SD-OCT
- OCT-A (to be conducted at sites with proper equipment available)
- FA (if not done within the last 30 days)
- CFP
- Low-luminance visual acuity (to be conducted at sites with proper equipment available)
- AE Assessment

6.1.2 Informed Consent

It is the responsibility of the Investigator to obtain signed written consent for the study from each patient prior to participating in the study to provide for the protection of the patients by following applicable regulations and institutional policies and procedures. The Informed Consent Form (ICF) used during the informed consent process must be reviewed by the Sponsor or designee and approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

6.1.3 Medical History and Concomitant Medication Review

A detailed medical history will be obtained by the Investigator or qualified designee. This will include a comprehensive medical history and a complete review of systems, with specific attention to inclusion and exclusion criteria. The historical anti-VEGF should be collected for OU in the preceding 6 months prior to Screening should be documented in the concomitant medication log. All historical imaging and ophthalmological assessments done for OU (when available) in the preceding 6 months prior to Screening should be entered into the designated eCRF. BCVA and CST values should be entered into EDC. Past medical history deemed by the Investigator as not clinically relevant to the patient's overall health status or to his or her wet AMD will not be captured. Relevant medical history will be recorded in the electronic case report form (eCRF).

All medications taken for wet AMD will be recorded in the eCRF Concomitant Medication Log.

6.1.4 Physical Examination

Physical examination includes assessments of the skin, head and neck, lungs, heart, abdomen, lymph nodes, extremities, and body weight. Height will be measured at Screening only.

Complete physical examinations will be performed by a licensed physician (or a physician's assistant or nurse practitioner) at Screening, Visit 8 (Day 169), Visit 14 (Day 337) or ET. Aside

from those timepoints, symptom-directed physical examinations are required to be performed as clinically indicated.

6.1.5 Vital Signs and Body Weight

Vital signs (blood pressure, respiratory rate, pulse rate, and oral temperature) will be obtained in the sitting position. The patient must be in the sitting position for 5 minutes prior to obtaining vital signs. In regard to COVID, if the site has a COVID related protocol, exceptions can be made to collect forehead temperature readings. Sites must remain consistent with how that data is collected across all study visits for a study participant.

Vital signs and body weight assessment will be performed at all study visits.

6.1.6 Laboratory Tests

The Laboratory Manual contains detailed instructions for the collection and preparation of samples, directions with respect to the utilization of specialized tubes and requirements for dispensing of aliquots, and storage and shipment of samples to the Sponsor's designated central laboratory.

6.1.7 Pregnancy Test

Serum pregnancy tests will be performed at Screening, and urine pregnancy tests will be performed pre-dose at Visit 1, Visit 3, Visit 4, Visit 8, Visit 14, and at Unscheduled Visits/ET for all females of childbearing potential.

6.1.8 Electrocardiography

Evaluation will be performed at Screening for baseline reference, Visit 8, Visit 14, and at Unscheduled Visits/ET.

6.1.9 Ocular Evaluations

BCVA: should be assessed using the ETDRS chart starting at 4 meters at Screening, on Visits 1-14 and Unscheduled Visits/ET. BCVA should be done prior to IVT injection or sham procedure or rescue treatment. See the Ophthalmic Manual for details.

- Anterior Segment Evaluation: should be performed prior to pupillary dilation, unless that contradicts the site Standard of Care. Any abnormalities of the anterior chamber, eyelids, conjunctivae, pupil, iris, lens and cornea should be documented at Screening, on Visits 1-14, and Unscheduled/ET. Any anterior chamber inflammation (cells and flare), phakic status, and posterior lens capsule status should also be noted. Pre-IVT injection or sham procedure should be completed in OU. Post IVT injection or sham procedure should be completed in the SE only.

- Posterior Segment Evaluation/Ophthalmoscope Examination: should be performed after pupillary dilation to examine the vitreous body, optic nerve head, macula, posterior pole, and peripheral retina at Screening, on Visits 1-14, and Unscheduled/ET. Any vitreous inflammation (haze and cells) should also be noted. Pre-IVT injection or sham procedure should be completed in OU. Post IVT injection or sham procedure should be completed in the SE only.

