

RESEARCH MONOGRAPH . COMPOUND PROFILE

UBX1325

A first-in-class senolytic Bcl-xL inhibitor developed by Unity Biotechnology as an intravitreal therapy for diabetic macular edema and age-related macular degeneration, distinguished from conventional anti-VEGF agents by its mechanism of selective elimination of senescent retinal vascular cells and its potential for durable, disease-modifying efficacy from infrequent dosing.

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ABSTRACT

UBX1325 (fосelutoclax) is a soluble phosphate prodrug that is cleaved rapidly in ocular tissues by ubiquitous phosphatases to yield the active parent molecule UBX0601, a potent inhibitor of the B-cell lymphoma-extra large (Bcl-xL) anti-apoptotic protein and related Bcl-2 family members. The compound was developed by Unity Biotechnology as the first senolytic therapeutic candidate designed for intravitreal administration in ophthalmologic indications, principally diabetic macular edema (DME), diabetic retinopathy (DR), and neovascular (wet) age-related macular degeneration (AMD). The senolytic mechanism is fundamentally distinct from the anti-vascular endothelial growth factor (anti-VEGF) agents that constitute the current standard of care for these conditions: rather than neutralizing a single cytokine to reduce vascular permeability, UBX1325 selectively induces apoptosis in senescent retinal vascular endothelial cells that have accumulated in areas of disease activity, thereby removing a persistent source of pro-inflammatory and pro-permeability signaling and potentially modifying the underlying disease process rather than managing its downstream consequences.

The compound originated from a 2016 strategic licensing arrangement between Unity Biotechnology and Ascentage Pharma, under which Unity screened Ascentage's Bcl-2 family compound library for candidates with senolytic activity against age-related disease targets. The selected molecule, BM-962, was optimized as a phosphate prodrug (UBX1325/fосelutoclax) to improve aqueous solubility for ophthalmic formulation. Preclinical studies demonstrated that intravitreal administration

of UBX1325 in oxygen-induced retinopathy and streptozotocin-induced diabetic retinopathy mouse models selectively eliminated senescent cells from diseased retinal vasculature while sparing healthy tissue, reduced retinal vascular permeability, and improved retinal function as measured by electroretinography. A Phase 1 single ascending dose study in 12 patients with advanced DME and wet AMD (NCT04537884) established safety and tolerability at doses up to 10 micrograms, with no dose-limiting toxicities, no treatment-related serious adverse events, and encouraging signals of visual acuity improvement and retinal thickness reduction persisting through 12 weeks. The Phase 2 BEHOLD trial (NCT04857996) enrolled 65 patients with DME who had suboptimal response to prior anti-VEGF therapy and randomized them to a single intravitreal injection of 10 micrograms UBX1325 or sham; at 48 weeks, UBX1325-treated patients gained a mean of 6.2 ETDRS letters from baseline (5.6 letters over sham), with 53 percent of treated patients requiring no anti-VEGF rescue through the full study duration compared to 22 percent in the sham arm. These results, published in Nature Medicine in 2024, represent the first clinical demonstration of senolytic therapy in ophthalmology. The Phase 2 ENVISION trial (NCT05275205) in wet AMD did not meet its primary non-inferiority endpoint versus aflibercept at 24 weeks, though 40 percent of UBX1325-treated patients required no anti-VEGF rescue through 48 weeks. The Phase 2b ASPIRE trial (NCT06011798) evaluated repeat dosing of UBX1325 every 8 weeks versus aflibercept every 8 weeks in 52 DME patients; at 36 weeks, UBX1325 produced mean gains of 5.5 ETDRS letters, achieving non-inferiority to aflibercept at most time points except the pre-specified primary endpoint (average of weeks 20 and 24),

with superior performance in a pre-specified subgroup of patients with baseline central subfield thickness below 400 microns.

This monograph reviews the chemistry, prodrug design, and molecular pharmacology of UBX1325; the senolytic mechanism of action through Bcl-xL inhibition; the preclinical pharmacology in retinal disease models; the complete clinical evidence base across Phase 1, BEHOLD, ENVISION, and ASPIRE trials; reconstitution and handling considerations for intravitreal formulation; stack interactions with anti-VEGF agents and corticosteroids; the adverse-event and safety profile; and a structured comparative assessment of five alternative approaches to DME therapy (aflibercept, faricimab, ranibizumab, navitoclax, and dasatinib plus quercetin) against UBX1325 on five competency standards. The compound is not approved by any regulatory authority as of the monograph revision date. Unity Biotechnology is advancing development toward registrational trials.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name (proposed): Foselutoclax.

Development code: UBX1325 (Unity Biotechnology). The development code is the canonical identifier in the clinical and preclinical literature and the identifier under which all Phase 1 and Phase 2 trials have been registered and reported.

Parent compound code: UBX0601 (the active dephosphorylated metabolite released by phosphatase cleavage of the prodrug in ocular tissues).

Originator compound code: BM-962 (Ascentage Pharma). BM-962 is the identifier used in the 2016 licensing arrangement between Ascentage Pharma and Unity Biotechnology under which the compound was selected from Ascentage's Bcl-2 family inhibitor library for development as a senolytic agent in age-related diseases [1].

Chemical Abstracts Service registry number: 2271269-01-1 (foselutoclax/UBX1325 prodrug form).

ClinicalTrials.gov identifiers: NCT04537884 (Phase 1, advanced vascular eye disease), NCT04857996 (Phase 2 BEHOLD, DME), NCT05275205 (Phase 2 ENVISION, wet AMD), NCT06011798 (Phase 2b ASPIRE, DME).

1.2 Structural class and chemistry

UBX1325 (foselutoclax) is a BH3-mimetic small molecule belonging to the structural class of Bcl-2 family protein inhibitors. It is a phosphate prodrug designed to improve aqueous solubility for ophthalmic formulation; the phosphate ester moiety is cleaved rapidly in tissues by ubiquitous phosphatases to yield UBX0601, the pharmacologically active parent compound [2, 3].

Molecular formula: C₅₃H₅₉ClF₃N₆O₁₀PS₃ (prodrug, foselutoclax).

Molecular weight: Approximately 1159.69 g/mol (prodrug).

Structural features: The compound incorporates a pyrrole-carboxylic acid core bearing a chlorophenyl substituent, an isopropyl group, a piperazine linker, a sulfonamide bridge, a trifluoromethylsulfonyl group, a phenylthio ether, and a phosphonoxy-piperidine moiety that constitutes the prodrug element. The phosphate group confers the aqueous solubility required for intravitreal injection formulation and is the structural feature that distinguishes UBX1325 from the parent active compound UBX0601.

Physical properties: The compound is formulated as a clear, colorless to pale yellow aqueous solution for intravitreal injection at a concentration of 10 micrograms per injection volume (typically 50 to 100 microliters). The prodrug form is freely soluble in aqueous media at physiological pH, consistent with the design intent of the phosphate modification.

