A Phase 2b, Prospective, Multicenter, Randomized, Double-Masked, Active-Controlled Study to Assess the Efficacy and Safety of Repeat Intravitreal Injections of Foselutoclax (UBX1325) in Patients with Diabetic Macular Edema (Aspire)

Investigational Product(s)	UBX1325
Protocol Number	UBX1325-04
Version Number	3.0
Version Date	26 March 2024
IND Number	145348
Sponsor	UNITY Biotechnology, Inc.
Sponsor's Legal Representative	CBI CBI CBI CBI CBI

	Date
Original Protocol:	31 May 2023, Version 1.0
Amendment 1:	06 October 2023, Version 2.0
Amendment 2:	26 March 2024, Version 3.0

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**
The following changes were made to the Inclusion (IC) / Exclusion (EC) criterion: IC #4: BCVA in the SE (most affected) of 70 to 30 **(inclusive)** ETDRS letters (equivalent to 20/40 to 20/250 on the Snellen Chart) **at all run-in visits during Screening** and at Day 1 IC #5: IOP ≤23 mmHg on Day 1 pre aflibercept injection. Post injection, result must be ≤30 mmHg **(with or without therapy)** in order to proceed to the foselutoclax injection or sham procedure EC #1: Explicitly excluded Proliferative Diabetic Retinopathy (PDR) EC #6: Removed the timeframe of 'within 3 months' for history of panretinal photocoagulation IC #6 & EC #1: Added language to imaging related eligibility criteria to specify which will be assessed by the PI in addition to the Central Reading Center EC #18: Rearranged the details on which conditions are explicitly excluded and which are based on PI discretion [Synopsis] and [Section 4.2.1 Patient Population Selection] and [Section 4.4 Inclusion Criteria] and [Section 4.5 Exclusion Criteria]	Revisions were made to be more explicit and increase clarity
mfERG will be conducted at prequalified sites with the appropriate equipment [Schedule of Events] and [Section 5.1 Study Procedures]	mfERG will provide an objective way to measure retinal responses in addition to the more common imaging assessments in this study
Added results of the recently completed Ph 2 study, UBX1325-03 ENVISION, conducted in patients with wet AMD [Section 2.3.5.1 Previous Human Experience with BCL-2 Inhibitors]	The summary from this 48-week study further supports the favorable safety and tolerability profile of foselutoclax (UBX1325)

Area of change	Rationale
Rescue criteria revisions: - worsening CST determined from baseline (Day 1) versus from trough - decrease in BCVA determined from baseline (Day 1) instead of peak - added PI discretion as a criterion with a request for rationale to be documented in the Electronic Database Capture (EDC) - added guidance related to rescuing during visits with planned study injections - added Sponsor's preference to have unmasked injector administer rescue [Section 5.1.10 Rescue Criteria]	Adjustments were made based on what best linked to clinical practice and from additional understanding garnered in prior Phase 2 foselutoclax studies Sponsor's preference to have the unmasked injector administer rescue is to support the consistent collection of data across study procedures
Revised guidance on timing of AE collection to start from Screening (**during** the aflibercept run-in #1) [Section 7.2.1 Timeframe for Collection]	Clarified the intent to have AEs reported while the run-in #1 is being administered
The Screening visits through Visit 1 (Day 1) randomization may be conducted by unmasked or masked personnel. The unmasked personnel can likewise complete the corresponding data entry but will be restricted thereafter to view only access in EDC. Post injection IOP at Visits 1, 3 and 5 may be conducted by a qualified unmasked designee (in lieu of the unmasked injector) [Section 6.8 Masked and Unmasked Study Staff] and [Schedule of Events] for post injection IOP detail in Footnote 'c'	During screening, run-in injections are open label so masked and unmasked personnel can conduct the assessments and enter data in EDC. On Day 1, all activities through the randomization of a patient can be done by both masked and unmasked staff, but only the unmasked staff would receive the randomization code and manage the remainder of Day 1 study activities Add flexibility to post injection unmasked assessments (specifically IOP) to aid in patient and clinic flow
Added data from legacy pharmacokinetic studies [Section 2.3.4.3 Pharmacokinetics]	Additional data further supports Q8W dosing
Removed the requirement for oral temperature as long as it's collected consistently across all study visits [Section 5.1.6 Vitals]	Flexibility allows for sites to follow their internal SOP for this data collection

Area of change	Rationale
YAG capsulotomy allowed ≥2 weeks prior to Screening run-in #1 (prohibited during study participation unless needed for an AE) On Day 1, glaucoma medications and any SOC for lowering IOP post aflibercept injection is permitted (enter the AE and concomitant medication in EDC) [Section 6.10.1 Permitted Treatments]	Clarified the details around the permitted YAG capsulotomy and added the detail about permitted glaucoma meds to support the update to IC #5

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**
Extended the follow-up period from 24 weeks to 36 weeks, subsequently, the number of visits increased from 7 to 10. [Schedule of Events] and [Section 5.1 Study Procedures]	To assess longer term effects of study drug through repeat injections of foselutoclax. The number of study visits between Week 24 and 36 aligns with standard of care for DME patient population (approximately Q4W).
Incorporated an additional secondary endpoint related to rescue treatment. Secondary and Exploratory endpoints specify the 36-week timeframe. [Synopsis] and [Section 3 Study Endpoints]	To assess durability beyond the original 24 weeks.
Biosimilars were always permitted historical anti-VEGF, but now it's explicitly stated that they may be the anti-VEGF preceding the Screening run-in #1which is part of the stratification at Day 1. [Section 6.2 Method for Assigning Patients to the Treatment Group]	This clarification was necessary to maintain the patient pool and to be clear that this biosimilar data will be used to support the stratification of patients.

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCPs) as outlined by International Council for 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 Institutional Review Board (IRB) for the protocol and all materials provided to potential patients. Screening at a site may not begin prior to approval from the IRB and the Sponsor.

Any amendments to the protocol or changes to the consent document will be approved by the IRB 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 GCPs training, as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	A Phase 2b, Prospective, Multicenter, Randomized, Double-Masked, Active-Controlled Study to Assess the Efficacy and Safety of Repeat Intravitreal Injections of foselutoclax (UBX1325) in Patients with Diabetic Macular Edema (Aspire)
Protocol Number	UBX1325-04
Version Number	3.0
Version Date	26 March 2024

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**
CBI	Head of Ophthalmology and Chief Development Officer	CBI	3/28/2024

INVESTIGATOR'S AGREEMENT

I have read the protocol, and accessory materials related to Study UBX1325-04 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
aAMD	atrophic age-related macular degeneration
AMD	age-related macular degeneration
AE	adverse event
AUC	area under the curve
AUC_{0-672}	area under the curve from t=0 to t=672
AUC_{0-t}	area under the curve from t=0 to t
AUC_{0-inf}	area under the curve from t=0 to infinity
$AUC_{\%extrap}$	percent of the area under the curve extrapolated from AUC_{0-t} to AUC_{0-inf}
AR	adverse reaction
BCL-2	B-cell lymphoma 2
BCVA	best corrected visual acuity
CFP	color fundus photography
CL/F	apparent total clearance of the drug from plasma after intravitrealinjection
C_{max}	maximum concentration
CRA	clinical research associate
CST	central subfield thickness
CV	coefficient of variation
DLT	dose-limiting toxicity
DME	diabetic macular edema
DNA	deoxyribonucleic acid
DR	diabetic retinopathy
DRSS	diabetic retinopathy severity scale
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ERM	epiretinal membrane
ET	early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FDA	Food and Drug Administration
FE	fellow eye
ffERG	Full-field electroretinogram
FIH	first-in-human
GCP	good clinical practice
GLP	good laboratory practice
HbA1C	hemoglobin A1C
hERG	human ether-à-go-go-related gene
HRMEC	human retinal microvascular endothelial cells
IB	Investigator's Brochure

Abbreviation	Definition
ICAM-1	intercellular adhesion molecule-1
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IL	interleukin
IND	investigational new drug (application)
INN	International Nonproprietary Name
IOP	intraocular pressure
IRB	institutional review board
IV	intravenous
IVT	intravitreal
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
mfERG	Multifocal electroretinography
MRI	magnetic resonance imaging
MTD	maximally tolerated dose
NCA	non-compartmental analyses
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
NOAEL	no-observed-adverse-effect level
NV	neovascularization
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
OU	both eyes
PAD	pharmacologically active dose
PDR	proliferative diabetic retinopathy
PDGF	platelet-derived growth factor
PEDF	pigment epithelium-derived growth factor
PK	pharmacokinetic
POC	proof-of-concept
PS 80	polysorbate 80
RCT	randomized control trials
RPE	retinal pigment epithelium
SAC	safety assessment committee
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction

Abbreviation	Definition
SASP	senescence-associated secretory phenotype
SD-OCT	spectral domain optical coherence tomography
SE	study eye
SLE	slit lamp exam
SnCs	senescent cells
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
T_{max}	time at which the maximum plasma concentration is observed
TA	triamcinolone acetonide
TGF	tumor growth factor
TNF	tumor necrosis factor
US	United States
VA	visual acuity
Vd/F	apparent volume of distribution after non-intravenous administration
VEGF	vascular endothelial growth factor
VEP	visual evoked potential
VO	vaso-obliteration
WHO	World Health Organization