- IOP: should be measured using Goldmann Applanation tonometry at Screening, on Visits 1-14 and Unscheduled/ET. IOP should be done pre and post IVT injection or sham procedure or rescue treatment. The post assessment should be done 30 minutes ±15 minutes. Tonometry should be performed prior to pupillary dilation when possible.
    - On coadministration days on Week 24 and Week 32, IOP should be done pre and post each IVT injection or sham procedure. Pre-IVT injection or sham procedure should be completed in OU. Post IVT injection or sham procedure should be completed in the SE only.
- CFP: should be obtained at Screening, Visits 3, 4, 6, 8, 11, 14 and Unscheduled/ET.
- SD-OCT: should be obtained at Screening, on Visits 1-14 and Unscheduled/ET.
- OCT-A: to be conducted at sites with the proper equipment available and should be obtained at Screening, Visits 3, 4, 6, 8, 11, 14 and Unscheduled/ET.
- FA: should be obtained at Screening, Visits 3, 4, 6, 8, 11, 14 and Unscheduled/ET (if it had not been done within 30 days prior).
- mfERG: to be conducted as the first ocular evaluation, and at sites with proper equipment available and should be obtained at Visits 1, 3, 4, 8, 11 and 14. mfERG should be done pre IVT injection or sham procedure.
- Low-luminance visual acuity: to be conducted at sites with proper equipment available and should be obtained at Screening, on Visits 3, 4, 6, 8, 11, 14 and Unscheduled/ET.

CFP, SD-OCT, FA, OCT-A (if done) and mfERG (if done) images should be transmitted to the Central Reading Center at each applicable visit.

6.1.10 Rescue Criteria

If at any visit after Week 8 (Day 57), patients exhibit increase in disease activity, defined as any of the following: new, or clinically relevant worsening of, IRF/SRF/cysts compared to Day 1, new blood or heme present compared to previous visit, decrease in BCVA by ≥ 10 ETDRS letters from peak (best VA) within-study level, or CST increase ≥ 75 µm from trough (lowest), they can be rescued with aflibercept. Rescued patients will continue their visit schedule as safety follow-up through Week 48. Prior to administration of rescue medication, or for any questions on rescue criteria, please contact the Medical Monitor or designee. Rescued patients continue with study visits per protocol. If additional visits are required outside of study visit windows, these will be considered unscheduled visits.

6.1.11 End of Study

The study will be considered complete when the last patient has completed the last study visit.

6.2 Discontinuation or Withdrawal

6.2.1 Individual Patients

6.2.1.1 Withdrawal from Study

Patients can voluntarily withdraw from the study for any reason at any time. They are to be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any reason. Patients withdrawing from the study because of an AE should be followed for at least 30 days, until resolution of the AE, or until no further improvement is expected, whichever comes first. Patients withdrawing from the study should be encouraged to complete all assessments under the Unscheduled/ET visit described in Table 1.

The Investigator may withdraw a patient from the study for any of the following reasons:

A protocol violation occurs,
A serious or intolerable AE occurs,
The Sponsor or Investigator terminates the study, or
The patient requests to be discontinued from the study.

6.2.1.2 Replacement of Patients

Enrollment may be extended to replace patients who discontinued or are lost to follow up during the study.

6.3 Study Termination

The Sponsor may suspend or terminate the study or any part of the study at any time for any reason. If the Investigator suspends or terminates that site's participation in the study, the Investigator will promptly inform the Sponsor and the IRB/IEC and provide a detailed written explanation. Upon study completion, the Investigator will provide the Sponsor with final reports and summaries as required by regulations. Upon study suspension, completion, or termination, the Investigator will return all Study Drug and other study materials to the Sponsor or designee or destroy the materials at the investigative site per the Sponsor's instructions.

7 STUDY INTERVENTIONS

7.1 Description of Product

The Study Drug (UBX1325) to be provided to the clinical sites will be bulk packaged (sites will be supplied with adequate overage, which will be accounted for as part of Study Drug accountability). The term “Study Drug” when used throughout this protocol means UBX1325 in solution. Each vial and carton will be individually labeled. Study Drug labeling will include identification required by local law, drug identification, and dosage. The packaging and labeling of the Study Drug will be in accordance with the Sponsor’s standards and local regulations. The Study Drug was manufactured at Vetter Pharma Development Services USA, Skokie, Illinois.