1.3 Synthesis and prodrug design

The synthesis of UBX1325 has not been disclosed in full in the peer-reviewed literature as of the monograph revision date. The compound was selected from Ascentage Pharma's Bcl-2 family compound library through a screen conducted under a 2016 strategic licensing arrangement with Unity Biotechnology [1]. Ascentage Pharma retains rights to the compound in the Greater China region. The phosphate prodrug strategy was applied by Unity Biotechnology's formulation team to address the limited aqueous solubility of the parent molecule UBX0601 for intravitreal delivery. Phosphate prodrug approaches are well established in ophthalmic drug development (for example, prednisolone sodium phosphate, dexamethasone sodium phosphate) and leverage the high activity of alkaline phosphatase and other non-specific phosphatases in ocular tissues to achieve rapid, essentially complete prodrug conversion at the site of injection.

2. Abstract

UBX1325 (foselutoclax) is a first-in-class senolytic small-molecule inhibitor of the anti-apoptotic protein Bcl-xL, formulated as a phosphate prodrug for intravitreal injection and developed by Unity Biotechnology for the treatment of diabetic macular edema, diabetic retinopathy, and neovascular age-related macular degeneration [2, 3]. The compound represents a mechanistically novel approach to retinal vascular disease: rather than neutralizing vascular endothelial growth factor (VEGF) to reduce vascular permeability (the mechanism of the current standard-of-care agents aflibercept, ranibizumab, and faricimab), UBX1325 selectively induces apoptosis in senescent retinal vascular endothelial cells that have accumulated in areas of disease activity and that constitute a persistent source of pro-inflammatory cytokines, matrix metalloproteinases, and pro-permeability signaling collectively termed the senescence-associated secretory phenotype (SASP) [4, 5].

The senolytic hypothesis for retinal vascular disease is grounded in the observation that sustained hyperglycemia and oxidative stress in diabetic retinopathy provoke irreversible cell-cycle arrest (cellular senescence) in subsets of retinal vascular endothelial cells, and that these senescent cells display perturbed transendothelial junctions, impaired barrier function, and constitutive secretion of SASP factors including interleukin-1 beta, interleukin-6, interleukin-8, tumor necrosis factor alpha, VEGF, and monocyte chemoattractant protein-1 [4, 6]. The accumulation of senescent cells in the retinal vasculature therefore both drives and sustains the vascular permeability, macular edema, and neuroinflammation that characterize DME. Anti-VEGF therapy addresses one downstream effector of this process; senolytic therapy aims to remove the upstream cellular source.

Preclinical studies demonstrated that UBX1325 preferentially eliminated senescent cells from diseased retinal tissue while sparing non-senescent cells in healthy vasculature, reduced retinal vascular permeability in diabetic mouse models, and improved retinal function [3, 4]. Clinical development has advanced through Phase 1 (NCT04537884), Phase 2 BEHOLD in DME (NCT04857996), Phase 2 ENVISION in wet AMD (NCT05275205), and Phase 2b ASPIRE in DME (NCT06011798), with the BEHOLD results published in Nature Medicine in 2024 representing the first clinical

demonstration of senolytic therapy in ophthalmology [7, 8]. The compound is not approved by any regulatory authority. Unity Biotechnology is advancing toward registrational Phase 3 trials.

3. Discovery and Development History

3.1 Origin and the senolytic hypothesis

Unity Biotechnology was founded in 2011 with the mission of developing senolytic medicines to treat age-related diseases. The founding scientific thesis was based on the landmark Baker et al. (2011) demonstration in transgenic mice that selective elimination of p16Ink4a-positive senescent cells delayed age-related pathology across multiple organ systems, and on the subsequent Zhu et al. (2015) identification of navitoclax (ABT-263, a systemic Bcl-2/Bcl-xL/Bcl-w inhibitor) as a pharmacological senolytic agent [9, 10]. Unity's initial development program targeted musculoskeletal diseases, principally osteoarthritis, with the locally administered senolytic candidate UBX0101 (an MDM2 inhibitor). A Phase 2 trial of UBX0101 in osteoarthritis of the knee failed to meet its primary efficacy endpoint in August 2020, prompting a strategic restructuring [11].

3.2 Pivot to ophthalmology

In September 2020, Unity Biotechnology announced a restructuring to focus resources on senolytic programs in ophthalmology and neurology [11]. The ophthalmology program was built on emerging evidence that cellular senescence plays a causal role in diabetic retinal vascular disease and age-related macular degeneration. Unity identified Bcl-xL as a molecular target highly expressed in diseased retinal blood vessels during retinopathy and engaged pathways of cellular senescence [3, 4].

3.3 Licensing of the compound from Ascentage Pharma

Under a 2016 strategic licensing arrangement, Unity Biotechnology screened Ascentage Pharma's proprietary library of Bcl-2 family inhibitors for compounds with senolytic activity suitable for development in age-related diseases [1]. The compound BM-962 was selected from this screen on the basis of potent Bcl-xL inhibition, selectivity for senescent over non-senescent cells, and a structural profile amenable to prodrug modification for intravitreal delivery. Unity redesignated the compound as UBX0601 (active parent) and UBX1325 (phosphate prodrug), with the

proposed international nonproprietary name foselutoclax assigned subsequently. Ascentage Pharma retains development and commercialization rights in the Greater China region.

3.4 Preclinical development (2019 to 2020)

Unity presented preclinical data at the Association for Research in Vision and Ophthalmology (ARVO) annual meetings in 2021 and 2022. The preclinical package demonstrated that UBX1325 selectively promoted apoptosis in senescent retinal vascular endothelial cells in oxygen-induced retinopathy (OIR) models and streptozotocin (STZ)-induced diabetic retinopathy models, reduced retinal vascular permeability, decreased neovascularization and avascular area, and improved retinal function as measured by electroretinography [3, 4]. These findings supported the Investigational New Drug (IND) application and the initiation of Phase 1 clinical studies.

3.5 Clinical development timeline

The Phase 1 single ascending dose study (NCT04537884) dosed the first patient in the second half of 2020 and reported 12-week data in July 2021 [12]. The Phase 2 BEHOLD study (NCT04857996) began enrollment in 2021 and reported 48-week results in May 2023, with full results published in Nature Medicine in February 2024 [7, 8]. The Phase 2 ENVISION study in wet AMD (NCT05275205) reported 24-week and 48-week results in 2023 [13]. The Phase 2b ASPIRE study (NCT06011798) reported 24-week topline results in late 2024 and complete 36-week results in May 2025 [14, 15]. Unity Biotechnology has indicated plans to advance toward registration Phase 3 trials, with Ascentage Pharma as a development partner in the Greater China region.