1 SYNOPSIS

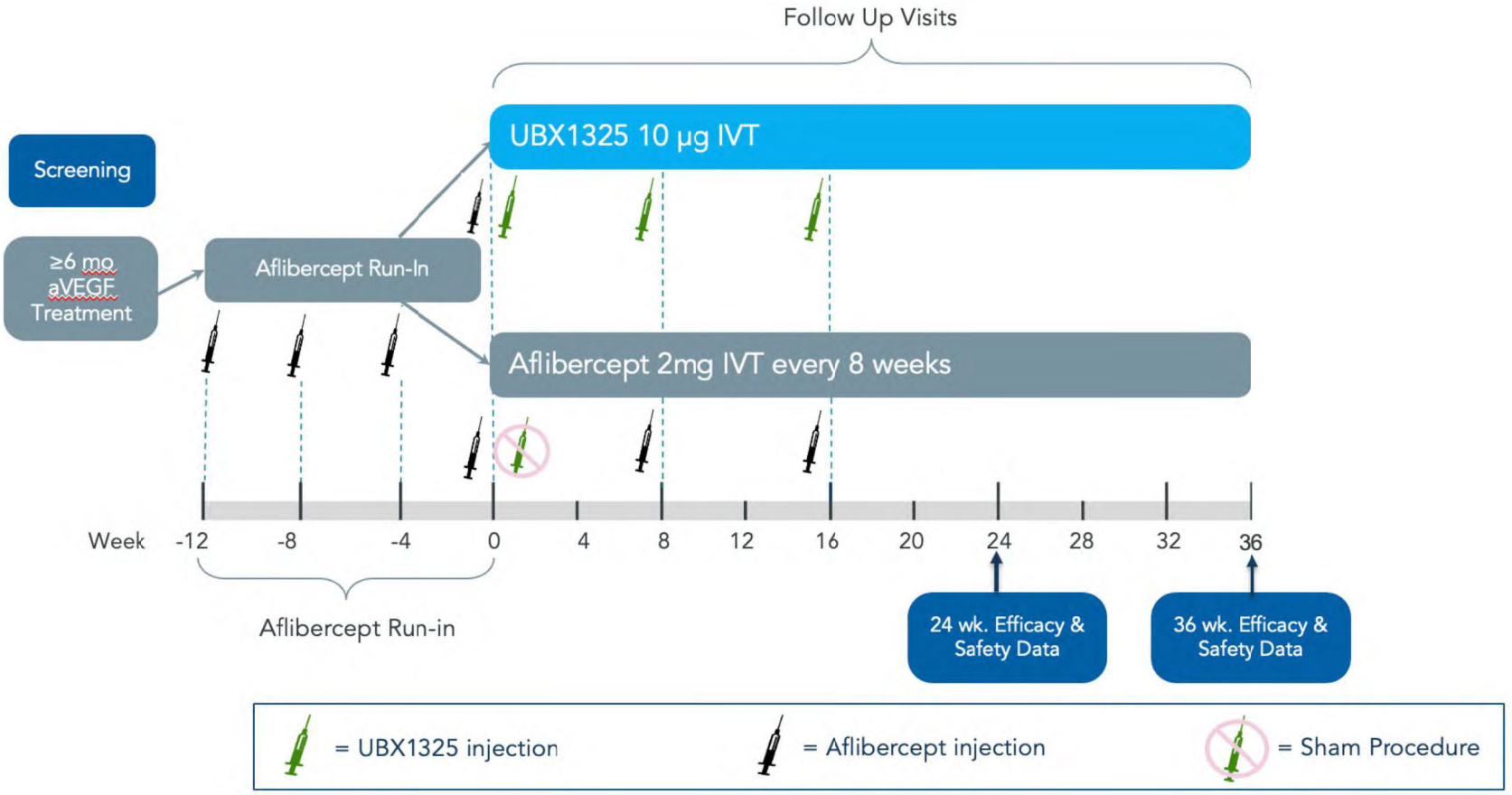
Title	A Phase 2b, Prospective, Multicenter, Randomized, Double-Masked, Active-Controlled Study to Assess the Efficacy and Safety of Repeat Intravitreal Injections of foselutoclax (UBX1325) in Patients with Diabetic Macular Edema (Aspire)
Phase	Phase 2b
Study Design	Approximately 40-50 patients will be enrolled and randomized 1:1 into either the foselutoclax (UBX1325) arm,10 µg given 8 weeks apart or an anti-vascular endothelial growth factor (VEGF) control arm of aflibercept, 2 mg every 8 weeks in order to assess the primary objective. All patients will be followed for approximately 36 weeks. The injector will be unmasked but the evaluator will remain masked throughout the study.
Rationale	This study is intended to assess the efficacy and safety of foselutoclax (UBX1325), a phosphate pro-drug, and its active parent molecule (UBX0601) following repeat intravitreal (IVT) injections of foselutoclax (UBX1325) in patients with Diabetic Macular Edema (DME).
Target Population	This study will enroll participants ≥18 years of age with active DME disease despite treatment, with best corrected visual acuity (BCVA) between 70 to 30 (inclusive) Early Treatment Diabetic Retinopathy Study (ETDRS) letters (equivalent to 20/40 to 20/250 on the Snellen chart) at every Screening run-in visit and at Day 1. Once patients meet inclusion/exclusion criteria, they will receive 3 run-in injections of aflibercept approximately 4 weeks apart, with the last aflibercept injection approximately 4–6 weeks prior to Day 1.
Number of Patients	Approximately 40-50 patients
Length of Participation	Approximately 48 weeks per patient (approximate 12-week screening period + 36-week follow-up period)
Intervention	Participants will receive 3 run-in aflibercept IVT injections, 4 weeks apart, and will then be randomized to 1 of 2 arms. • 10 µg foselutoclax (UBX1325) (50 µl of 0.2 µg/µl solution) IVT on Day 1 and Weeks 8 and 16. 2 mg aflibercept (50 µl of 40 µg/µl solution) on Day 1 • 2 mg aflibercept (50 µl of 40 µg/µl solution) IVT on Day 1 and Weeks 8 and 16. A sham procedure will be administered on Day 1
Primary Objective and Corresponding Endpoint	**Objective:** Assess the efficacy of foselutoclax (UBX1325) compared to aflibercept **Endpoint:** The primary objective of non-inferiority will be evaluated by comparing the difference between treatments in BCVA mean change from baseline to Week 24

Secondary Objectives and Corresponding Endpoints	**Objective:** Assess other measures of efficacy of foselutoclax (UBX1325) compared to aflibercept. **Endpoints**: • Changes in BCVA from baseline to each visit through Week 36 • Change in central subfield thickness (CST) from baseline to each visit through Week 36 as assessed by spectral domain optical coherence tomography (SD-OCT) and read by a Central Reading Center • Changes in BCVA area under the curve (AUC) from baseline to Week 36 and from Week 8 to Week 36, as well as the average of the last 2 visits • Changes in BCVA from baseline to last observation at or prior to Week 36 • Proportion of participants gaining ≥15, ≥10, ≥5, or ≥0 ETDRS letters in BCVA from baseline in the study eye (SE) to Week 36 • Proportion of participants who do not require rescue **Objective:** Assess the safety and tolerability of foselutoclax (UBX1325) **Endpoints**: • Percentage of participants with at least 1 treatment-emergent adverse event (TEAE) • Percentage of participants with at least 1 treatment-emergent ocular adverse event in the SE or the fellow eye (FE) • Percentage of participants with at least 1 treatment-emergent non-ocular adverse event (AE) • Percentage of participants with at least 1 treatment-emergent serious adverse event
Exploratory Objectives and Corresponding Endpoints	**Objective:** Assess efficacy parameters and retinal structure improvement after treatment of foselutoclax (UBX1325) compared to anti-VEGF alone. **Endpoint:** • Change in Diabetic Retinopathy Severity Scale (DRSS) score from Baseline to Week 36
Number of Sites	21 sites in the United States (US)
Study Duration	Approximately 19 months from screening to last patient visit
Safety Assessment Committee	A Safety Assessment Committee (SAC) will be established for adjudication of AEs or possible safety signals. The committee will meet on an ad hoc basis.

1.1.1 Study Schematic

The study schematic is presented in Figure 1.

Figure 1 Schema of Phase 2b Efficacy and Safety Study



1.2 Schedule of Events

The schedule of events is presented in Table 1.

Table 1 Schedule of Events

Test/Procedure	3 Screening Visits			Visit 1 Week 0 Day 1[b]	Visit 2 Week 4 Day 29 ± 7	Visit 3 Week 8 Day 57 ± 7	Visit 4 Week 12 Day 85 ± 7	Visit 5 Week 16 Day 113 ± 7	Visit 6 Week 20 Day 141 ± 7	Visit 7 Week 24 Day 169 ± 7	Visit 8 Week 28 Day 197 ± 7	Visit 9 Week 32 Day 225 ± 7	Visit 10 Week 36 Day 253 ± 7	Unscheduled Visit/ET[d]
	Run-in #1 (4-6 weeks post last SOC anti-VEGF)	Run-in #2 (28 days ± 5 from Run-in # 1)	Run-in #3 (28 days ± 5 from Run-in # 2) Day -42 to -28											
Informed Consent	X													
Demographics	X													
Medical/Ophthalmic & Medication History	X													
Concomitant Medications & Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (including ht/wt)[f]	X												X	X
Vital Signs	X			X	X	X	X	X	X	X	X	X	X	X
Labs: Hematology and Chemistry	X												X	X
Pregnancy Test	X (serum)[a]			X (urine)									X (urine)	X (urine)
BCVA OU (pre IVT)[c]	X	X (SE only)	X (SE only)	X	X	X	X	X	X	X	X	X	X	X
Hand Motion VA (post IVT)[c]	X	X	X	XX		X		X						
Anterior Segment Evaluation[c]	XX (pre/post IVT)			XXX (pre/2 post IVT)	X	XX (pre/post IVT)	X	XX (pre/post IVT)	X	X	X	X	X	X
Posterior Segment Evaluation[c]	X (pre IVT)			X (pre IVT)	X	X (pre IVT)	X	X (pre IVT)	X	X	X	X	X	X
Central Retinal Artery Perfusion Exam (post IVT)[c]	X	X	X	XX		X		X						
IOP[c]	XX (pre/post IVT)	X (post IVT)	X (post IVT)	XXX (pre/2 post IVT)	X	XX (pre/post IVT)	X	XX (pre/post IVT)	X	X	X	X	X	X

Test/Procedure	3 Screening Visits			Visit 1 Week 0 Day 1[b]	Visit 2 Week 4 Day 29 ± 7	Visit 3 Week 8 Day 57 ± 7	Visit 4 Week 12 Day 85 ± 7	Visit 5 Week 16 Day 113 ± 7	Visit 6 Week 20 Day 141 ± 7	Visit 7 Week 24 Day 169 ± 7	Visit 8 Week 28 Day 197 ± 7	Visit 9 Week 32 Day 225 ± 7	Visit 10 Week 36 Day 253 ± 7	Unscheduled Visit/ET[d]
	Run-in #1 (4-6 weeks post last SOC anti-VEGF)	Run-in #2 (28 days ± 5 from Run-in # 1)	Run-in #3 (28 days ± 5 from Run-in # 2) Day -42 to -28											
SD-OCT	X			X	X	X	X	X	X	X	X	X	X	X
FA	X			X									X	X
CFP	X			X									X	X
DRSS Score[g]				X									X	X
mfERG[h]				X		X		X		X			X	X
Eligibility Criteria[a]	X	X	X	X										
Aflibercept Run-In Administration[e]	X	X	X											
Study Drug Arm[e]				XX		X		X						
Aflibercept Control Arm[e]				XX		X		X						
AE assessment	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; DRSS = diabetic retinopathy severity scale; ET = Early Termination; FA = fluorescein angiography; IOP = intraocular pressure; IVT = intravitreal; SD-OCT = spectral domain optical coherence tomography; mfERG = multifocal electroretinography.

[a] Screening visit Run-in #1 requires the following assessments to be completed; however, the results related to study eligibility will not be immediately available and need to be verified prior to Screening visit Run-in #2.

- Serum pregnancy test and lab results will be available within 72 hours
- SD-OCT, FA, and CFP images should be promptly transmitted to the Central Reading Center. Eligibility reports will be issued within 2 weeks

Screening visits Run-in #2 and Run-in #3 require the following assessment to be resulted before proceeding with all other procedures required for Run-in #2 and #3.

- BCVA SE only- if the results show ≥10 letter gain in the SE, then this is a screen fail

Visit 1 (Day 1) requires the following assessments to be performed and results available before proceeding to randomization.

- Urine pregnancy test (kit included in lab supplies) for females of childbearing potential
- BCVA OU- if the results show ≥10 letter gain in the SE, then this is a screen fail
- IOP ≤23 mmHg in the SE
- Medication history (anti-VEGF taken in OU 6 months prior to Screening is needed so the randomization module can accurately stratify)

[b] Screening visit Run-in #1 requires the following assessments to be completed; however, the results related to study eligibility will not be immediately available and need to be verified prior to Screening visit Run-in #2.

- Serum pregnancy test and lab results will be available within 72 hours
- SD-OCT, FA, and CFP images should be promptly transmitted to the Central Reading Center. Eligibility reports will be issued within 2 weeks

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- Urine pregnancy test (kit included in lab supplies) for females of childbearing potential
- BCVA OU- if the results show ≥10 letter gain in the SE, then this is a screen fail
- IOP ≤23 mmHg in the SE
- Medication history (anti-VEGF taken in OU 6 months prior to Screening is needed so the randomization module can accurately stratify)

[c] On Day 1 patients will either get coadministration of aflibercept and foselutoclax (UBX1325), or aflibercept and a sham procedure. Aflibercept should be administered first, then conduct the post-injection assessments before proceeding to either foselutoclax (UBX1325) administration or sham procedure. See footnote c for timing of post-injection procedures.