7.1.1 UBX1325

7.1.1.1 Formulation, Storage, Preparation, and Handling

UBX1325 is formulated as a sterile, clear, colorless to pale yellow solution at a concentration of 1 mg/mL in pH 7.4 phosphate buffered saline that contains 0.3% polysorbate 80 (PS 80), and will be provided in a glass vial, stoppered and crimp-sealed with a teal flip cap for IVT administration. Each vial contains 1 mg/mL of UBX1325 and is *single-use only*. UBX1325 *must be stored at -20°C* upon receipt.

UBX1325 will be provided to the investigational site along with a Pharmacy Manual, which details clinical product presentation and dilutions to be prepared using aseptic technique. Sterile diluent (pH 7.4 phosphate buffered saline) will be provided in a glass vial with a white flip cap along with sterile syringes and sterile needles for the preparation of the Study Drug. Each vial of sterile diluent is *single-use only*.

Post-dilution solutions for clinical administration will be held no more than 1 hour at room temperature.

Storage and dose preparation of Study Drug will be conducted in accordance with instructions in the Pharmacy Manual and under aseptic conditions.

The Investigator is responsible for drug accountability at the investigational site, appointing a qualified individual to oversee the storage, preparation, and dispensing of Study Drug, and keeping records of such activity in accordance with the requirements of the Sponsor.

All used and unused Study Drug must be stored at site and stored in accordance with the directions given in the Pharmacy Manual.

7.2 Method for Assigning Patients to the Treatment Group

After a patient has been identified as potentially eligible for the study, the patient will be invited to participate. If the patient agrees to study participation, written informed consent will be obtained before any study-specific procedures are performed. Patients who have consented to participate in the study will be assigned a screening number.

After the patient has been consented and completed all screening procedures confirming eligibility, they may proceed to be randomized in a 1:1 ratio on Day 1 (Visit 1) to receive UBX1325 or aflibercept.

Patients randomized to the UBX1325 arm will receive UBX1325 on Day 1 and Weeks 4, 24, 28 and sham procedure on Weeks 8, 16, 24, 32, and 40.

Patients randomized to the aflibercept arm will receive aflibercept on Day 1, Weeks 8, 16, 24, 32, 40 and sham procedure on Weeks 4 and 28. Coadministration of UBX1325 with aflibercept will occur at Weeks 24 and 32.

Patients will be randomly allocated to receive treatment through the randomization system, which administers the randomization code generated by the Sponsor's biostatistician or designee. Following receipt of the treatment assignment, the site staff will prepare the Study Drug as instructed by the Pharmacy Manual. Patients who are randomized but do not receive treatment may be replaced.

7.3 Randomization Code Creation and Storage

Randomization personnel of the Sponsor or designee will generate the randomization schedule prior to the start of the study. An interactive web response system will be used for patient randomization. All randomization information will be stored in a secured area, accessible only by authorized personnel.

7.4 Administration of UBX1325

UBX1325 is administered via IVT injection. Following the IVT injection, patients will be monitored for elevation of IOP, decreased optic nerve head perfusion, and for possible injection complications (e.g., vitreous hemorrhage, retinal tears, etc.). Additionally, patients should immediately report any symptoms suggestive of endophthalmitis, such as ocular pain, swelling, redness, haze and gradual loss of vision.

Patients may be prescribed prophylactic antibiotic eye drops following any IVT injection or sham procedure per the site's preferred practice patterns. Such drops, if prescribed, should be documented in the patient's eCRF.

Sites are to use numbing agents per their preferred practice and documented in the patient's eCRF. Use of numbing agents should be consistent for IVT injections and sham procedures.

7.5 Administration of Sham Procedure

Sham procedures will be performed to maintain double-masking on the study. A sham procedure involves a needleless, empty sterile syringe that touches the surface of the SE to mimic an IVT injection. The unmasked team will administer IVT injections or sham procedures according the patient's randomization status and per Study Schematic in Figure 1. Please refer to the current Pharmacy Manual for details on how to prepare and administer the sham procedure.

Patients may be prescribed prophylactic antibiotic eye drops following a sham procedure per the site's preferred practice patterns. Such drops, if prescribed, should be documented in the patient's eCRF.

Sites are to use numbing agents per their preferred practice and documented in the patient's eCRF. Use of numbing agents should be consistent for IVT injections and sham procedures.