4. Mechanism of Action

4.1 Cellular senescence in retinal vascular disease

Cellular senescence is a state of irreversible cell-cycle arrest accompanied by morphological changes, resistance to apoptosis, and constitutive secretion of the senescence-associated secretory phenotype (SASP), a complex mixture of pro-inflammatory cytokines (interleukin-1 beta, interleukin-6, interleukin-8, tumor necrosis factor alpha), chemokines (monocyte chemoattractant protein-1), matrix metalloproteinases (MMP-1, MMP-3, MMP-9), growth factors (VEGF, platelet-derived growth factor), and bioactive lipids [4, 5, 6]. In the context of diabetic retinal vascular disease, sustained hyperglycemia, advanced glycation end-product accumulation, and oxidative stress provoke cellular senescence in subsets of retinal vascular endothelial cells and pericytes. These senescent cells display perturbed transendothelial junctions associated with impaired barrier function, and their SASP secretion drives a self-amplifying cycle of micro-inflammation, vascular leakage, and recruitment of additional cells into the senescent state.

The accumulation of senescent cells in areas of disease activity in DME therefore constitutes a persistent upstream source of the vascular permeability, macular edema, and neuroinflammation that characterize the condition. Anti-VEGF therapy neutralizes one downstream effector (VEGF) of this process but does not address the senescent cells themselves; upon cessation of anti-VEGF treatment, the senescent cells continue to produce VEGF and other SASP factors, necessitating repeated and indefinite injections. The senolytic hypothesis proposes that selective elimination of the senescent cell population could provide a more durable, potentially disease-modifying intervention by removing the upstream source of pathological signaling [4, 7].

4.2 Bcl-xL as the senolytic target

Senescent cells resist apoptosis through upregulation of anti-apoptotic pathways, prominently including the Bcl-2 family of proteins. The Bcl-2 family comprises both pro-apoptotic (Bax, Bak, Bad, Bid, Bim, Noxa, Puma) and anti-apoptotic (Bcl-2, Bcl-xL, Bcl-w, Mcl-1, A1) members that regulate the intrinsic (mitochondrial) apoptotic

pathway through interactions at the mitochondrial outer membrane [5, 9]. Senescent retinal vascular endothelial cells display elevated expression of Bcl-xL (B-cell lymphoma-extra large, encoded by the BCL2L1 gene), which sequesters pro-apoptotic BH3-only proteins and prevents mitochondrial outer membrane permeabilization, cytochrome c release, and caspase activation [3, 4].

UBX0601 (the active metabolite of UBX1325) is a BH3-mimetic small molecule that binds the hydrophobic groove of Bcl-xL, displacing pro-apoptotic BH3-only proteins (Bim, Bad, Bid) and thereby de-repressing the intrinsic apoptotic pathway [2, 3]. In senescent cells, where the apoptotic threshold is lowered by accumulated pro-apoptotic signals that are held in check only by elevated Bcl-xL, the pharmacological inhibition of Bcl-xL is sufficient to trigger caspase activation and apoptotic cell death. In non-senescent cells with lower basal pro-apoptotic signaling and normal Bcl-xL expression, the same pharmacological intervention does not reach the apoptotic threshold, producing the selectivity for senescent over healthy cells that is the hallmark of the senolytic mechanism [4].

UBX0601 also inhibits other Bcl-2 family anti-apoptotic proteins, including Bcl-2 and Bcl-w, though the senolytic activity in retinal endothelial cells appears to be driven predominantly by Bcl-xL inhibition based on target expression profiling in diseased retinal tissue [3].

4.3 Prodrug conversion and local pharmacology

UBX1325 (foselutoclax) is a phosphate ester prodrug of UBX0601. Following intravitreal injection, the phosphate group is cleaved rapidly by alkaline phosphatase and other nonspecific phosphatases present at high activity in ocular tissues, releasing the active parent molecule UBX0601 at the site of injection [2, 7]. The prodrug strategy serves two purposes: it confers the aqueous solubility required for formulation as an injectable solution (the parent molecule UBX0601 has limited aqueous solubility), and it limits systemic exposure by confining the generation of active compound to the vitreous cavity and retinal tissues.

The local pharmacology following intravitreal injection involves diffusion of UBX0601 from the vitreous humor to the retinal vasculature, binding to Bcl-xL on senescent endothelial cells, induction of apoptosis in those cells, phagocytic clearance of apoptotic debris, and restoration of normal vascular architecture and barrier function in the treated retinal areas. The duration of effect observed clinically (sustained visual acuity improvement and reduced retinal thickness through 48

weeks after a single injection in the BEHOLD trial) is consistent with a disease-modifying rather than palliative mechanism: once the senescent cells are eliminated, the source of SASP-driven pathology is removed, and the benefit persists until new senescent cells accumulate through ongoing disease processes [7, 8].

4.4 Distinction from anti-VEGF mechanism

The mechanistic distinction between UBX1325 and anti-VEGF agents (aflibercept, ranibizumab, bevacizumab, faricimab) is fundamental. Anti-VEGF agents bind and neutralize VEGF in the vitreous and retina, reducing VEGF-driven vascular permeability and neovascularization. The effect is dose-dependent, concentration-dependent, and time-limited; as the anti-VEGF agent is cleared from the vitreous (typical half-life 5 to 10 days for antibody fragments, longer for larger molecules), VEGF levels recover and disease activity resumes, necessitating injections every 4 to 12 weeks indefinitely [16]. UBX1325, by contrast, removes the senescent cells that produce VEGF (among many other SASP factors), and the benefit persists as long as the treated cell population remains cleared. The two mechanisms are complementary rather than competitive, and combination therapy (anti-VEGF plus senolytic) is a plausible clinical strategy that has been explored in the ENVISION trial Part B extension [13].

5. Pharmacokinetics and Routes of Administration

5.1 Route of administration

UBX1325 is administered exclusively by intravitreal injection. The injection volume is typically 50 to 100 microliters, delivering 10 micrograms of foselutoclax per injection. Intravitreal injection is the standard route for ophthalmic biologics and small molecules targeting the posterior segment, including aflibercept, ranibizumab, bevacizumab, faricimab, and dexamethasone implants.

5.2 Ocular pharmacokinetics

The phosphate prodrug UBX1325 is converted rapidly to the active parent compound UBX0601 in the vitreous humor and retinal tissues by endogenous phosphatases. The conversion is expected to be essentially complete within minutes to hours of injection, based on the known kinetics of phosphate prodrug hydrolysis in ocular tissues [2]. UBX0601 distributes from the vitreous to the retina by diffusion, with retinal concentrations sufficient to achieve Bcl-xL inhibition and senolytic activity in diseased vascular endothelial cells. Detailed human ocular pharmacokinetic data (vitreous half-life, retinal tissue concentrations, clearance kinetics) have not been published in the peer-reviewed literature as of the monograph revision date. The clinical observation of sustained efficacy through 48 weeks after a single injection in the BEHOLD trial suggests that the pharmacodynamic effect (elimination of senescent cells) outlasts the pharmacokinetic residence of the drug in the vitreous, consistent with the disease-modifying senolytic mechanism [7, 8].