[d] Procedure to be performed pre-dose in OU and post-dose in SE only. Post-dose procedures will be done by the unmasked injector or a qualified unmasked designee, 30 minutes ± 15 minutes and no more than 2 hours post dose. On Day 1, when there is either coadministration of aflibercept and foselutoclax (UBX1325), or aflibercept and a sham procedure, these assessments should be done pre and at each post IVT injection.

[e] For Unscheduled Visits, tests/procedures can be performed per Investigator discretion. For ET Visits, all tests/procedures need to be performed. FA should only be completed if it has not been performed within the preceding 30 days.

[f] After all other study procedures have been completed, optional post-injection prophylactic antibiotics may be administered. Sites should follow their standard practice and document all medication given.

[g] Complete physical examinations inclusive of height and weight will be performed at Screening as a baseline assessment and at Visit 10 (Day 253) or ET. Symptom-directed physical examinations may be conducted at all other times as clinically indicated and as part of an AE assessment.

[h] DRSS scores will be generated by the Central Reading Center, so it is important that sites promptly transmit the CFP.

[i] mfERG to be conducted as the first ocular evaluation at prequalified sites with the proper equipment available and completed prior to the first IVT injection.

2 INTRODUCTION

Foselutoclax (UBX1325) is a new molecular entity that is being investigated by UNITY Biotechnology, Inc. (the Sponsor) for the treatment of diabetic macular edema (DME).

DME is a complication of diabetic retinopathy (DR) following chronic, poorly controlled diabetes, and is the most common form of sight-threatening retinopathy in people with diabetes (Tan, 2017; IDF,2019). Approximately one in 14 patients with diabetes has some degree of DME (Coney 2019).

The overall prevalence of DR in patients with diabetes using retinal images was estimated to be 35%, with vision-threatening DR present in 12% (WHO,2015). Prevalence depends on the type of diabetes and the duration of the disease. For both type 1 diabetes and type 2 diabetes, after 25 years duration, prevalence approximates 30% (Browning., 2018).

In the United States (US), at least 5.5 million individuals older than 40 years of age are estimated to have DR in the absence of DME, and an additional 800,000 to 1 million patients have DME. According to some estimates, only 40% of patients are diagnosed and treated, and about 5% are diagnosed and observed (IDF,2019; VanderBeek, 2016).

Fewer than half of all US adults with diabetes adhere to guideline-recommended eye screening schedules. Patients with DR typically have no symptoms in the early stage of the disease and may not seek medical evaluation until DR advances and results in vision impairment. These delays in diagnosis and treatment may result in visual impairment that is permanent and irreversible (Coney 2019).

Despite advances in diagnosis and management of ocular disease in patients with diabetes, eye complications from diabetes continue to be a leading cause of vision loss and new onset blindness in working-age individuals in the US (Aiello,2005; Antonetti, 2012).

2.1 Overview of DME

The most common early clinically visible manifestations of DR include microaneurysm formation and intraretinal hemorrhages. Microvascular damage (e.g., retinal capillary non--perfusion, cotton wool spots, increased numbers of hemorrhages, venous abnormalities, and intraretinal microvascular abnormalities) leads to increased vasopermeability, which can subsequently result in retinal thickening and/or exudates that may lead to loss in central visual acuity (VA).

When the blood-retinal barrier is further compromised, pooling of fluid within the retina's central area, the macula, may ensue and cause DME. Capillary leakage causes diffuse edema, whereas focal or multifocal leakage from grouped microaneurysms leads to localized edema (IDF,2019).

The natural history of DME is characterized by a slow progression of retinal thickening until the center of the macula is involved, causing VA deterioration. Spontaneous resolution of DME is rare and usually secondary to improvement in systemic risk factors, such as glycemic control, hypertension, or hypercholesterolemia. If untreated, 29% of eyes with

DME and foveal involvement experience moderate visual loss (doubling of the visual angle) after 3 years.

Spontaneous visual recovery is also unusual, with improvement of at least 3 Early Treatment Diabetic Retinopathy Study (ETDRS) lines occurring in 5% of cases (Bandello, 2017).

No difference in the prevalence of DME was observed when patients were analyzed by age or gender; however, non-Hispanic Black individuals had greater odds of having DME compared with non-Hispanic White individuals (Varma, 2014). Systemic risk factors associated with DME include longer duration of diabetes, high systolic blood pressure, and elevated hemoglobin A1C (HbA1C) levels. Other studies found that lipid and triglyceride levels, advanced diabetic nephropathy, and pregnancy are also associated risk factors. The sole ocular factor associated with DME is DR severity, as increasing severity is associated with increasing prevalence of DME (Browning, 2018; Kim, 2019).

The macula in DME is thickened due to increased extracellular fluid derived from hyperpermeable retinal capillaries. Prolonged hyperglycemia in uncontrolled diabetes leads to reduced inner retinal oxygen tension, venous dilation, increased vascular endothelial growth factor (VEGF) concentration within the retina, leukocyte stasis, and dysregulated growth factor levels, which together are associated with increased exudation of serum out of the retinal vasculature and into the extracellular space. The retinal pigment epithelium (RPE) pump is overwhelmed by the exudation of serum and macular swelling results (Browning, 2018).

While the underlying pathophysiology of DME is believed to be VEGF-mediated, there is a growing body of evidence suggesting that inflammatory mediators and cytokines contribute to the vascular permeability and edema in DME (Ascaso, 2014, Owen and Hartnett 2013, Browning, 2018). Increased inflammation, characterized by leukostasis, accumulation of macrophages, intercellular adhesion molecule-1 (ICAM-1), and prostacyclin upregulation, is associated with capillary non-perfusion and breakdown of the blood-retinal barrier (Browning, 2018). Patients with DME have elevated vitreous levels of VEGF, ICAM-1, interleukin (IL)-6, and monocyte chemoattractant protein-1 compared with non-diabetic patients (Funatsu, 2009).

Inflammatory cytokines, such as tumor necrosis factors alpha and beta, alpha 4 integrin, nitric oxide, and IL-1β, mediate vascular permeability. High lipid levels may cause endothelial dysfunction and increased vascular permeability through a local inflammatory response and higher levels of advanced glycation end products (Miljanovic, 2004). Many other small molecules and growth factors may contribute to the development of DME, although the details of the pertinent pathways are incompletely understood (Kent, 2000; Patel, 2006, Browning, 2018).

2.2 Standard of Care for DME

Photocoagulation has been the standard of care for DME for decades. However, a substantial group of patients are unresponsive to laser therapy and fail to improve after photocoagulation (Bandello, 2017). Some studies show that conventional photocoagulation is effective in

reducing macular thickness in patients with DME; however, it causes visible laser scars that may enlarge once treatment is finished. In addition, the thermal effects of photocoagulation can trigger complications, including choroidal neovascularization, subretinal fibrosis, and visual field loss. Subthreshold diode micropulse laser therapy and selective retinal therapy may be valuable for treating sub-clinically significant DME that is diagnosed early (Park, 2014). However, given the risk of progression and general lack of early detection, in addition to adverse events (AEs), other treatment modalities for DME have been investigated.

Intravitreal (IVT) administration of steroids has provided promising results for the treatment of DME (Sarao, 2014). The anti-inflammatory, angiostatic, and anti-permeability properties of these compounds have gained interest for the treatment of chronic retinal conditions such as DME. A complete understanding of the mechanism of action of corticosteroids has not been fully clarified.

However, corticosteroids have been shown to interfere with many regulatory components of gene expression, inhibiting the expression of VEGF and key proinflammatory genes (tumor necrosis factor α and other inflammatory chemokines), while inducing genes functioning as anti-inflammatory factors (pigment epithelium-derived growth factor [PEDF]) (Tsaprouni, 2002; Tong., 2006; Kim., 2019; Zhang., 2006). The anti-inflammatory- activity of steroids is also related to the inhibition of the phospholipase A2 pathway, to the lower release of inflammatory cell mediators, and to reduced leukocyte chemotaxis (Bandello. 2017). Additionally, triamcinolone acetonide (TA) seems to reduce the expression of matrix metalloproteinases and down-regulates ICAM-1 in choroidal endothelial cells (Mizuno., 2007). Intravitreal and peribulbar injections of TA must be repeated every 2 to 4 months to maintain effect. Several steroid applications have been studied to prolong the intervals between treatments, such as biodegradable dexamethasone extended-release implant (Ozurdex®), fluocinolone acetonide (Iluvien®), and TA implants (Bandello., 2017).

Side effects of steroids are a concern, especially considering the limited availability of anti-VEGF medications that have minimal ocular side effects. The primary risks associated with IVT administration of corticosteroids for DME are cataract progression and development of glaucoma, which is why it is sometimes contraindicated in patients with glaucoma or ocular hypertension. Nonetheless, steroid treatment can be considered a first--line treatment in special populations, such as patients who have had a recent history of cardiovascular event(s), pregnant women, patients unable to adhere to monthly treatments, or persons undergoing cataract surgery (Zur, 2019).

Surgical vitrectomy was proposed as a treatment option for DME in the early 1990s. Eyes with DME were observed to have lower prevalence of posterior vitreous detachment than eyes without DME, and it was thought that vitreomacular adhesion might promote DME. This was further supported by the observation that resolution of DME could occur after posterior vitreous detachment and that surgical induction of a vitreomacular separation might improve DME. With the advent of optical coherence tomography (OCT), vitreomacular adhesion was shown to be a risk factor for DME (Browning., 2018). A controversy exists regarding the effects of vitrectomy for DME. Some reports suggest that vitrectomy reduces macular thickening but does not improve VA, yet others report improved VA and decreases

in macular thickening. Prospective, randomized clinical studies have not been conducted to evaluate the effect of vitrectomy on diverse DME patient population. Nonetheless, there is a general acceptance that vitrectomy has a role in the management of at least some cases of DME (Browning, 2018).

Studies have shown the safety and efficacy of IVT anti-VEGF treatments in patients with DME, some of which were the basis for Food and Drug Administration (FDA) approval of anti-VEGF therapies for the treatment of DME (Elman., 2010; Nguyen, 2012; Brown, 2015).The Diabetic Retinopathy Clinical Research Network trial, Protocol T, was a 660-patient study comparing 3 IVT anti-VEGF treatments in patients with DME, who were followed for 2 years of treatment. Focal/grid laser was added if DME persisted and was not improving at 6 months or later. Results showed that focal/grid laser was administered as a supplement in 41%, 64%, and 52% of aflibercept, bevacizumab, and ranibizumab groups, respectively. From Baseline to 2 years, mean VA letter score improved by 12.8 with aflibercept, 10.0 with bevacizumab, and 12.3 with ranibizumab. Treatment group differences varied by baseline VA (Wells, 2016).

A meta-analysis published by Virgili, 2018 concluded that anti-VEGF treatments are effective at improving vision in patients with DME, with 3 to 4 in every 10 patients being likely to experience an improvement of 3 or more EDTR lines VA at 1 year. Aflibercept may confer some advantage over ranibizumab and bevacizumab in patients with DME at 1 year in visual and anatomic terms, but it is unclear whether this applied to the long-term. Overall, the safety profile between the 3 anti-VEGF drugs, aflibercept, ranibizumab, or bevacizumab is similar (Virgili., 2018).