7.6 Administration of aflibercept

Aflibercept should be administered per standard of care.

7.7 Coadministration of Aflibercept and UBX1325 or Sham

On coadministration days (week 24 and week 32), aflibercept or sham should be administered first before UBX1325 or sham.

IOP taken post aflibercept injection or sham should be equal to or less than 30 mmHg prior to administering UBX1325 or sham. Administration of UBX1325 or sham after aflibercept or sham should be no less than 15 mins apart and no longer than 2 hours unless there are safety concerns, in which case the site should contact the unmasked medical monitor.

7.8 Masked and Unmasked Study Staff

This study will be double-masked. Patients, Investigators, visual acuity technicians, photographers, reading center personnel and the Sponsor are masked. Sites will have a qualified injector who is unmasked in order to perform the IVT injection (UBX1325 or aflibercept) or sham procedure, as well as certain post-injection assessments on Visits 1, 3, 4, 6, 8, 9, 10, and 12. Specifically post injection, the unmasked injector will do the anterior and posterior segment exams, IOP and AE assessment on the SE. Other supporting activities such as Study Drug preparation and Study Drug accountability will be performed by designated unmasked personnel. The Screening visit may be conducted by unmasked or masked personnel; however, unmasked personnel should not be involved in any other study procedures outside of visits when an IVT injection or sham procedure is required. It is important the randomization code is not revealed to anyone in order to maintain the integrity of the double-masking.

7.9 Extent of Maintenance of Double-Masking

In addition to the patients and Investigators being masked, any Sponsor or designee team members who are actively engaged with the site will be masked.

There will be no planned unmasking. If there is an unplanned or unintentional unmasking, the randomization system will be used to manage the roles and permissions with respect to the ability to break the masking. The Investigator must contact the Medical Monitor to discuss any need to unmask, unless medical emergency dictates otherwise. The randomization code and records related to the unmasking will be filed as essential study documents.

A patient who has unplanned or unintentional unmasking during the study will be asked to continue in the study through Week 48 for safety follow-up (AE and concomitant medication reporting, vital signs, physical examinations and laboratory testing).

7.10 Permitted and Prohibited Concomitant Treatments

7.10.1 Permitted Treatments

Permitted concomitant treatments in/for the SE and non-SE include:

- Sites should follow their standard of care for numbing the eye. Lidocaine, proparacaine, etc. are permitted if consistently administered to all patients regardless of sham or IVT injection and should be entered on the concomitant medication source log and in EDC.
    - This should be entered as PRN for each eye individually
- Fluorescein used for IOP and IVFA/OCT-A needs to be documented as a concomitant medication
    - This should be entered as PRN for each eye individually

- Treatment of the fellow eye (FE) during Screening is permitted given aflibercept run-in is open label
    - For visits with masked study drug, FE treatment is to be completed 7 days from SE treatment (e.g., D1, Week 4, 8, and 16)
    - For Visit 8/Week 24, Visit 9/Week 28, Visit 10/Week 32 and Visit 12/Week 40, the SE treatment and FE treatment no longer require a separation window of 7 days. FE treatment is done after SE treatment.
- Topical antibiotics administered prophylactically with IVT injection or sham procedure, and topical/systemic antibiotics used for AE treatment
- Artificial tears
- Steroid use is permitted only for the following conditions:
    - Topical (e.g., for atopic dermatitis treatment), inhaled (e.g., for asthma treatment), or locally injected (e.g., for epidural or joint injection)
    - Topical use of steroids in the fellow eye
    - Topical use of steroids for treatment of inflammation in the SE (e.g., uveitis)

Concomitant intravitreal therapy in the non-SE is permitted but cannot be administered within 7 days of treatment with masked Study Drug.

7.10.2 Prohibited Treatments

There are no known contraindications to the administration of UBX1325 injection.

Patients will not be permitted to receive treatments for the management of wet AMD in the SE, once randomized to this study, unless it is aflibercept as a rescue treatment (see Section 6.1.10).

Systemic (oral, intramuscular, and intravenous) or intravitreal steroids are not allowed unless for an AE treatment. All systemic steroids are prohibited 6 months before Screening.

Patients should not have received any therapy that would preclude an IVT injection or can potentially exhibit retinal toxicity (such as tamoxifen, hydroxychloroquine, and trastuzumab.