5.3 Systemic exposure

Intravitreal administration of 10 micrograms of UBX1325 in a 50 to 100 microliter injection volume produces minimal systemic exposure. The dose is approximately 1000-fold lower than systemic doses of Bcl-2/Bcl-xL inhibitors studied in oncology (navitoclax, venetoclax), and the intravitreal route limits systemic absorption to the fraction that diffuses from the vitreous through the retinal pigment epithelium and

choroid into the systemic circulation. Clinical trial safety monitoring for systemic Bcl-2 inhibitor-related toxicities (principally thrombocytopenia, neutropenia, and lymphopenia) has not identified such events in any published UBX1325 trial [7, 8, 12, 13, 14].

5.4 Special populations

No specific pharmacokinetic studies in special populations (renal impairment, hepatic impairment, pediatric, geriatric) have been reported. The intravitreal route and negligible systemic exposure make organ-function-based dose adjustment unlikely to be required. The clinical trial populations have been predominantly elderly (mean age in the BEHOLD trial approximately 62 to 65 years), consistent with the age distribution of DME and wet AMD, and the safety and efficacy data therefore reflect a geriatric population [7, 8].

6. Preclinical Pharmacology

6.1 In vitro senolytic activity

UBX0601 (the active parent compound) demonstrated selective induction of apoptosis in senescent human retinal microvascular endothelial cells (HRMECs) in vitro while sparing non-senescent HRMECs under identical culture conditions [3, 4]. Senescence was induced by replicative exhaustion, oncogene activation (H-RasV12), or oxidative stress (hydrogen peroxide exposure). Apoptosis was measured by caspase-3/7 activation, Annexin V staining, and TUNEL assay. The selectivity for senescent over non-senescent cells was consistent with the Bcl-xL-dependent apoptotic resistance mechanism described in Section 4.2.

6.2 Oxygen-induced retinopathy model

In the mouse oxygen-induced retinopathy (OIR) model, which recapitulates key features of proliferative diabetic retinopathy including pathological neovascularization and avascular area formation, intravitreal injection of UBX1325 produced significant reductions in neovascularization area and avascular area compared to vehicle-treated controls [3]. The compound selectively promoted apoptosis in senescent vascular cells within the retinopathy lesions (identified by p16Ink4a and p21 staining) while sparing normoxic control tissue.

6.3 Streptozotocin-induced diabetic retinopathy model

In the streptozotocin (STZ)-induced diabetic retinopathy mouse model, intravitreal administration of UBX1325 reduced retinal vascular permeability (measured by Evans blue dye leakage) and preserved retinal function (measured by electroretinography amplitude recovery) [3, 4]. The diabetes-induced accumulation of senescent vascular endothelial cells, identified by senescence-associated beta-galactosidase staining and p16Ink4a immunohistochemistry, was significantly reduced in treated eyes compared to vehicle-treated contralateral eyes.

6.4 Pharmacological elimination of senescent cells in diabetic retina

The Crespo-Garcia, Sapieha et al. (2024) publication in Nature Medicine provided the most comprehensive preclinical-to-clinical characterization of the UBX1325 mechanism [7]. The study demonstrated that pharmacological elimination of senescent cells in a mouse model of DME reduced diabetes-induced retinal vascular leakage and preserved retinal function, establishing the preclinical rationale for the Phase 1 clinical study reported in the same publication. The preclinical data showed that senescent cell burden correlated with disease severity, that Bcl-xL expression was elevated specifically in senescent vascular cells within the diabetic retina, and that UBX1325 treatment reduced senescent cell burden in a dose-dependent manner.

6.5 Safety pharmacology

Preclinical ocular safety studies demonstrated that intravitreal injection of UBX1325 at the clinical dose and at multiples of the clinical dose did not produce retinal toxicity, intraocular inflammation, or structural damage to the anterior segment in rabbit and non-human primate models. Systemic exposure after intravitreal administration was below the quantification limit in plasma at all tested doses, supporting the negligible systemic exposure profile [7, 12].

7. Clinical Evidence Base

7.1 Phase 1: Single ascending dose study (NCT04537884)

The Phase 1 study was a single ascending dose, open-label, multicenter safety trial in 12 patients with advanced DME (n=8) and wet AMD (n=4) for whom anti-VEGF therapy was no longer considered beneficial [7, 12]. Patients received a single intravitreal injection of UBX1325 at doses of 0.5, 1, 2.5, 5, or 10 micrograms. The primary objective was assessment of safety and tolerability.

Safety: UBX1325 was well tolerated at all dose levels with no dose-limiting toxicities, no treatment-related serious adverse events, and no clinically significant systemic adverse events. There were no cases of intraocular inflammation, retinal artery occlusion, endophthalmitis, or vasculitis. Two non-serious adverse events (unrelated to the study drug) were reported [7, 12].

Efficacy signals: In the high-dose groups (5 and 10 micrograms), 5 of 6 patients demonstrated gains in ETDRS letter score from baseline in best-corrected visual acuity (BCVA) at 12 weeks. Across all dose levels, 8 of 12 patients showed BCVA gains at 12 weeks. Reductions in central subfield thickness (CST) and improvements in sub-retinal and intra-retinal fluid were observed in the majority of treated patients [12].

Dose selection: The 10 microgram dose was selected for advancement to Phase 2 on the basis of the safety, tolerability, and efficacy signal profile.

7.2 Phase 2 BEHOLD: Single injection in DME (NCT04857996)

BEHOLD was a Phase 2, double-masked, sham-controlled, multicenter, proof-of-concept trial that enrolled 65 patients with DME who had suboptimal response to prior anti-VEGF therapy [7, 8]. Patients were randomized to receive a single intravitreal injection of 10 micrograms UBX1325 (n=33) or sham injection (n=32). The primary objective was assessment of safety and tolerability as measured by ocular and

systemic treatment-emergent adverse events (TEAEs). Secondary and exploratory endpoints included change from baseline in BCVA, change from baseline in CST, and time to first anti-VEGF rescue injection.

Primary endpoint (safety): UBX1325 demonstrated a favorable safety and tolerability profile. There were no cases of intraocular inflammation, retinal artery occlusion, endophthalmitis, or vasculitis. The incidence of TEAEs was similar between the UBX1325 and sham arms [7, 8].

Visual acuity: At 48 weeks, UBX1325-treated patients gained a mean of 6.2 ETDRS letters from baseline, compared to 0.6 letters in the sham arm, representing a treatment difference of 5.6 letters. This difference was both statistically significant and clinically meaningful (the generally accepted threshold for clinically meaningful BCVA change is 5 ETDRS letters or approximately one line on the Snellen chart) [7, 8].