Evidence from randomized controlled trials may not apply to real-world practice, where patients in need of anti-VEGF treatment are often under-treated and under-monitored. In a number of studies, the full effect of anti-VEGF agents is not experienced for up to 12 months, and in many patients, even after 12 months, significant retinal fluid remains. This suggests that other therapeutic options with more rapid and complete effects could have an important role in the treatment of this disease.

Despite the success achieved with anti-VEGF treatment for DME, patients' poor compliance with the regimen (monthly and/or bimonthly IVT injections or a treat-and-extend regimen), refractory cases to anti-VEGF treatment (50% of DME patients) (AAO PPP for AMD 2019; AAO PPP for DR 2017), the long-term complication of retinal fibrosis, and the prolonged time it takes to achieve maximal response account for the unmet need that remains in DME. Although VEGF has been identified as a primary biomarker for the neovascular disease, other biomarkers are present in DR (including IL-1 β, tumor necrosis factor [TNF]-α, IL-6, and tumor growth factor [TGF- β], among others) and it could be argued that anti-VEGF treatment alone does not address the multifactorial nature of the disease.

Analysis of electronic medical records from a geographically and demographically diverse sample of US retina specialists revealed that real-world outcomes of anti-VEGF therapies in DME are meaningfully poorer than those shown in anti-VEGF randomized control trials (RCTs) (Ciulla, 2018). Overall, this electronic medical records study demonstrated that best corrected visual acuity (BCVA) outcomes in DME patients treated with anti-VEGF agents in

the real world are inferior to those in RCTs by approximately 1 line of VA at 1 year (Ciulla, 2018). A subsequent study by the same group confirmed that real-world patients with DME undergo fewer anti-VEGF injections and exhibit worse 1-year VA gains compared with patients in RCTs, regardless of anti-VEGF medication (Ciulla, 2020). This underscores the importance of a safe drug that has long durability of effect on DME patients.

2.2.1 *Target Indication and Population*

This study will enroll patients ≥18 years of age with DME with BCVA of 70 to 30 (inclusive) ETDRS letters (equivalent to 20/40 to 20/250 on the Snellen chart).

2.3 Scientific Rationale for foselutoclax (UBX1325) as a Treatment for DME

The Sponsor hypothesizes that the accumulation of senescent cells (SnCs) in the retina contributes to retinal disease. Foselutoclax (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. In preclinical studies, activation of the apoptotic cascade was selective for animals with a senescent cell burden. Intravitreal administration of foselutoclax (UBX1325) in diabetic animals led to improvements in retinal vascular leakage, providing support for the treatment of DME.

2.3.1 *Role of Senescence in Retinal Diseases*

The principal feature of senescence, a regulated, stress-induced, 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, 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, 2016; Lamoke, 2015; Ma, 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 the senescence-associated secretory phenotype (SASP). Although many factors of SASP have been identified in neovascular age-related macular degeneration and DR, a list of the most relevant factors associated with each disease have been studied and identified, with many of them having a proinflammatory role (Funk, 2009; Sato, 2018; Schori, 2018).

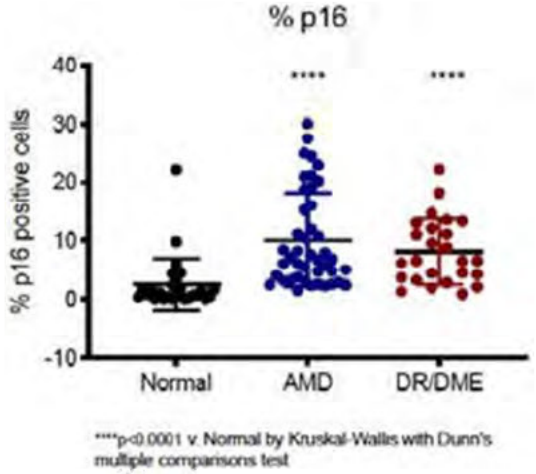
Blasiak, 2017 demonstrated the role of SASP in RPE cells, photoreceptors, and choriocapillaris and postulated that, in the central retina, RPE cells cannot be easily replaced by peripheral RPE cells, leading to deoxyribonucleic acid (DNA) damage response, autophagy, photoreceptor degeneration, and eventually, 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 the presence of SnCs in aged primates (Mishima, 1999), and the

proliferation potential of human RPE cells in vitro is suggested to be influenced by donor age (Flood, 1980). Recently, Lopez, 2017 reported the presence of $p16^+$ cells in the retinal vasculature of aged human donors and vessels associated with microaneurysms.

Immunohistochemistry staining performed by the Sponsor of retinal sections from patients with DR/DME and age-related macular degeneration (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.

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



AMD = age-related macular degeneration; 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 4',6-diamidino2-phenylindole, and % cells positive for p16 were calculated for each donor globe.
N = 27–43 per group.

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. Foselutoclax (UBX1325) has the potential to remove SnCs from a tissue without altering the healthy resident cells in the eye and slow 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 more effectively address the multifactorial character of the disease and may decrease the proportion of patients who respond either poorly or partially to anti-VEGF, the need for repeated treatments, and long-term complications like fibrosis and macular atrophy.

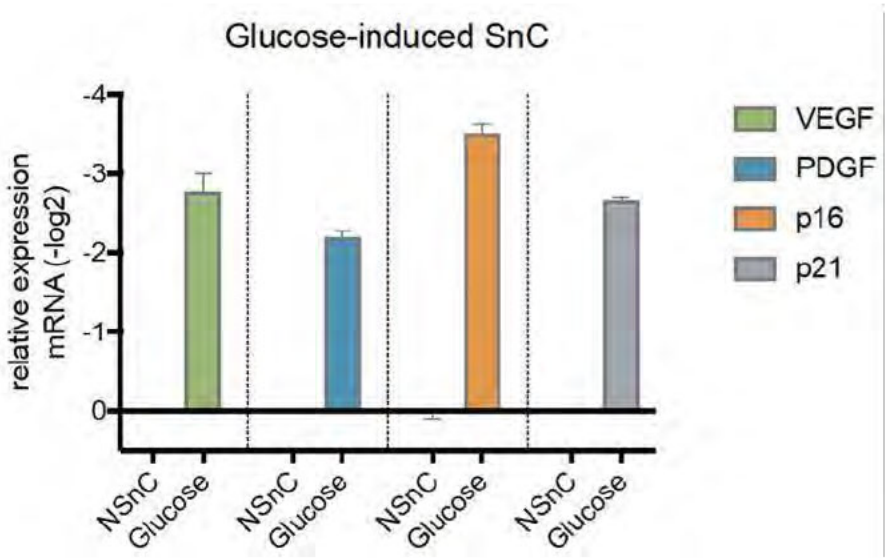
2.3.2 *Disease-relevant SASP from Senescent Retinal Cells*

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, 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, 2013; Boss, 2017; Ghodasra, 2016; Sato, 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 foselutoclax (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, 2016; Klaassen, 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 Diabetic Retinopathy-relevant Genes AfterGlucose Treatment



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

2.3.3 *Description of foselutoclax (UBX1325)*

Foselutoclax (UBX1325) is a soluble, small-molecule phosphate pro-drug, which is cleaved rapidly in tissues by ubiquitous phosphatases to yield the active parent molecule UBX0601. Foselutoclax (UBX1325) was designed to improve the solubility of UBX0601 as an ophthalmic formulation. In this protocol, the phrase "Study Drug" refers to the administered phosphate form [foselutoclax (UBX1325)], not the active inhibitor UBX0601. In all nonclinical studies, Study Drug is administered as foselutoclax (UBX1325), and converted

rapidly to UBX0601, which potently inhibits subtypes within the B-cell lymphoma 2 (BCL-2) family of apoptosis regulatory proteins, including BCL-2, BCL-xL, and BCL-w.

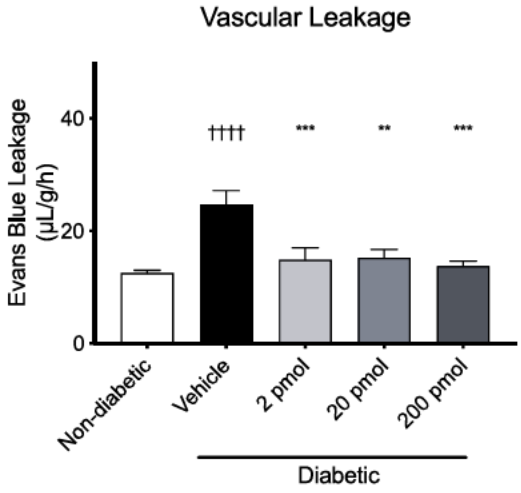
The World Health Organization (WHO) selected “foselutoclax” as the proposed International Nonproprietary Name (INN) for the UBX1325 substance. The stem –toclax designates BCL-2 inhibitors and is on par considering the structural similarity with pelcitoclax (UNITY, Data on file).

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 programmed cell 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, 2016). Binding of retinal BCL-xL by UBX0601 in senescent HRMEC acts to activate promote caspase and the apoptotic cascade, ultimately leading to cell death. In mouse models of retinal dysfunction, foselutoclax (UBX1325) demonstrated inhibition of disease -relevant endpoints, suggesting the potential for efficacy.

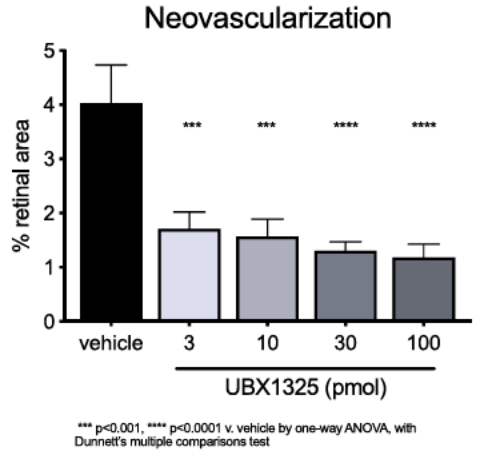
In a streptozotocin-induced DR mouse model, IVT administration of foselutoclax (UBX1325) resulted in decreased vascular leakage at all doses tested (2–200 pmol) (Figure 4). In a mouse model of retinal neovascularization (oxygen-induced retinopathy model), IVT administration of foselutoclax (UBX1325) led to a decrease in the total area of neovascularization at all doses tested (3–100 pmol) (Figure 5). Refer to the Investigator’s Brochure (IB) for additional details.

Figure 4 Improved Vascular Leakage in the Diabetic Mouse



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 Foselutoclax (UBX1325) (2–200 pmol, intravitreal) significantly reduced vascular leakage.

Figure 5 Decreased Neovascularization in the Oxygen-induced Retinopathy Mouse



Neovascular area was determined from isolectin B4-stained images of oxygen-induced retinopathy. All 4 dose levels of foselutoclax (UBX1325) (3–100 pmol, intravitreal) significantly reduced retinal neovascularization as compared to vehicle control animals.

2.3.3.1 Justification for Dosing Strategy

The foselutoclax (UBX1325) dose regimen planned for evaluation in this study was selected based on the safe dose established in the Phase 1 single-ascending dose (SAD) and BEHOLD Phase 2a studies.