Patients are prohibited from receiving any medication for the SE that, in the opinion of the Investigator and/or the Medical Monitor, may have an effect on the study results.

Patients who have received brolucizumab as their anti-VEGF treatment prior to Screening may be eligible given there were no complications associated with its use and given it was not administered within 8 weeks prior to Visit 1. Historical use of brolucizumab is not excluded.

8 SAFETY MONITORING

At each visit, patients will undergo ophthalmologic evaluation and assessment for signs of potential toxicity.

For all patients, all acquired data may be reviewed by the SAC. This process will be detailed in the SAC Charter.

8.1 Definitions

- **AE**: An AE is any untoward medical occurrence associated with the use of an intervention in humans whether or not it is considered intervention related.
- **Suspected unexpected serious adverse reaction** (SUSAR): A serious adverse reaction (AR) that is unexpected based on current product information.
- **Serious adverse event (SAE)**: An event is considered “serious” if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes:
  - Death
  - A life-threatening AE (An event is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected AR that, had it occurred in a more severe form, might have caused death.)
  - 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 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.
- **Causality or relatedness**: AEs should be considered probably or possibly treatment-related, unless they fulfill the following criteria (in which circumstances it should be considered unlikely related or unrelated):
  - Evidence exists that the AE has an etiology other than the Study Drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or
  - The AE has no plausible temporal relationship to administration of the Study Drug (e.g., a new cancer diagnosed 2 days after first dose of Study Drug).

Relatedness to Study Drug will be graded as “probably,” “possibly,” “unlikely,” or “unrelated” as follows:

Probably related: The AE

- Follows a reasonable temporal sequence from drug administration
- Abates upon discontinuation of the drug
- Cannot be reasonably explained by the known characteristics of the patient's clinical state

Possibly related: The AE

- Follows a reasonable temporal sequence from drug administration
- Could have been produced by the patient's clinical state or by other modes of therapy administered to the patient

Unlikely related: The AE

- Is most likely to be explained by the patient's clinical state or by other modes of therapy administered to the patient

Unrelated: The AE

- Does not follow a reasonable sequence from drug administration
- Is readily explained by and considered by the Investigator to be an expected complication of the patient's clinical state, concurrent medical conditions, or by other modes of therapy administered to the patient

- **AR**: An AR is any AE caused by a drug.

- **Suspected adverse reaction** (SAR): An SAR is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of the investigational new drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the **drug** and the AE. SAR implies a lesser degree of certainty about causality than AR.

- **Unexpected**: An event is considered unexpected if it is not listed in the IB, is not listed at the specificity or severity that has been observed, or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the IND. Unexpected also refers to events that are mentioned in the IB 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.

- **Severity or intensity:** The severity of an event describes the degree of impact upon the patient and/or the need for medical care necessary to treat the event. AEs reported for patients participating in this study will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03). The Investigator will grade the severity of each AE using, when applicable, the NCI CTCAE v4.03. For AEs not included in the NCI CTCAE v4.03, the criteria outlined in Table 2 should be used as a general guideline.

Table 2 Grading for Adverse Events Not Covered in the NCI CTCAE

Severity	Description
Grade 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 – Moderate	Minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental ADL
Grade 3 – Severe	Medically significant but not life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4 – Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5 – Fatal	Death

ADL = activities of daily living; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

8.2 Documenting Adverse Events

8.2.1 Timeframe for Collection

AEs and SAEs will be collected from Screening (with the aflibercept run-in, prior to aflibercept should be collected as medical history) through the last follow-up visit at Visit 14, Week 48, or ET. All events prior to this will be documented as medical history. TEAEs will be collected from Visit 1 through Week 48, or ET.

The Investigator must follow up on all AEs through Week 48/ET. Nonserious AEs may be followed to resolution past the patient's last study visit at the discretion of the Investigator and/or Medical Monitor if in the best interest of the patient and the assessment of safety of UBX1325. The Investigator must follow up on all SAEs until the events have subsided, returned to baseline, or, in case of permanent impairment, the condition stabilizes.

8.2.2 Classification of Events

Although AEs should be based on the signs or symptoms detected during the physical examination and on the clinical evaluation of the patient, a specific diagnosis should be reported as the AE whenever feasible. In addition to the information obtained from those sources, the patient should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

8.3 Reporting Adverse Events

All AEs and SAEs must be recorded on source documents and collected in the electronic data capture (EDC) system. Any unanticipated risks to the patients must be reported by the Investigator promptly to the Sponsor and IRB/IEC.