Rescue treatment: Approximately 53 percent of UBX1325-treated patients completed the 48-week study without requiring any anti-VEGF rescue injection, compared to 22 percent in the sham arm. The median time to first rescue injection in the UBX1325 arm exceeded 48 weeks (at least 30 weeks longer than in the sham arm) [7, 8].

Retinal structure: CST was maintained in UBX1325-treated patients throughout the study duration, consistent with sustained barrier function improvement.

Publication: The combined preclinical and Phase 1/Phase 2 BEHOLD results were published by Crespo-Garcia, Sapieha et al. in Nature Medicine in February 2024, representing the first peer-reviewed clinical demonstration of senolytic therapy in ophthalmology [7].

7.3 Phase 2 ENVISION: Single injection in wet AMD (NCT05275205)

ENVISION was a Phase 2, double-masked, active-controlled study in patients with wet AMD [13]. The study evaluated UBX1325 monotherapy (single injection followed by as-needed rescue) versus aflibercept (every 8 weeks). The primary endpoint was non-inferiority of UBX1325 to aflibercept in mean change from baseline in BCVA through 24 weeks.

Part A (24 weeks): UBX1325 treatment generally maintained visual acuity (mean change of -0.8 ETDRS letters from baseline), with a majority of patients not requiring anti-VEGF rescue. However, the study did not meet the non-inferiority threshold compared to aflibercept, which produced an early and sustained gain of 3.5 letters, an unexpectedly strong control-arm performance [13].

Part B (48 weeks): Patients originally randomized to aflibercept were switched at week 24 to a combination of aflibercept and UBX1325. These patients maintained the vision gains achieved with aflibercept alone through week 48. In a pre-specified subgroup of patients with poor baseline visual acuity (60 ETDRS letters or fewer), combination therapy produced a gain of 3.2 letters between weeks 24 and 48. In the UBX1325 monotherapy arm, mean BCVA change was +0.1 letters at week 24 and -1.5 letters at week 48. Forty percent of UBX1325-treated patients required no anti-VEGF rescue through 48 weeks, and 64 percent achieved an anti-VEGF treatment-free period exceeding 24 weeks [13].

Safety: UBX1325 demonstrated a favorable safety profile in both monotherapy and combination arms, with no cases of significant intraocular inflammation, retinal artery occlusion, or endophthalmitis [13].

Interpretation: The ENVISION results suggest that UBX1325 monotherapy may be insufficient to match the efficacy of aflibercept in wet AMD (where the pathological mechanism is dominated by choroidal neovascularization driven by factors beyond cellular senescence), but that the compound provides durable anti-VEGF-sparing activity consistent with the senolytic mechanism and that combination therapy with anti-VEGF agents is a viable clinical strategy.

7.4 Phase 2b ASPIRE: Repeat dosing in DME (NCT06011798)

ASPIRE was a Phase 2b, multicenter, randomized, double-masked, active-controlled study that enrolled 52 patients with DME who had suboptimal response to prior anti-VEGF therapy [14, 15]. Patients were randomized 1:1 to receive either intravitreal UBX1325 (10 micrograms) or aflibercept (2 mg) every 8 weeks for 6 months after randomization. The primary efficacy endpoint was non-inferiority to aflibercept as assessed by mean change from baseline in BCVA at the average of weeks 20 and 24.

Primary endpoint: The study did not meet its primary endpoint of non-inferiority to aflibercept at the pre-specified time point (average of weeks 20 and 24). UBX1325-treated patients had a mean BCVA change of +5.2 ETDRS letters at 24 weeks compared to +6.3 letters in the aflibercept arm [14, 15].

Extended follow-up (36 weeks): At 36 weeks, UBX1325-treated patients gained a mean of 5.5 ETDRS letters from baseline, achieving non-inferiority to aflibercept at most individual time points through 36 weeks [15].

Subgroup analysis: In a pre-specified subgroup of patients entering the study with CST below 400 microns (approximately 60 percent of enrolled patients), UBX1325 generally outperformed aflibercept across time points [15].

Safety: UBX1325 demonstrated a favorable safety profile consistent with the BEHOLD and ENVISION data. No cases of intraocular inflammation, vasculitis, or other significant ocular adverse events were reported [14, 15].

Interpretation: The ASPIRE results confirm the clinical activity of repeat-dose UBX1325 in DME, with vision gains comparable to aflibercept at 36 weeks. The narrowly missed primary endpoint likely reflects the small sample size (n=52) and the stringent non-inferiority margin rather than a clinically meaningful efficacy deficit. The subgroup analysis suggesting superior performance in patients with lower baseline CST (a marker of less severe edema and potentially greater senescent-cell-driven pathology) is hypothesis-generating and may inform patient selection for Phase 3 trials.

7.5 Multifocal electroretinography substudy

A substudy of the ENVISION trial evaluated multifocal electroretinography (mfERG) changes after foselutoclax treatment in neovascular AMD [17]. The study reported improvements in retinal function as measured by mfERG amplitudes in UBX1325-treated patients, supporting the hypothesis that senolytic therapy improves retinal function beyond what can be attributed to edema reduction alone. This finding is consistent with the elimination of senescent cells that impair local retinal function through SASP-mediated neurotoxicity and inflammation.

8. Sourcing and Quality Verification

UBX1325 (foselutoclax) is not commercially available as a registered medicine in any jurisdiction as of the monograph revision date. The compound is available only through clinical trial programs sponsored by Unity Biotechnology and through research-grade suppliers.

Research-grade supply: UBX1325 (foselutoclax) is listed by MedChemExpress, ProbeChem, MedKoo, and other specialty chemical suppliers at research-grade purity (typically greater than 95 percent by HPLC). The compound is supplied as the phosphate prodrug form (CAS 2271269-01-1) in milligram quantities. Pricing is in the range of \$200 to \$800 per 5 milligrams at the time of monograph preparation, consistent with the limited availability and specialized synthesis of BH3-mimetic compounds.

Quality verification: Investigators acquiring research-grade UBX1325 should confirm compound identity and purity through:

- High-performance liquid chromatography (HPLC) area-percent purity, ideally greater than 95 percent
- Mass spectrometry confirmation of molecular weight (expected [M+H]⁺ consistent with the molecular formula C₅₃H₅₉ClF₃N₆O₁₀PS₃)
- Nuclear magnetic resonance spectroscopy confirmation of structural identity
- Residual solvent analysis
- Phosphate content analysis to confirm prodrug integrity (incomplete phosphorylation would reduce aqueous solubility and alter conversion kinetics)

Clinical-grade supply: Clinical-grade UBX1325 for intravitreal injection is manufactured under Good Manufacturing Practice (GMP) conditions by or on behalf of Unity Biotechnology. The clinical formulation is a sterile, clear, colorless to pale yellow aqueous solution at a concentration sufficient to deliver 10 micrograms per injection volume. Access to clinical-grade material is limited to registered clinical trial sites.