In the Phase 1 SAD study, single IVT doses of 0.5, 1, 5, and 10 µg were studied. The highest dose of 10 µg was selected for this study, and a sentinel dosing design was followed in Cohort 1 and Cohort 2, in which only one subject was dosed initially, followed by a review of safety and tolerability data by the SAC. If the dose was found to be safe, the remaining patients in the cohort were dosed, and escalation to the next cohort proceeded if the safety data was favorable. The design was further supported by the safety profile defined in the preclinical toxicology package and the supportive nonclinical data, which demonstrated activity in the retina and evaluated the potential for systemic toxicity. The dosing strategy allowed for a thorough assessment of the acute toxicity associated with the administration of foselutoclax (UBX1325) while minimizing risk to subjects.

In BEHOLD, a Phase 2a study of patients with DME, foselutoclax (UBX1325) 10 µg was administered intravitreally once, and patients were followed for a period of 48 weeks. In this study, foselutoclax (UBX1325) had a favorable safety and tolerability profile with no evidence of intraocular inflammation.

The rationale for a repeat dose of foselutoclax (UBX1325) is to verify that patients are not under-dosed with foselutoclax that could undermine the ability to demonstrate non-inferiority. Additionally, the 2 arms have equal number of treatments (whether on foselutoclax or aflibercept) to not advantage any one arm over the other.

2.3.4 *Supportive Nonclinical Data*

All nonclinical pharmacology, toxicology, and pharmacokinetic (PK) studies briefly described in this section were conducted by or for the Sponsor. More detailed information is provided in the current version of the foselutoclax (UBX1325) IB.

2.3.4.1 Pharmacology

Foselutoclax (UBX1325) (pro-drug) and UBX0601 (active parent molecule) were studied in cellular and animal models of ocular disease to demonstrate activity in the retina. Foselutoclax (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, foselutoclax (UBX1325) demonstrated inhibition of disease-relevant endpoints such as neovascularization (NV) and vascular leakage. Foselutoclax (UBX1325) is a phosphate pro-drug of UBX0601, which is cleaved rapidly in tissues by a ubiquitously present enzyme, phosphatase.

2.3.4.2 Toxicology

Foselutoclax (UBX1325) has been evaluated in Good Laboratory Practice (GLP) ocular toxicity studies in New Zealand White 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 foselutoclax (UBX1325) and aflibercept with a 4-week recovery period was completed. Also, in order to evaluate the potential for systemic toxicity, 1-month GLP studies were conducted in which foselutoclax (UBX1325) was given as a once weekly intravenous (IV) dose to rats and dogs. The no-observed-effect level following IVT injection in rabbits at which there were no findings was 5 µg/eye; the no-observed-adverse-effect level

(NOAEL) in monkeys was 25 µg/eye. In the systemic repeat-dose 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 on Day 29 (NOAEL = 0.3 mg/kg, C_{max} = 1260 ng/mL and AUC_{last} = 649 hr·ng/mL; NOAEL = 0.1 mg/kg, C_{max} = 568 and AUC could not be determined) are not anticipated to be observed following IVT dosing.

Cardiovascular, respiratory, and neurobehavioral safety pharmacology studies following IV dosing of foselutoclax (UBX1325) up to 0.3 mg/kg UBX1325 did not result in any adverse findings. Of note, the cardiovascular study in dogs did not show any effect on QT prolongation, consistent with in vitro results evaluating the effect of foselutoclax (UBX1325) and UBX0601 on the human ether-à-go-go-related gene (hERG) channel. The combination of foselutoclax (UBX1325) with aflibercept was well tolerated with no effects on intraocular pressure (IOP), electroretinograms, or clinical and anatomic pathology endpoints with the NOAEL being the high dose combination of 25/500 ug/eye foselutoclax (UBX1325) /aflibercept. Findings were generally similar to single agent studies in the cynomolgus monkey. There was no apparent impact of foselutoclax (UBX1325) /UBX0601 on systemic aflibercept concentrations. In addition, foselutoclax (UBX1325) and UBX0601 were not genotoxic in either in vitro or in vivo studies. Further development of foselutoclax (UBX1325) is supported by the available data.

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

Intravitreal administration of foselutoclax (UBX1325) (on Study Day 15) in combination with aflibercept (on Study Days 1 and 29), was well tolerated. There was no mortality and no foselutoclax (UBX1325) /aflibercept or aflibercept-related clinical observations or changes in food consumption or body weight, no foselutoclax (UBX1325) /aflibercept or aflibercept-related IOP changes or effects on ffERG (full-field electroretinogram) or VEP (visual evoked potential), and no clinical or anatomic pathology effects.

Foselutoclax (UBX1325) /aflibercept-related findings were limited to non-adverse and reversible findings noted ophthalmoscopically and on OCT.

2.3.4.3 Pharmacokinetics

The ocular concentration of foselutoclax (UBX1325) and UBX0601 following a single IVT injection of foselutoclax (UBX1325) was evaluated in rabbits and cynomolgus monkeys. In rabbits, serial necropsy and tissue analyses were performed at 2, 24, 72, 168, 240, and 336 hours post-dose after a single IVT injection of 50 µg/eye and at 2, 24, 48, 72, 168, 336, 504 and 672 hours post-dose after a single IVT injection of 8 µg/eye in a separate study. The calculated half-lives of UBX0601 in the vitreous humor, retina, lens, choroid, and iris-ciliary body were 87 hours, 75 hours, 192 hours, 47 hours and 80 hours, respectively. Aqueous humor concentrations of UBX0601 appeared to remain at a very low level of 0.02 µg/mL and did not allow for half-life estimation. Based on the assumption that 5 half-lives constitute 97% of drug eliminated, UBX0601 is expected to be eliminated from the vitreous humor in 18 days, retina in 16 days, lens in 40 days, choroid in 10 days and iris-ciliary body in 17 days. In the lens, the concentration of UBX0601 showed a slower rate of decline in

comparison to other ocular tissues. Nonparametric superposition simulations were performed to estimate accumulation of UBX0601 in the lens after every 4 and 8 weeks of dosing of UBX1325, which demonstrated negligible accumulation of UBX0601 (1.1-fold) after every 4 weeks dosing and no accumulation of UBX0601 after every 8 weeks of dosing. These data suggest that dosing every 8 weeks will carry a low risk of accumulation in retinal tissues, including the lens. Systemic exposure to foselutoclax (UBX1325) /UBX0601 following intraocular administration was minimal and usually below the lower limit of quantification in the assay (1 ng/mL), suggesting rapid clearance once UBX0601 reaches the systemic circulation.

Intravenous injection of foselutoclax (UBX1325) in rats and dogs resulted in dose-related increases in exposures with increasing dose and minimal accumulation following repeat doses.

2.3.5 *Benefit: Risk Assessment*

2.3.5.1 Previous Human Experience with BCL-2 Inhibitors

Foselutoclax (UBX1325) is in a class of agents known to inhibit certain members of the BCL-2 family that are apoptosis regulatory proteins. 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. 2008; Touzeau.,2014; Souers, 2013). To the best of the Sponsor's knowledge, BCL-2 inhibitors have not previously been investigated in an ocular setting outside of foselutoclax (UBX1325) studies as detailed in the IB. 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. Because they are in the same class of molecules, and in view of similar systemic toxicities noted in foselutoclax (UBX1325) IV nonclinical studies, the Sponsor monitored for potential BCL-2 inhibitor related toxicities (e.g., cytopenia) that may emerge from foselutoclax (UBX1325) IVT treatment. However, based on available exposure data following IVT dosing, the potential to observe such systemic events was low. Previous clinical studies of foselutoclax (UBX1325) reported no such events.

The proof-of-concept Phase 2a BEHOLD study was a multicenter, randomized, double-masked, sham-controlled study designed to evaluate the safety, tolerability, efficacy, and durability of a single 10 µg dose of foselutoclax (UBX1325) in patients with DME evaluated through 48 weeks. The study enrolled 65 patients being actively treated with anti-VEGF who had a VA deficit (73 ETDRS letters, approximately 20/40, or worse) and residual retinal fluid (central subfield thickness [CST] ≥300 microns).

The study of foselutoclax (UBX1325) demonstrated a favorable safety and tolerability profile with no serious adverse events related to the treatment. Moreover, patients treated with foselutoclax (UBX1325) showed significant improvements in BCVA and maintenance of CST compared to the sham group. Specifically, foselutoclax (UBX1325) resulted in a mean

change in BCVA of +6.2 ETDRS letters from baseline to 48 weeks, with a +7.6 ETDRS letter advantage over sham based on last observation before anti-VEGF rescue or end of study participation. Furthermore, approximately 53% of foselutoclax (UBX1325) -treated patients went 48 weeks without requiring any anti-VEGF rescue treatment, which is a promising result for patients with DME.

The recently completed Phase 2 ENVISION study was a multicenter, randomized, double-masked, active-controlled study designed to evaluate the safety, tolerability and evidence of activity of a repeat IVT injection of foselutoclax (UBX1325) in patients with wet AMD. This study had an aflibercept run-in injection at Screening for all patients and was composed of Part A which was the first 24 weeks and Part B which was the latter 24 weeks. Part A had foselutoclax (UBX1325) 4 weeks apart or aflibercept 8 weeks apart, and Part B had foselutoclax (UBX1325) 4 weeks apart (second cycle to those patients who received foselutoclax in the first 24 weeks) or aflibercept plus foselutoclax (UBX1325) 8 weeks apart and an aflibercept only injection at Week 40 (to those patients who were on the aflibercept-only arm in the first 24 weeks). Results indicate that foselutoclax (UBX1325) met the primary objective of safety and demonstrated favorable safety and tolerability profile. There were no instances of endophthalmitis, vasculitis or retinal artery occlusion. There was a single case of iritis (uveitis) in the aflibercept and foselutoclax (UBX1325) combination arm that resolved with the use of topical steroids.

Overall, foselutoclax (UBX1325) as a monotherapy did not achieve non-inferiority to aflibercept control on change from baseline in BCVA through 24 weeks. At 24 weeks, foselutoclax (UBX1325)-treated patients demonstrated a change from baseline in BCVA of -0.8 ETDRS letters vs. 3.1 ETDRS letters in the aflibercept control arm. The change from baseline of 3.1 letters in the aflibercept-treated patients was an unexpected result based on prior anti-VEGF use history and the literature in patients heavily treated with anti-VEGF. Foselutoclax (UBX1325)-treated patients had stability of visual acuity through 24 weeks with less than one letter change from baseline along with an approximately 80% reduction in the need for anti-VEGF use. Amongst the patients treated with foselutoclax (UBX1325), 52% did not require anti-VEGF treatment through at least 24 weeks. At 48 weeks, foselutoclax (UBX1325)-treated patients demonstrated a change from baseline in BCVA of -1.5 ETDRS letters (MMRM hypothetical strategy). At 48 weeks, aflibercept/UBX1325 combination patients demonstrated a change from baseline in BCVA of 1.7 ETDRS letters (MMRM hypothetical strategy). Among the patients treated with foselutoclax (UBX1325), 40% did not require anti-VEGF treatment through at least 48 weeks.