All SAEs, whether or not deemed drug-related or expected, must be reported by the Investigator or qualified designee within 24 hours of first becoming aware of the event. The Investigator or qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF, which will automatically result in distribution of the information to the Sponsors Pharmacovigilance provider. If the eCRF system is temporarily unavailable, the event, including the Investigator-determined causality to Study Drug, should be reported via fax using

an SAE form to the appropriate Sponsor or Pharmacovigilance contact. Upon return of the availability of EDC system, the SAE information must be entered on the SAE eCRF.

The Sponsor (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the Sponsor will make a determination as to whether the criteria for expedited reporting have been met. The Medical Monitor should also be contacted immediately for any fatal or life-threatening SAE that is considered possibly or probably related to Study Drug.

The Sponsor (or designee) is responsible for reporting relevant SAEs to the relevant regulatory authorities and participating Investigators, in accordance with FDA regulations 21 Code of Federal Regulations 312.32, International Conference on Harmonisation (ICH) Guidelines, European Clinical Trials Directive (Directive 2001/20/European Commission, and/or local regulatory requirements and monitoring the safety profile of the Study Drug. To meet this requirement, the Sponsor (or designee) may request additional information from the sites including, but not limited to, hospitalization records, discharge summaries, or autopsy reports. Any requests for such information should be addressed in a timely manner. Additionally, any SAE considered by an Investigator to be possibly or probably related to the Study Drug that is brought to the attention of the Investigator at any time outside of the time period specified for SAE reporting also must be reported immediately to one of the individuals listed on the Sponsor contact information page.

Reporting of SAEs by the Investigator to the IRB or IEC will be done in accordance with the standard operation procedures and policies of the IRB/IEC. Adequate documentation must be maintained showing that the IRB/IEC was properly notified.

8.4 Adverse Events of Special Interest

No AEs of special interest have been identified for UBX1325.

8.5 Clinical Laboratory Findings

Clinical laboratory tests will include the analytes in Table 3. Patients should be in a seated or supine position during blood collection.

Table 3 Laboratory Parameters

Hematology:	Serum Chemistry:
• Hematocrit • Hemoglobin • Platelet count • RBC count • Mean corpuscular volume • WBC count with differential	• Albumin • Alkaline phosphatase • Alanine aminotransferase • Aspartate aminotransferase • Blood urea nitrogen • Calcium • Carbon dioxide • Chloride • Creatinine[a] • Globulin • Glucose • Human chorionic gonadotropin[b] • Lactate dehydrogenase • Phosphorus • Potassium • Sodium • Total and direct bilirubin • Total cholesterol • Total protein

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; RBC = red blood cell; WBC = white blood cell

[a] Creatinine clearance will be calculated by the CKD-EPI method.

[b] Serum human chorionic gonadotropin is required only for females who are of childbearing potential.

8.6 Pregnancy

Although not considered an SAE, cases of pregnancy exposure by parent to the Study Drug must be recorded, reported, and followed up as indicated for an SAE. After the patient has been enrolled in the study and received Study Drug by IVT injection, the Investigator must report immediately (within 24 hours or next business day whichever is the shorter) any drug exposure during pregnancy to the Sponsor using the Sponsor-supplied Pregnancy Reporting Forms, using the same contact method for SAE reporting. Information about exposure in pregnancy encompasses the entire course of pregnancy and delivery and perinatal and neonatal outcomes, even if there were no abnormal findings. All reports of pregnancy must be followed for information about the course of the pregnancy and delivery, as well as the condition of the newborn. When the newborn is healthy, additional follow-up is not needed. Pregnancies occurring up to 12 weeks after last administration of the Study Drug must be reported to the Investigator.

8.7 Overdose or Misuse

Although not considered an SAE, cases of overdose (e.g., a dose higher than that indicated in the protocol, with or without an AE) must be recorded, reported, and followed up as indicated for an SAE.