9. Reconstitution and Handling

UBX1325 is supplied for clinical use as a ready-to-use sterile aqueous solution for intravitreal injection. No reconstitution is required for the clinical formulation.

Storage: Clinical-grade material should be stored according to the manufacturer's specifications (typically 2 to 8 degrees Celsius, protected from light). The aqueous solution should not be frozen.

Research-grade handling: Research-grade UBX1325 (typically supplied as a lyophilized solid or powder) should be stored at -20 degrees Celsius in a desiccated container protected from light. For in vitro studies, the compound can be reconstituted in dimethyl sulfoxide (DMSO) to prepare concentrated stock solutions (typically 10 to 50 mM), which can then be diluted into cell culture media at the desired working concentrations. For formulation studies or ex vivo tissue studies, reconstitution in phosphate-buffered saline or balanced salt solution at concentrations consistent with aqueous solubility (the phosphate prodrug form has substantially greater aqueous solubility than the parent compound UBX0601) is appropriate.

Stability: The phosphate prodrug is stable in aqueous solution at neutral pH and refrigerated temperature. Investigators should be aware that tissue homogenates, serum-containing media, and other biological matrices contain phosphatase activity that will convert the prodrug to the active parent compound; experiments designed to study the prodrug form specifically should use phosphatase-free conditions or include phosphatase inhibitors.

Intravitreal injection procedure (clinical): The injection is performed under aseptic conditions using standard intravitreal injection technique: topical anesthesia, povidone-iodine antisepsis, speculum placement, injection through the pars plana (3.5 to 4.0 mm posterior to the limbus) using a 30-gauge needle. Post-injection monitoring includes assessment of light perception and intraocular pressure measurement.

10. Stack Interactions and Combinations

10.1 Anti-VEGF agents

The principal clinical interaction of interest is the combination of UBX1325 with anti-VEGF agents (aflibercept, ranibizumab, bevacizumab, faricimab). The ENVISION trial Part B evaluated combination therapy (aflibercept plus UBX1325) and demonstrated maintenance of aflibercept-induced vision gains with addition of UBX1325, and a signal of additional benefit in patients with poor baseline visual acuity [13]. The two mechanisms are complementary: anti-VEGF addresses the downstream cytokine driving vascular permeability, while the senolytic addresses the upstream senescent cells producing the cytokine. Combination therapy may reduce the frequency of anti-VEGF injections required (the "anti-VEGF-sparing" hypothesis supported by the BEHOLD rescue-treatment data) and may provide incremental efficacy in patients with suboptimal anti-VEGF response.

10.2 Corticosteroids

Intravitreal corticosteroids (dexamethasone implant, triamcinolone acetonide, fluocinolone acetonide) are used in DME as second-line therapy, particularly in pseudophakic eyes. No formal drug-drug interaction studies with UBX1325 have been conducted. The mechanisms are non-overlapping (corticosteroid anti-inflammatory action versus senolytic apoptosis induction), and combination use is plausible but unstudied. Corticosteroids may theoretically reduce the inflammatory response to apoptotic cell clearance following senolytic therapy, though this interaction is speculative.

10.3 Other senolytic agents

Concurrent use with other senolytic compounds (navitoclax, dasatinib plus quercetin, fisetin) is pharmacologically redundant for the Bcl-xL-mediated senolytic mechanism and may produce additive cytotoxicity in tissues with physiological Bcl-xL expression (principally platelets and lymphocytes for systemic

senolytics). The intravitreal route of UBX1325 limits this concern to the ocular compartment, but combination with systemic senolytics has not been studied and is not recommended outside of controlled research settings.

10.4 Photodynamic therapy

Verteporfin photodynamic therapy (PDT) is used in some wet AMD subtypes. No interaction data with UBX1325 exist. The PDT mechanism (photochemical vascular occlusion) is mechanistically distinct from senolytic apoptosis induction, and temporal separation of the two treatments would be prudent pending further characterization.

10.5 Systemic medications

The negligible systemic exposure following intravitreal injection of 10 micrograms UBX1325 makes systemic drug-drug interactions unlikely. The sponsor has monitored for systemic Bcl-2 inhibitor-related toxicities (cytopenia) in clinical trials and has not observed such events [7, 8, 12]. Concurrent systemic Bcl-2/Bcl-xL inhibitor therapy (venetoclax, navitoclax, used in hematological malignancies) would theoretically add to systemic Bcl-xL inhibition, but the intravitreal dose contribution to systemic exposure is negligible and clinically irrelevant.

11. Adverse Events and Safety

11.1 Ocular adverse events

Across the Phase 1, BEHOLD, ENVISION, and ASPIRE clinical trials, UBX1325 has demonstrated a favorable ocular safety profile [7, 8, 12, 13, 14, 15]:

- No cases of intraocular inflammation attributable to UBX1325
- No cases of retinal artery occlusion
- No cases of endophthalmitis
- No cases of vasculitis
- No cases of retinal detachment attributable to UBX1325
- Mild, transient adverse events consistent with the intravitreal injection procedure itself (conjunctival hemorrhage, eye pain, vitreous floaters) at rates comparable to sham injection arms

The absence of intraocular inflammation is notable given that the senolytic mechanism involves induction of apoptosis in retinal cells, which could theoretically provoke an inflammatory response during phagocytic clearance. The clinical data suggest that the apoptotic cell death pathway (in contrast to necrotic or pyroptotic pathways) produces immunologically silent cell clearance in the retina at the doses studied.

11.2 Systemic adverse events

No clinically significant systemic adverse events attributable to UBX1325 have been reported in any published trial. Specifically, the sponsor monitored for Bcl-2/Bcl-xL inhibitor class effects including thrombocytopenia, neutropenia, and lymphopenia (the dose-limiting toxicities of systemic Bcl-xL inhibitors such as navitoclax), and none were observed [7, 8, 12]. This finding is consistent with the negligible systemic exposure from the 10 microgram intravitreal dose.

11.3 Comparison to anti-VEGF safety profile

The safety profile of UBX1325 compares favorably to the anti-VEGF standard of care. Anti-VEGF agents (aflibercept, ranibizumab, faricimab) are generally well tolerated by the intravitreal route but carry low-frequency risks of endophthalmitis (approximately 0.02 to 0.05 percent per injection), retinal detachment, retinal pigment epithelium tear, and sustained intraocular pressure elevation [16]. The UBX1325 trials have not identified these events, though the total patient exposure (fewer than 200 patients across all trials) is insufficient to characterize rare events. The key safety advantage of UBX1325, if confirmed in larger trials, would be the substantially lower injection frequency (potentially 2 to 3 injections per year versus 6 to 12 per year for anti-VEGF agents), which would reduce cumulative injection-related adverse event risk.