3 OBJECTIVES AND ENDPOINTS

Tier	Objective	Endpoints
Primary	Assess the efficacy of foselutoclax (UBX1325) compared to aflibercept	• The primary objective of non-inferiority will be evaluated by comparing the difference between treatments in BCVA mean change from baseline to Week 24
Secondary	Assess other measures of efficacy of foselutoclax (UBX1325) compared to aflibercept	• Changes in BCVA from baseline to each visit through week 36 • Change in CST from baseline to each visit through Week 36 as assessed by SD-OCT and read by a Central Reading Center • Changes in BCVA AUC from baseline to Week 36, and from Week 8 to Week 36, as well as the average of the last 2 visits • Changes in BCVA from baseline to last observation at or prior to Week 36 • Proportion of participants gaining ≥15, ≥10, ≥5, or ≥0 ETDRS letters in BCVA from baseline in the SE to Week 36 • Proportion of participants who do not require rescue
	Assess the safety and tolerability of foselutoclax (UBX1325)	• Percentage of participants with at least one TEAE • Percentage of participants with at least one treatment-emergent ocular AE in the SE or FE • Percentage of participants with at least one treatment-emergent non-ocular AE • Percentage of participants with at least one treatment-emergent serious adverse event
Exploratory	Assess efficacy parameters and retinal structure improvement after treatment of foselutoclax (UBX1325) compared to anti-VEGF alone	• Change in DRSS score from baseline to Week 36

4 STUDY PLAN

4.1 Study Design

The study is a Phase 2b, randomized, parallel group, multicenter study of foselutoclax (UBX1325) in patients with DME. The study will enroll approximately 50 patients, who will be randomized in a 1:1 ratio to receive foselutoclax (UBX1325) 10 µg given 8 weeks apart or an anti-VEGF control arm of aflibercept 2 mg every 8 weeks in order to assess the primary objective. All patients will be followed for approximately 36 weeks.

Prior to randomization, participants will receive 3 IVT injections of aflibercept over 4-week intervals. After this run-in period, participants will be randomly assigned to 1 of 2 treatment arms:

- foselutoclax (UBX1325) arm: Participants will receive 10 µg foselutoclax (UBX1325) (50 µl of 0.2 µg/µl solution) IVT on Day 1 and Weeks 8 and 16. 2 mg aflibercept (50 µl of 40 µg/µl solution) will also be administered on Day 1.

- Anti-VEGF control arm: Participants will receive 2 mg aflibercept (50 µl of 40 µg/µl solution) IVT on Day 1, Weeks 8, and 16. A sham procedure will also be administered on Day 1.

The injector will be unmasked but the evaluator remains masked throughout the study. See Section 6.9 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 (Investigator Brochure), scientific rationale (see Section 2.3), and the clinical experience of foselutoclax (UBX1325) in a Phase 1 and Phase 2a studies in patients with DME, the Sponsor asserts that foselutoclax (UBX1325) can continue to be tested for safety and efficacy in DME patients.

This study will enroll patients who are at least 18 years old and diagnosed as having DME (as defined by the AAO PPP DME Guidelines 2019) with BCVA in the study eye of 70 to 30 (inclusive) ETDRS letters (equivalent to 20/40 to 20/250 on the Snellen chart) at all Screening run-in visits and at Day 1.

4.2.2 *Dose and Regimen Rationale*

As of 01 May 2023, for patients with advanced DME and wet AMD in the SAD Phase 1 study and for patients with NPDR to moderate PDR and DME in the BEHOLD Phase 2a study, foselutoclax (UBX1325) was well tolerated with favorable acute safety profile supporting development. In the Phase 1 SAD study, there were no dose-limiting toxicities in any of the dose cohorts, including the high dose of 10 µg. Likewise, in the BEHOLD study, there was a favorable safety and tolerability profile with no evidence of intraocular

inflammation. Additionally, 10 µg of foselutoclax (UBX1325) was administered in patients with wet AMD in the ENVISION study in 2 cycles: at Day 1, Week 4 and again on Week 24 and Week 28. Foselutoclax (UBX1325) met the primary objective of safety and demonstrated a safety and tolerability profile supportive of continued development without specific restrictions. There were no instances of retina artery occlusion, endophthalmitis, or vasculitis. The planned dose is 10 µg based on the aforementioned studies.

In terms of mechanism of action, of the drug and based on preclinical models, a single injection of Foselutoclax (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 foselutoclax (UBX1325) can potentially be clinically beneficial.

Based on BEHOLD Ph 2a study, optimum efficacy and durability in this Phase 2b DME population may benefit from a repeat dose of foselutoclax (UBX1325).

The preclinical studies of single and repeat IVT doses in rabbits and monkeys support infrequent repeat doses in clinical studies. The completed ocular toxicology program is considered to be sufficient to support this dose regimen at low doses. No further repeat-dose ocular toxicology studies are planned based on the infrequent dosing in the clinic of no more than 6 doses per year.

4.3 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 one or more eligibility criteria or who has withdrawn consent prior to randomization. Screen failures may be rescreened once, and in consultation with the Sponsor's Medical Monitor.

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

4.4 Inclusion Criteria

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

1. Patients aged ≥18 years.
2. Patients with nonproliferative DR and DME as read by a Central Reading Center, who:

   - Are treatment experienced with at least 6 months of treatment with anti-VEGF in the SE (one or more of the following agents: aflibercept, bevacizumab, ranibizumab or faricimab) and no less than 3 injections in this time period. The last injection must be received within 4–6 weeks of Screening.
3. Center-involved DME with CST ≥325–900 µm on SD-OCT (Heidelberg Spectralis) or ≥310–885 µm (Zeiss Cirrus) at Screening as determined by a Central Reading Center.
4. BCVA in the SE (most affected) of 70 to 30 (inclusive) ETDRS letters (equivalent to 20/40 to 20/250 on the Snellen chart) at all Screening run-in visits and at Day 1. If both

eyes are equal, then the SE may be selected at the Investigator's discretion. BCVA cannot be ≥10 letter gain between any Screening run-in visit and on Day 1 to be eligible for randomization.

5. IOP ≤ 23 mmHg in the SE on Day 1 prior to the aflibercept injection. Post aflibercept injection, IOP in the SE must be ≤30 mmHg (with or without therapy) in order to proceed to the foselutoclax (UBX1325) injection or sham procedure.
6. Clear ocular media and adequate pupillary dilation to permit color fundus photography (CFP) and adequate BCVA evaluation (e.g., no dense posterior subcapsular opacity that prohibits imaging). It is important to ensure that participants have clear media for accurate imaging and evaluation of the study outcomes. This evaluation should be conducted by the PI in addition to the Central Reading Center.
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.

4.5 Exclusion Criteria

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

1. Concurrent disease in the study eye (SE) or structural damage, other than DME, 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 which will be assessed by the PI in addition to the Central Reading Center:
    - Macular edema of etiologies other than diabetes
    - Clinically significant subretinal fibrosis (involving the center 1 mm subfield)
    - Subfoveal lipid (involving the center 1 mm subfield)
    - Cataract of severity possibly requiring surgery during the study period
    - RPE atrophy or tear or rips involving the macula
    - Clinically significant macular hole (lamellar macular hole or full thickness macular hole involving the foveal center point)
    - Clinically significant noninfectious uveitis (evidence of active uveitis)
    - Vitreomacular traction (involving the macula)
    - Clinically significant epiretinal membrane (involving the center 1 mm subfield)
    - Aphakia
    - Pseudophakia with anterior chamber intraocular lens
    - Proliferative Diabetic Retinopathy (active or inactive/historical PDR)
2. HbA1c ≥ 12 and/or recent signs of uncontrolled diabetes.
3. Any ocular/intraocular/periocular infection or inflammation in either eye in the past 4 weeks prior to Screening (mild blepharitis is acceptable).

4. History of vitreous hemorrhage in the SE within 2 months prior to Screening.
5. History of vitrectomy in the SE.
6. 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.
7. History of panretinal photocoagulation (at any point) or macular/focal laser photocoagulation (within 3 months) in the SE prior to Day 1.
8. History of corneal transplant in the SE.
9. Patients with glaucoma who are poorly controlled in the opinion of the Investigator or who are receiving more than 3 medications (whether administered as single agents or in combination formulations).
10. Presence of severe myopia (-8 diopters or greater) in the SE.
11. History of systemic or intraocular steroid use for or in the SE for 6 months prior to Day 1. The use of intravitreal nonbiodegradable steroid implants (e.g., Iluvien®, Yutiq®, Retisert®) is prohibited.
12. Significant media opacities, including cataract, or posterior capsule opacification, which might interfere with VA, assessment of toxicity, or fundus imaging in either eye.
13. Known allergy to dye injected during FA.
14. Known allergy to any component in the Study Drug.
15. 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.
16. 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.
17. Patients who within 3 months of screening received or are concurrently on another investigational drug or vaccine study, or patients who previously received treatment in either eye in a foselutoclax (UBX1325) study at any time. COVID-19 vaccinations are permitted prior to or during the course of the study. Refer to Section 6.10.
18. The following medical conditions are excluded:
    - a history of malignancy within the past 5 years (excluding stable superficial basal or squamous cell carcinoma of the skin)
    - a history of myocardial infarction within the past 6 months
    - severe hepatic and/or renal insufficiency including patients receiving ongoing dialysis

- individuals with a medical history of altered mental status or dementia, who may be unable to complete scheduled study visits or require a Power of Attorney for Medical Care
- any findings in the lab results, medical history or in the pre-study assessments, that constitute a risk to the patient or that could interfere with the study objectives, conduct, or evaluation or prevent the patient from fully participating in all aspects of the study
- any medical condition that is uncontrolled and may prevent participation in this study or disqualify individuals from enrollment, as determined by the Investigator

5 STUDY CONDUCT

The expected duration of study participation for each patient will be approximately 48 weeks, which includes an approximate 12-week Screening period and 36 weeks of follow-up.

The study procedures are outlined below and in the schedule of events (Table 1).

5.1 Study Procedures

5.1.1 *Study Screening and Treatment Periods*

5.1.1.1 Screening Run-in Injection #1 (Occurs 4–6 Weeks After Last Standard of Care Injection)

- Informed Consent
- Demographics
- Medical/Ophthalmic & Medication History
- Concomitant Medications & Procedures
- Physical Examination (complete) with Height/Weight
- Vital Signs
- Laboratory Tests: Hematology and Chemistry*
- Pregnancy Test (serum)*
- BCVA OU (pre-dose)
- Hand Motion VA (post-dose)
- Anterior Segment Evaluation (pre-dose in OU and post-dose in SE)
- Posterior Segment Evaluation (pre-dose in OU)
- Central Retinal Artery Perfusion Exam (post-dose in SE)
- IOP (pre-dose in OU and post-dose in SE)
- SD-OCT**
- FA**
- CFP**
- Eligibility Criteria
- Aflibercept Run-in Administration
- AE Assessment

*the results will be available within 72 hours and must be verified prior to proceeding to the 2nd screening visit (run-in injection #2)

**images must be promptly transmitted to the Central Reading Center in order to have eligibility reports available within 2 weeks. Results must be verified prior to proceeding to the 2nd screening visit (run-in injection #2)

5.1.1.2 Screening Run-in Injection #2 (28 Days ± 5 from Run-in #1)

- Concomitant Medications & Procedures
- BCVA SE (pre-dose)
- Hand Motion VA (post-dose in SE)
- Central Retinal Artery Perfusion Exam (post-dose in SE)
- IOP (Post-dose in SE)
- Eligibility Criteria
- Aflibercept Run-in Administration
- AE Assessment

5.1.1.3 Screening Run-in Injection #3 (28 Days ± 5 from Run-in #2) Visit must be 4–6 Weeks Prior to Day 1

- Concomitant Medications & Procedures
- BCVA SE (pre-dose)
- Hand Motion VA (post-dose in SE)
- Central Retinal Artery Perfusion Exam (post-dose in SE)
- IOP (post-dose in SE)
- Eligibility Criteria
- Aflibercept Run-in Administration
- AE Assessment

5.1.1.4 Visit 1 Baseline (Day 1)

This is the only visit at which there will be coadministration of either aflibercept and foselutoclax (UBX1325) or aflibercept and sham procedure, depending on to which arm the patient is randomized.