9 STATISTICAL METHODS

9.1 General Considerations

All study parameters will be listed, and a selected list of parameters will be summarized descriptively by dose cohort and overall. The descriptive statistics will include number of patients, mean, standard deviation, median, minimum, and maximum for continuous parameters and frequency and percent for categorical parameters. Details about the statistical analyses for this study will be provided in the Statistical Analysis Plan (SAP), which will be developed and finalized before database lock.

9.2 Determination of Sample Size

The sample size is for exploratory statistical analysis purposes only. There are no formal confirmatory hypotheses to be tested.

A total of approximately 46 patients will be randomized 1:1 into the UBX1325 repeat dose or aflibercept arm. With 23 UBX1325 repeat dose patients, a single group t-test with a 0.10 two-sided significance level will have approximately 80% power to detect a 5-letter change from baseline in BCVA, assuming the standard deviation is 9 letters.

9.3 Analysis Populations

9.3.1 Full Analysis Set

The Full Analysis Set will include all randomized patients who received study treatment, have a baseline and at least one post baseline BCVA assessment. The Full Analysis Set will be the primary population for evaluating all efficacy variables.

9.3.2 Safety Analysis Set

The Safety Analysis Set will include all patients who received study treatment. The Safety Analysis Set will be the primary population for evaluating all safety variables and patient characteristics.

9.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics include sex, age, race, ethnicity, weight, height, and other parameters as appropriate. These variables will be listed and summarized using descriptive statistics for each study arm and overall, based on the Safety Analysis Set.

Medical history will be summarized using MedDRA (Medical Dictionary for Regulatory Activities) terms. Prior medications will be tabulated using World Health Organization (WHO) Drug Dictionary terms.

9.5 Efficacy Analysis

The Full Analysis Set will be used for all efficacy analyses.

Change in BCVA and CST from Baseline to each visit will be analyzed by a mixed model for repeated measures (MMRM). The details of MMRM and the analysis methods for other efficacy endpoints described in Section 3 will be provided in the SAP.

9.6 Safety Analysis

The Safety Analysis Set will be used for all safety analyses.

Ocular and systemic safety and tolerability of a repeat IVT injection of UBX1325 will be evaluated by treatment emergent adverse events (TEAEs). The safety variables will be summarized descriptively.

AEs will be coded using the MedDRA. Patients with any AEs will be tabulated by system organ classification and preferred term specified in the MedDRA. AEs will also be summarized by relationship to treatment and maximum severity. In addition, SAEs and discontinuations due to AEs will be summarized.

9.7 Exploratory Analysis

Additional exploratory analyses may be carried out to better inform interpretation of treatment effects depending on examination of the summary statistics originally planned as mentioned above and in the SAP.

9.8 Planned Interim Analysis

Formal interim analyses may be performed at 16 and 24 weeks. The SAP will specify what proportion of patients with Week 16 and Week 24 data are needed for the interim analyses.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

This study will be conducted in compliance with the protocol approved by the IRB/IEC, and in accordance with ICH Good Clinical Practice (GCP) standards. Any amendments to the protocol or changes to the consent document will be approved by the IRB/IEC before implementation of that amendment. The study will be conducted in accordance with the ethical principles, which have their origins in the Declaration of Helsinki.

10.2 Ethics Review

The study and any amendments will be reviewed by an appropriately constituted and composed IRB/IEC. Written IRB approval for the protocol, amendments, ICF, and Investigator(s) will be obtained in accordance with GCP. The IRB/IEC will be notified of SAEs in accordance with IRB/IEC Policy.

10.3 Informed Consent

An initial sample ICF is provided for the Investigator and IRB/IEC to prepare the informed consent document to be used at his or her site. The site-specific informed consent document will be submitted for review to the central IRB and the IRB-approved informed consent document will be held in the site study file and in the Sponsor's Trial Master File.

The ICF is to be prepared in the language(s) of the potential patient population for this study. The languages under consideration are English and Spanish.

Before a patient's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific procedures are performed.

The Investigator is also responsible for asking the patient if the patient has a primary care physician and if the patient agrees to have his/her primary care physician informed of the patient's participation in the clinical study. If the patient agrees to such notification, the Investigator is to inform the patient's primary care physician of the patient's participation in the clinical study. If the patient does not have a primary care physician and the Investigator will be acting in that capacity, the Investigator is to document such in the patient's medical record. The acquisition of informed consent and the patient's agreement or refusal of his/her notification of the primary care physician, if relevant, is to be documented in the patient's medical records, and the ICF is to be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient.