11.4 Long-term safety considerations

The long-term safety of repeated senolytic therapy in the retina is a theoretical concern that has not been fully characterized. Selective elimination of senescent cells is the intended pharmacological effect, but the boundary between senescent cells (pathological) and quiescent or stress-adapted cells (physiological) is not absolute, and the potential for off-target effects on non-senescent cells with moderate Bcl-xL expression (including photoreceptors, retinal pigment epithelium, and Muller glia) requires continued monitoring in longer-term studies. The BEHOLD 48-week and ENVISION 48-week data have not revealed such concerns, but registrational Phase 3 trials with larger patient populations and longer follow-up will provide more definitive characterization.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative approaches to DME therapy against UBX1325, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected to span the range of currently approved and investigational therapies for DME, from established anti-VEGF agents to investigational senolytic approaches.

12.1 Aflibercept (Eylea)

Mechanism: Recombinant fusion protein (VEGF trap) that binds VEGF-A, VEGF-B, and placental growth factor (PlGF), preventing their interaction with VEGF receptors on the vascular endothelium. Administered by intravitreal injection at 2 mg every 4 to 8 weeks, with an 8 mg high-dose formulation (Eylea HD) approved for extended 12 to 16 week dosing intervals [16].

Novelty: Low. Aflibercept was approved for DME by the FDA in 2014 and is the most widely used anti-VEGF agent in ophthalmology globally. The mechanism is well characterized and the drug class (anti-VEGF) has been the standard of care for over 15 years.

Effect size: Substantial. In the VISTA and VIVID Phase 3 trials, aflibercept produced mean BCVA gains of approximately 10 to 12 ETDRS letters at 52 weeks in treatment-naïve DME patients, with CST reductions of approximately 150 to 200 microns [16]. In the anti-VEGF-refractory populations studied in the UBX1325 trials, the ASPIRE aflibercept arm produced gains of approximately 6 letters at 36 weeks, reflecting the diminished response in this more difficult-to-treat population.

Promising potential: Moderate. Aflibercept is an established, approved therapy with well-characterized efficacy and safety. The principal limitation is the requirement for frequent intravitreal injections (every 4 to 8 weeks for standard dose), which creates patient burden, compliance challenges, and cumulative procedure-related risks. The high-dose formulation addresses this partially by extending intervals to 12 to 16 weeks.

Side-effect profile: Generally well tolerated. Low-frequency risks include endophthalmitis (approximately 0.02 to 0.05 percent per injection), retinal detachment, retinal pigment epithelium tear, intraocular pressure elevation, and thromboembolic events (rare, debated). The cumulative injection burden over years of treatment amplifies the per-injection risk.

Overall validation: High. Aflibercept is the most extensively validated therapy for DME, supported by multiple Phase 3 registration trials, extensive real-world evidence, and over a decade of clinical use. It is the current gold standard against which new therapies are measured.

Comparison to UBX1325: UBX1325 offers a fundamentally different mechanism (senolytic versus anti-VEGF) with the potential for substantially lower injection frequency and disease-modifying rather than palliative activity. In the ASPIRE trial, UBX1325 achieved comparable efficacy to aflibercept at 36 weeks in anti-VEGF-refractory patients. The principal advantage of UBX1325 over aflibercept is the durability of effect from fewer injections; the principal advantage of aflibercept over UBX1325 is the depth and certainty of its clinical evidence base.

12.2 Faricimab (Vabysmo)

Mechanism: Bispecific monoclonal antibody that simultaneously inhibits VEGF-A and angiopoietin-2 (Ang-2), a dual-target approach designed to enhance vascular stability and reduce leakage beyond what VEGF inhibition alone achieves. Approved for DME and wet AMD in 2022 [18].

Novelty: Moderate. The dual VEGF-A/Ang-2 mechanism is novel within the anti-VEGF class but remains fundamentally an anti-cytokine approach rather than a disease-modifying senolytic approach.

Effect size: Substantial. The YOSEMITE and RHINE Phase 3 trials demonstrated BCVA gains comparable to aflibercept (approximately 10 to 11 letters at 52 weeks) with the advantage of extended dosing intervals (up to every 16 weeks) in a proportion of patients [18]. In patients refractory to prior anti-VEGF therapy, switching to faricimab has produced additional benefit in some studies, with mean recurrence intervals extending from approximately 6 weeks to approximately 11 weeks.

Promising potential: High. Faricimab is commercially available and gaining market share. The dual mechanism and extended dosing intervals represent meaningful advances over first-generation anti-VEGF agents.

Side-effect profile: Similar to aflibercept with the addition of a low-frequency intraocular inflammation signal (approximately 1 to 2 percent of patients), including rare cases of retinal vasculitis and retinal artery occlusion reported in the post-approval period.

Overall validation: High. Supported by two large Phase 3 registration trials, real-world evidence accumulating since 2022 approval, and head-to-head non-inferiority to aflibercept.

Comparison to UBX1325: Both faricimab and UBX1325 address the limitations of first-generation anti-VEGF agents, but through different strategies. Faricimab adds a second cytokine target (Ang-2) to extend durability within the anti-cytokine paradigm. UBX1325 addresses the upstream cellular source of multiple cytokines through senolytic elimination. UBX1325 has the potential for greater reduction in injection frequency if the senolytic mechanism proves durably disease-modifying. The two approaches are complementary and could potentially be combined.

12.3 Ranibizumab (Lucentis)

Mechanism: Recombinant humanized monoclonal antibody fragment (Fab) that selectively binds all isoforms of VEGF-A. Smaller molecular size compared to aflibercept, enabling faster retinal penetration and shorter vitreous half-life. Approved for DME in 2012, now available as biosimilar [16].

Novelty: Low. Ranibizumab was the first anti-VEGF agent specifically designed for intraocular use and has been in clinical practice for nearly two decades. The mechanism is well characterized.

Effect size: Moderate to substantial. The RISE and RIDE Phase 3 trials produced mean BCVA gains of approximately 10 to 12 letters at 24 months in treatment-naïve DME [16]. In the DRCR.net Protocol T comparative trial, ranibizumab was equivalent to aflibercept at 2 years in eyes with mild-to-moderate visual acuity loss but inferior to aflibercept in eyes with more severe baseline visual acuity loss.

Promising potential: Low to moderate. Ranibizumab is being displaced by aflibercept and faricimab in clinical practice due to shorter durability and the availability of newer agents. The port delivery system (Susvimo) was an innovation that addressed injection frequency but was voluntarily withdrawn from the market in 2023.

Side-effect profile: Similar to aflibercept. Well-characterized safety profile from extensive clinical experience.

Overall validation: High. Supported by extensive Phase 3 data, real-world evidence, and nearly two decades of clinical use.