The following procedures will be done pre-dose:

- Concomitant Medications & Procedures
- Vital Signs
- Pregnancy Test (urine dipstick)
- BCVA OU
- Anterior Segment Evaluation OU
- Posterior Segment Evaluation OU
- IOP OU
- SD-OCT
- FA
- CFP
- DRSS (score will be generated by the Central Reading Center)
- mfERG (to be conducted at prequalified sites with the proper equipment)
- Eligibility Criteria

The following procedures will be done post-dose *after each injection*:

- Hand Motion VA in SE
- Anterior Segment Evaluation in SE
- Central Retinal Artery Perfusion Exam in SE
- IOP in SE
- AE Assessment

5.1.1.5 Visits 2, 4, 6, 8 and 9 (Days 29, 85, 141, 197 and 225)

- Concomitant Medications & Procedures

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

5.1.1.6 Visits 3 and 5 (Days 57 and 113)

The following procedures will be done pre-dose:

- Concomitant Medications & Procedures
- Vital Signs
- BCVA OU
- Anterior Segment Evaluation OU
- Posterior Segment Evaluation OU
- IOP OU
- SD-OCT
- mfERG (to be conducted at prequalified sites with the proper equipment)

The following procedures will be done post-dose:

- Hand Motion VA in SE
- Anterior Segment Evaluation in SE
- Central Retinal Artery Perfusion Exam in SE
- IOP in SE
- AE Assessment

5.1.1.7 Visit 7 (Day 169)

- Concomitant Medications & Procedures

- Vital Signs
- BCVA OU
- Anterior Segment Evaluation OU
- Posterior Segment Evaluation OU
- IOP OU
- SD-OCT
- mfERG (to be conducted at prequalified sites with the proper equipment)
- AE Assessment

5.1.1.8 Visit 10 (Day 253)

- Concomitant Medications & Procedures
- Physical Examination (complete) with Height/Weight
- Vital Signs
- Pregnancy Test (urine dipstick)
- Laboratory Tests: Hematology and Chemistry
- BCVA OU
- Anterior Segment Evaluation OU
- Posterior Segment Evaluation OU
- IOP OU
- SD-OCT
- FA
- CFP
- DRSS (score will be generated by the Central Reading Center)
- mfERG (to be conducted at prequalified sites with the proper equipment)
- AE Assessment

5.1.1.9 Unscheduled Visit/Early Termination

- Concomitant Medications & Procedures
- Physical Examination
- Vital Signs and Weight
- Pregnancy Test (urine dipstick)
- Laboratory Tests: Hematology and Chemistry
- BCVA OU
- Anterior Segment Evaluation OU
- Posterior Segment Evaluation OU
- IOP OU
- SD-OCT
- FA (to be completed only if assessment has not been done within the last 30 days)
- CFP
- DRSS (score will be generated by the Central Reading Center)
- mfERG (to be conducted at prequalified sites with the proper equipment)
- AE Assessment

  NOTE: for Unscheduled Visits, assessments are done at the Investigator's discretion. For Early Termination Visits, all assessments are required.

5.1.2 *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 IRB.

5.1.3 *Medical/Ophthalmic History and Medication History*

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. Medical/ophthalmic history related to the patient's overall health status, eye-related conditions, or to his or her DME should be

captured. This data will be collected at the initial Screening visit and recorded in the electronic case report form (eCRF).

All historical imaging (CST results) and VA assessments when available for both eyes in the preceding 6 months prior to Screening should be entered into the designated eCRF.

Anti-VEGF use for both eyes in the preceding 6 months prior to Screening should be documented in the concomitant medication log.

5.1.4 *Concomitant Medications & Procedures*

In addition to the historical medications to be entered in the concomitant medication log, all medications taken from Screening through the final study visit (excluding the aflibercept run-ins and Study Drug) should be documented in the same log.

Concomitant procedures, surgeries, etc., will be documented in a separate log so specific details can be captured versus cross referenced across multiple eCRFs. Sites should enter all procedures despite clinical relevance.

5.1.5 *Physical Examination*

Physical examination includes assessments of the skin, head and neck, lungs, heart, abdomen, lymph nodes, and extremities. Additionally, height and body weight will be measured.

Complete physical examinations will be performed by a licensed physician (or a physician's assistant or nurse practitioner) at Screening, Visit 10 (Week 36) or Early Termination (ET) Visits. At other timepoints, symptom-directed physical examinations may be performed as clinically indicated.

5.1.6 *Vital Signs*

Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) will be obtained in the sitting position. The patient must be in the sitting position for 5 minutes prior to obtaining vital signs. Sites must remain consistent with how that data is collected across all study visits.

Vital signs assessment will be performed at all study visits except for Screening run-in injections #2 and #3.

5.1.7 *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, as mentioned in Section 7.5.

5.1.8 *Pregnancy Test*

For all females of childbearing potential, serum pregnancy tests will be performed pre-dose at Screening, and urine pregnancy tests will be performed pre-dose on Day 1 and at Visit 10

(Week 36) and the ET Visit. Testing at any Unscheduled Visit will be at the Investigator's discretion.

5.1.9 *Ocular Evaluations (must be conducted on both eyes unless advised otherwise below)*

- BCVA: should be assessed using the ETDRS chart starting at 4 meters at every Visit. For Visits with IVT injections, it will be done pre-dose at all 3 Screening Visits (though at run-in injection #2 and #3, only SE should be assessed), on Day 1 and at Weeks 8 and 16. See the Visual Function Evaluation Procedures Manual for details.

- Hand Motion VA: after an IVT injection, patients will need to confirm their ability to distinguish whether or not there is movement of the examiner's hand directly in front of their SE. This should be assessed post-dose at all visits that have an IVT injection, including the 3 Screening Visits, Day 1 (should be done twice), and Weeks 8 and 16.

- Anterior Segment Evaluation: should be performed prior to or after pupillary dilation, depending on the site standard of care as long as it is done the same way throughout the study. Any abnormalities of the anterior chamber, eyelids, conjunctivae, pupil, iris, lens, and cornea should be documented pre- and post-dose at each Visit with an IVT injection (all 3 Screening Visits, Day 1, and Weeks 8 and 16), as well as during Visits without an IVT injection, Weeks 4, 12, 20, 24, 28, 32 and 36 and Unscheduled/ET. Any anterior chamber inflammation (cells and flare), phakic status, and posterior lens capsule status should also be noted. For post-dose, only the SE should be assessed. Note: on Day 1, there will be 2 post-dose exams in the SE.

- 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 pre-dose at Visits with an IVT injection (all 3 Screening Visits, Day 1, and Weeks 8 and 16); as well as during Visits without an IVT injection; Weeks 4, 12, 20, 24, 28, 32 and 36; and Unscheduled/ET. Any vitreous inflammation (haze and cells) should also be noted. For post-dose, only the SE should be assessed by conducting a Central Retinal Artery Perfusion Exam versus a complete Posterior Segment Evaluation.

- IOP: required to be measured using Goldmann applanation tonometry and should be performed prior to pupillary dilation or as per site's standard procedures. It will be done OU pre-dose at Screening run-in injection #1, Day 1, and Weeks 8 and 16. It will be done post-dose in the SE only at all 3 Screening Visits, twice on Day 1, and at Weeks 8 and 16. It should be assessed 30 minutes ± 15 minutes post-dose; note that, on Day 1, IOP must be ≤23 mmHg in the SE pre-dose and ≤30 mmHg post-dose (after aflibercept) in order to remain eligible for this study. It will also be done OU at Visits without an IVT injection, which include Weeks 4, 12, 20, 24, 28, 32 and 36 and Unscheduled/ET.

- CFP: should be obtained at Screening (run-in injection #1), Day 1, Week 36 and Unscheduled/ET. DRSS scores will be generated by the Central Reading Center and not read by the site.

- FA: should be obtained at Screening (run-in injection #1), Day 1 and Week 36. For Unscheduled /ET Visits, it should be done if it was not assessed within the preceding 30 days.
- SD-OCT: should be obtained OU at all study visits except for the Screening run-in #2 and #3. At Visits with an IVT injection (Screening run-in #1, Day 1, and Weeks 8 and 16), SD-OCT will be done pre-dose.
- mfERG: prequalified sites with proper equipment available will conduct this at Visits 1, 3, 5, 7, 10 and ET. mfERG should be the first ocular evaluation done pre IVT injection.

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

5.1.10 *Rescue Criteria*

If at any visit, including Unscheduled, patients exhibit increase in disease activity, defined as any of the following: worsening CST by ≥75 µm from baseline (Day 1) per SD-OCT, a ≥10 letter decrease in BCVA compared to baseline (Day 1), new clinically significant blood or heme present compared to previous visit, or PI discretion (rationale to be documented in the EDC), they can be rescued with aflibercept. During Weeks 8 and 16 when there are planned injections with either foselutoclax or aflibercept, if the site is comfortable, they should please consider proceeding per protocol. There is always an opportunity to bring the patient back for an Unscheduled visit, reassess the need for rescue and administer at that time.

It is preferred that the unmasked injector administer the rescue injection as long as they are available. Please call the Medical Monitor or your CRA if you need accommodations. Rescued patients will continue their visit schedule through Week 24, unless advised otherwise by the Sponsor. For any questions on rescue criteria, and prior to administering rescue medication, when possible, please contact the Medical Monitor or designee. If additional visits are required outside of study visit windows, these will be considered Unscheduled Visits.

5.1.11 *End of Study*

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

5.2 Discontinuation or Withdrawal

5.2.1 *Individual Patients*

5.2.1.1 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,
- Lack of efficacy,
- A serious or intolerable AE occurs,
- The Sponsor terminates the study,
- The Investigator suspends or terminates that site's participation in the study, or
- The patient requests to be discontinued from the study.

5.3 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 informs the Sponsor and the IRB and provides a detailed written explanation. Upon completion of study, the Sponsor will provide the Investigator with final reports and summaries as required by regulations. Upon study suspension, completion, or termination, the Investigator will return all study materials to the Sponsor or designee or destroy the materials at the investigative site per the Sponsor's instructions.

6 STUDY INTERVENTIONS

6.1 Description of Product

The Study Drug [foselutoclax (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 foselutoclax (UBX1325) in solution. Each vial and carton will be individually labeled. The labeling of the Study Drug will include the required identification as per 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 Development Services USA, Skokie, Illinois.

Sham kits will be supplied by the central lab and will be included in the bulk ancillary supply shipment. There will be a needleless syringe to complete the sham procedure. These will also be accounted for as part of Study Drug accountability.

6.1.1 *Foselutoclax (UBX1325)*

Foselutoclax (UBX1325) is formulated as a sterile, clear, colorless to pale yellow solution at a concentration of 0.2 mg/mL in pH 7.4 phosphate buffered saline that contains 0.6 mg/mL polysorbate 80 (PS 80), and will be provided in a glass vial, stoppered and crimp-sealed with a blue flip cap for IVT administration. Each vial contains 1.75 mL of a 0.2 mg/mL solution of foselutoclax (UBX1325) and is single-use only. Foselutoclax (UBX1325) must be stored at -20°C upon receipt.

Foselutoclax (UBX1325) will be provided to the investigational site along with a Pharmacy Manual, which details clinical product presentation.

Study Drug intended for IVT administration can be thawed and held at room temperature for a maximum of 8 hours. Unused Study Drug, once thawed, cannot be refrozen and thawed for future IVT administration.