10.4 Data Privacy

All study-related laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patients' study data is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Patient personal health information that is accessed for this study will not be reused or disclosed to any other person or entity, or for other research.

10.5 Financial Disclosure

In connection with the clinical study described in the protocol, the Investigator certifies that the Investigator will read and answer the Clinical Investigator Financial Disclosure Form truthfully and to the best of Investigator's ability. The Investigator also certifies that, if asked, the Investigator will have any other applicable parties (e.g., Sub-Investigators) read and answer the Clinical Investigator Financial Disclosure Form as a condition of their participation in the study. If the financial interests reported on the Clinical Investigator Financial Disclosure Form change during the course of the study or within 1 year after the last patient has completed the study as specified in the protocol, the Investigator and the other applicable parties are obligated to update the Sponsor of financial disclosure in accordance with the Sponsor's standard procedures.

10.6 Biological Specimens and Data

Biological samples are only collected for safety and will be destroyed after analysis at Screening, Week 24, Week 48, and at Unscheduled/ET. Samples should be sent to the Sponsor's designated laboratory as detailed in the Laboratory Manual.

11 OVERSIGHT

11.1 Safety Assessment Committee

A SAC will be established to support pharmacovigilance activities for the study, such as adjudication of AEs or possible safety signals. The SAC Charter will describe the committee's structure, roles, and responsibilities.

11.2 Quality Control and Assurance

11.2.1 Monitoring and Audits

The Investigator will permit regular study-related monitoring by the Sponsor or designee, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

11.2.2 Protocol Deviations

Protocol violations/deviations will be documented in accordance with good documentation practice and reported to the IRB/IEC in accordance with IRB/IEC Policy. In case of a deviation necessary to eliminate an immediate hazard to a research participant, the deviation will be reported to the IRB/IEC as soon as possible. Investigational sites should make every effort to adhere to the processes and procedures described in this protocol.

11.2.3 Records

11.2.3.1 Data Capture and Management

An EDC system will be designed and managed on behalf of the Sponsor by the Sponsor's designated contract research organization. Clinical data will be entered by study site personnel within 5 business days of the patient visit or activity conduct. Monitoring of the study will be conducted on site by a designee of the Sponsor (clinical research associate), who will conduct document and source data review, as well as remote data monitoring in the intervals between monitoring visits. Data will be reviewed remotely by the Medical Monitor for safety oversight.

Investigator

All study-related information will be recorded on source documents. All required study data will be recorded in the eCRFs. All eCRF data must be submitted to the Sponsor throughout and at the end of study in a timely and accurate manner.

If an Investigator retires, relocates, or otherwise withdraws from conducting the study, the Investigator must notify the Sponsor to agree upon an acceptable storage solution.

Regulatory agencies will be notified with the appropriate documentation.

Sponsor

The data will be checked for completeness and correctness in real-time online.

Data are checked as they are entered into the EDC system. Offline checks will also be run to assess the need for additional data review. Discrepancy reports will be generated and transferred to the study center for resolution by the Investigator or its designee.

11.2.3.2 Records Retention

The Investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential, for the duration of (i) 2 years after the last marketing authorization for the Study Drug has been approved or the Sponsor has discontinued its research with respect to such Study Drug or (ii) such longer period as required by applicable global regulatory requirements. At the end of such period, the Investigator shall notify the Sponsor, in writing, of the intent to destroy all such material. The Sponsor shall have 30 days to respond to the Investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

12 PUBLICATION POLICY

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel at UNITY Biotechnology, Inc.

Authorship of any publications resulting from this study will be mutually agreed and determined on the basis of the Uniform Requirement for Manuscripts submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states the following:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or critically revising it for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. (Additional information on the current guidelines for publications can be found at the following location: http://www.icmje.org/).
- All publications (e.g., manuscripts, abstracts, oral/slide presentations, or book chapters) based on this study must be submitted to the Sponsor, for review. The Clinical Trial Agreement among the institution, Investigator, and the Sponsor will detail the procedures for, and timing of, the Sponsor’s review of publications.

13 FINANCING AND INSURANCE

Financial disclosure, site budget, and any insurance policies relevant to this clinical study are described in each Clinical Trial Agreement.

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