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.

6.2 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 will be assigned to treatment via stratified randomization. Strata are defined by anti-VEGF medication (including the respective biosimilar) prior to screening and baseline BCVA. The strata for anti-VEGF medication are 1) aflibercept vs 2) ranibizumab, bevacizumab or faricimab. The strata for baseline BCVA are ≤ 60 ETDRS letters vs BCVA >60 ETDRS letters. Within each of these 4 strata, patients will be randomized to treatment in a 1:1 ratio.

Patients randomized to the foselutoclax (UBX1325) arm will receive foselutoclax (UBX1325) and aflibercept on Day 1 and only foselutoclax (UBX1325) at Weeks 8 and 16.

Patients randomized to the aflibercept arm will receive aflibercept and a sham procedure on Day 1, and aflibercept only at Weeks 8 and 16.

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.

6.3 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.

6.4 Administration of Foselutoclax (UBX1325)

Foselutoclax (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 administration of foselutoclax (UBX1325) 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.

6.5 Administration of Sham Procedure

The sham procedure 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 procedure.

6.6 Administration of Aflibercept

Aflibercept should be administered per standard of care.

6.7 Coadministration of Aflibercept and foselutoclax (UBX1325) or Sham

On administration on Day 1 aflibercept should be administered first before foselutoclax (UBX1325) or sham.

Intraocular pressure taken post aflibercept injection should be ≤30 mmHg prior to administering foselutoclax (UBX1325) or sham. Administration of foselutoclax (UBX1325) or sham after aflibercept 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.

6.8 Masked and Unmasked Study Staff

This study will be double-masked. Patients, Investigators, VA technicians, photographers, some Clinical Research Coordinators, Central Reading Center personnel, and the Sponsor are masked. Sites will have a qualified injector who is unmasked in order to perform the IVT injection(s) [foselutoclax (UBX1325) and/or aflibercept], and/or sham procedure, as well as certain post-injection assessments on Visits 1 (Day 1), 3 (Week 8), and 5 (Week 16). Specifically, the unmasked injector will do the anterior segment exam, central retinal artery perfusion exam, IOP (IOP can be done by a qualified unmasked designee), and AE assessment. Other supporting activities, such as Study Drug preparation and Study Drug accountability, will be performed by designated unmasked personnel. The Screening visits through Visit 1 (Day 1) randomization may be conducted by unmasked or masked personnel as well, however, after randomization is completed, unmasked personnel should not be involved in any other study procedures outside of visits when an IVT injection is required, including Visits where a rescue injection is necessitated. In addition to conducting the Screening visits through Visit 1 (Day 1) randomization, the unmasked personnel can likewise complete the corresponding data entry but will be restricted thereafter to view only access in EDC. It is important the randomization code is not revealed to anyone in order to maintain the integrity of the double-masking.

6.9 Extent and Maintenance of Double-Masking

In addition to the patients and Investigators being masked, any Sponsor or designated 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 36 for safety follow-up (AE and concomitant medication reporting, vital signs, physical examinations, and laboratory testing).

6.10 Permitted and Prohibited Concomitant Treatments

6.10.1 *Permitted Treatments*

Permitted concomitant treatments in/for the SE and FE 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(s) 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 needs to be documented as a concomitant medication
    - This should be entered as "PRN" for each eye individually
- Topical antibiotics administered prophylactically with IVT injection and topical/systemic antibiotics used for AE treatment
- Artificial tears
- Biosimilars are permitted as historical anti-VEGF treatments, but not during the course of the study
- Steroid use is permitted only for the following conditions:
    - Topical (e.g., for atopic dermatitis treatment), inhaled (e.g., for asthma treatment), orlocally injected (e.g., for epidural or joint injection)
    - Topical use of steroids in the FE
    - Topical use of steroids for treatment of inflammation in the SE (e.g., uveitis).
- YAG capsulotomy ≥2 weeks prior to Screening run-in #1 (prohibited during study participation unless needed for an AE)
- On Day 1, glaucoma medications and any SOC for lowering IOP post aflibercept injection is permitted (enter the AE and concomitant medication in EDC)
- Treatment of the FE:
    - This is permitted during any of the Screening Visits, given aflibercept run-in injections are open label.
    - During Visits with masked Study Drug injections, FE treatment is permitted on the same day provided it is done after SE treatment.

6.10.2 *Prohibited Treatments*

Patients will not be permitted to receive treatments for the management of DME in the SE, once randomized to this study, unless it is a rescue treatment).

Systemic (oral, intramuscular, and intravenous) steroids are not allowed unless for AE treatment.

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 should not have received brolucizumab as their most recent anti-VEGF treatment. Historical use of brolucizumab is not excluded.

7 SAFETY MONITORING

At each visit, patients will undergo ophthalmologic evaluation and assessment for signs of potential toxicity. Safety monitoring activities will be an ongoing activity done by the Sponsor. The SAC will convene on an ad hoc basis to assess the ongoing safety of the clinical trial.

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

7.1 Definitions

- **Adverse event (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 conductnormal 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 suchmedical 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 they 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 available risk information. 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 diagnosticobservations 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.

7.2 Documenting Adverse Events

7.2.1 *Timeframe for Collection*

Adverse events and SAEs will be collected from Screening (during aflibercept run-in #1, but anything prior to run-in #1 injection should be reported as medical history) through the last follow-up visit at Week 36.

The Investigator must follow up on all AEs through Week 36. Non-serious AEs may be followed to resolution past the patient's last study visit at the discretion of the Investigator

and/or Medical Monitor if it is in the best interest of the patient and the assessment of safety of foselutoclax (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.

7.2.2 *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.

7.3 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.

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 Sponsor's Pharmacovigilance provider. If the eCRF system is temporarily unavailable, the event, including the Investigator-determined causality to Study Drug, should be reported directly to the appropriate Sponsor or Pharmacovigilance contact using an SAE form. 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, ICH Guidelines, European Clinical Trials Directive (Directive 2001/20/EC), 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 will be done in accordance with the standard operation procedures and policies of the IRB. Adequate documentation must be maintained showing that the IRB was properly notified.

7.4 Adverse Events of Special Interest

No AEs of special interest have been identified for foselutoclax (UBX1325) to date.

7.5 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 • HbA1c[b] • Human chorionic gonadotropin[c] • Lactate dehydrogenase • Phosphorus • Potassium • Sodium • Total and direct bilirubin • Total cholesterol • Total protein

HbA1c = hemoglobin A1c; RBC = red blood cell; WBC = white blood cell

[a] Creatinine clearance will be calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.

[b] All patients will be tested for HbA1c at baseline and at Week 36 or ET, as well as at an Unscheduled visit if needed; fasting is not required.

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

7.6 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 administration of the Study Drug must be reported to the Investigator.

7.7 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.

8 STATISTICAL METHODS

8.1 General Considerations

All study parameters will be listed, and a selected list of parameters will be summarized descriptively by treatment arm 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. No imputation of values for missing data will be performed. 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.

8.2 Determination of Sample Size

With 20 patients per arm, 10% early study discontinuation, a non-inferiority margin of -4.5 letters, a standard deviation in BCVA of 7, a correlation between repeated measures of 0.5, and $\alpha = 0.10$ the primary analysis has $\geq 93\%$ power if the true difference between foselutoclax (UBX1325) and aflibercept is ≥ 2. If the standard deviation is 9, then the corresponding power is 78%. A masked sample size re-estimation will be used. If the residual standard deviation from the primary mixed model for repeated measures (MMRM) analysis applied to the masked BCVA data is > 7, the sample size may be increased to 25 per arm. Additional details on this masked interim analysis will be provided in the SAP.

8.3 Analysis Populations

8.3.1 *Full Analysis Set*

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

8.3.2 *Safety Analysis Set*

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

8.4 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, based on the Full Analysis Set.

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

8.5 Efficacy Analysis

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

The primary estimand is as follows:

Treatment regimen: foselutoclax (UBX1325) 10 μg fixed dose and 2 mg aflibercept

Population: patients with DME as define by inclusion and exclusion criteria

Endpoint: BCVA ETDRS letters

Summary measure: difference between treatments in mean change from baseline to the average of weeks 20 and 24. If the lower bound of the two-sided 90% confidence interval is above -4.5 letters, foselutoclax (UBX1325) will be considered non-inferior to aflibercept. If the lower bound is above 0, foselutoclax (UBX1325) will be considered superior to aflibercept.

A similar set of analyses will be applied to the Week 36 data. Further details will be provided in the SAP.

Intercurrent events: A treatment policy strategy will be used to account for the intercurrent event of use of rescue medication, and a hypothetical strategy will be used to account for the intercurrent event of early study discontinuation.

A secondary estimand will be assessed which is identical to the primary estimand except a hypothetical strategy will be used for both use of rescue medication and early study discontinuation. The BCVA will be assessed using the ETDRS chart starting at 4 meters at each study visit. Change in BCVA from baseline to each visit will be analyzed by MMRM. The details of MMRM and the analysis methodsfor other efficacy endpoints described in Section 3 will be provided in detail in the SAP.

The primary analysis will be a restricted-maximum likelihood based MMRM. The model will include the fixed, categorical effects of treatment, visit, and the treatment-by-visit interaction, along with the continuous covariates of baseline score and the baseline score-by-visit interaction. Within patient errors will be modeled using an unstructured covariance structure. If that analysis fails to converge, more parsimonious error correlation structures will be tested in the following order: heterogeneous Toeplitz, heterogeneous compound symmetric, and compound symmetric.

A similar analysis will be implemented for the secondary and exploratory outcomes. Full details of these analyses will be specified in the SAP.

8.6 Safety Analysis

The Safety Analysis Set will be used for all safety analyses. The safety variables include the incidence of ocular and systemic safety and tolerability and will be summarized descriptively.

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

8.7 Multiplicity Control

Control of type I error across multiple endpoints will be detailed in the SAP.

8.8 Planned Interim Analysis

At least one (1) formal interim analysis may be performed in this study. The timing and the proportion of patient data needed for the interim analysis will be specified in the SAP.

9 ETHICAL CONSIDERATIONS

9.1 Good Clinical Practice

This study will be conducted in compliance with the protocol approved by the IRB, and in accordance with ICH GCP standards and applicable regulations. Any amendments to the protocol or changes to the consent document will be approved by the IRB 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.

9.2 Ethics Review

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

9.3 Informed Consent

An initial sample ICF is provided for the Investigator and IRB 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 languages 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 screening procedures or any Study Drug is administered.

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.

9.4 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.

9.5 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.

9.6 Biological Specimens and Data

Biological samples are only collected for safety and will be destroyed after analysis at Screening, Week 36 and at Unscheduled/ET. Samples should be sent to the Sponsor's designated laboratory as detailed in the Laboratory Manual.

9.7 Safety Assessment Committee

A SAC will be established and available ad hoc 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.

9.8 Quality Control and Assurance

9.8.1 *Monitoring and Audits*

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

9.8.2 *Protocol Deviations*

Protocol violations/deviations will be documented in accordance with good documentation practice and reported to the IRB in accordance with IRB policy. In case of a deviation

necessary to eliminate an immediate hazard to a research participant, the deviation will be reported to the IRB as soon as possible. Investigational sites should make every effort to adhere to the processes and procedures described in this protocol.

9.8.3 *Records*

9.8.3.1 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 (e.g., clinical research associate [CRA]), 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.

9.8.3.2 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.

10 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; and (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.

11 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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