Comparison to UBX1325: The comparison to ranibizumab reinforces the same themes as the aflibercept comparison. UBX1325 offers a mechanistically distinct approach with potential for greater durability; ranibizumab offers depth of clinical evidence and established clinical practice patterns. Ranibizumab's shorter durability (4-week dosing intervals for many patients) makes the injection-frequency advantage of UBX1325 particularly pronounced.

12.4 Navitoclax (ABT-263)

Mechanism: Systemic, orally bioavailable BH3-mimetic inhibitor of Bcl-2, Bcl-xL, and Bcl-w. Originally developed by AbbVie as an anti-cancer agent, subsequently characterized as a senolytic through its Bcl-xL inhibition [9, 10].

Novelty: Moderate. Navitoclax was among the first pharmacological senolytic agents identified and is the historical reference compound for the Bcl-xL-mediated senolytic mechanism. It has not been developed for ophthalmic indications.

Effect size: Not applicable to DME. Navitoclax has demonstrated senolytic activity in preclinical models of aging and age-related disease across multiple organ systems, including the retina, but has not been evaluated in clinical trials for DME or retinal vascular disease. In oncology, navitoclax has produced modest single-agent activity and has been studied principally as a combination partner.

Promising potential: Low for ophthalmic indications. The dose-limiting thrombocytopenia resulting from Bcl-xL inhibition of platelet survival precludes systemic dosing at levels required for robust senolytic activity in the retina. Navitoclax persists in oncology development (principally in combination with ruxolitinib for myelofibrosis) but has not been advanced for ophthalmic applications [10, 19].

Side-effect profile: The principal dose-limiting toxicity is thrombocytopenia, which is an on-target effect of Bcl-xL inhibition on platelets (platelets depend on Bcl-xL for survival). Dose-dependent reductions in platelet count to below 50,000 per microliter have been reported in clinical oncology studies. Additional toxicities include neutropenia and gastrointestinal adverse events [19].

Overall validation: Moderate as a research tool for senolytic biology; low as a therapeutic candidate for ophthalmic disease.

Comparison to UBX1325: UBX1325 was designed specifically to overcome the systemic toxicity limitation of navitoclax by confining Bcl-xL inhibition to the ocular compartment through intravitreal delivery of a locally acting prodrug. The two compounds share the core Bcl-xL inhibition mechanism but differ fundamentally in route of administration, systemic exposure, and therapeutic index. UBX1325's intravitreal administration eliminates the thrombocytopenia concern entirely, enabling therapeutically relevant Bcl-xL inhibition in retinal tissue without systemic dose-limiting toxicity.

12.5 Dasatinib plus Quercetin (D+Q)

Mechanism: Combination of dasatinib (a multi-target tyrosine kinase inhibitor, principally targeting SRC family kinases, ABL, and receptor tyrosine kinases) and quercetin (a plant flavonoid with senolytic activity through inhibition of PI3K, serpins, and other anti-apoptotic pathways). The combination was the first pharmacological senolytic regimen identified, demonstrated by Zhu et al. (2015) to selectively eliminate senescent cells in vitro and in vivo [10, 20].

Novelty: Moderate. D+Q was the first senolytic treatment discovered and has progressed to early clinical trials for various age-related conditions (idiopathic pulmonary fibrosis, Alzheimer's disease, diabetic kidney disease). It has not been evaluated specifically for DME or retinal vascular disease in clinical trials [20].

Effect size: Not applicable to DME. In preclinical aging models, D+Q reduced senescent cell burden and improved various functional endpoints across multiple organ systems. Clinical evidence from early trials in non-ophthalmic indications has produced mixed results. The relevance to retinal vascular disease is indirect; the combination has shown senolytic activity in retinal tissue in preclinical models but has not been optimized for ophthalmic delivery [6, 20].

Promising potential: Low for ophthalmic indications. Systemic administration produces broad tissue exposure with potential off-target effects (dasatinib is associated with pleural effusion, cytopenia, and other tyrosine kinase inhibitor class effects at the doses required for systemic senolytic activity). Intravitreal formulation

of the combination has not been developed. The D+Q combination persists as a research tool and as an investigational systemic senolytic, principally for age-related frailty and chronic kidney disease [20].

Side-effect profile: Dasatinib monotherapy is associated with pleural effusion, cytopenia (neutropenia, thrombocytopenia, anemia), gastrointestinal adverse events, rash, and fluid retention at oncological doses. At the lower intermittent doses used in senolytic regimens, the tolerability is improved but still substantially less favorable than intravitreal UBX1325.

Overall validation: Low for ophthalmic disease; moderate as a systemic senolytic research tool.

Comparison to UBX1325: D+Q and UBX1325 represent different generations and different optimization strategies within the senolytic field. D+Q is a first-generation, repurposed, systemically administered combination with broad senolytic activity but poor therapeutic index for localized retinal disease. UBX1325 is a purpose-built, locally administered, prodrug-optimized Bcl-xL inhibitor designed specifically for ophthalmic senolytic therapy. UBX1325 has fundamentally superior therapeutic index for retinal disease through intravitreal delivery and the absence of systemic senolytic exposure.

12.6 Comparator summary

The five comparators occupy distinct positions in the DME therapeutic landscape. **Aflibercept** is the gold-standard anti-VEGF agent with the deepest evidence base but requires frequent injections and does not address the upstream senescent cell pathology. **Faricimab** extends the anti-cytokine approach through dual VEGF-A/Ang-2 targeting with improved durability but remains fundamentally anti-cytokine rather than disease-modifying. **Ranibizumab** is an established but aging anti-VEGF agent with shorter durability than newer alternatives. **Navitoclax** shares the Bcl-xL senolytic mechanism with UBX1325 but is limited to systemic administration with dose-limiting thrombocytopenia that precludes ophthalmic therapeutic application. **Dasatinib plus quercetin** is a first-generation systemic senolytic combination that has not been developed for ophthalmic indications and has an unfavorable therapeutic index for localized retinal therapy.

UBX1325 occupies a unique position as the only purpose-built, intravitreally administered, Bcl-xL-targeted senolytic agent in clinical development for retinal vascular disease. Its principal clinical advantages are the mechanistic novelty (senolytic versus anti-VEGF), the potential for infrequent dosing with durable efficacy (53 percent of BEHOLD patients required no rescue through 48 weeks after a single injection), and the favorable safety profile in the intravitreal compartment. Its principal limitation relative to the established anti-VEGF agents is the early stage of clinical development (Phase 2 completed, Phase 3 pending) and the smaller evidence base. The ASPIRE data demonstrating comparable efficacy to aflibercept at 36 weeks in anti-VEGF-refractory patients, if replicated in Phase 3, would position UBX1325 as a complementary or alternative therapy for patients with suboptimal anti-VEGF response and as a potential injection-reducing strategy in the broader DME population.

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sion date. The compound is available only through registered clinical trials sponsored by Unity Biotechnology and through research-grade chemical suppliers. All clinical data cited are from press releases, conference presentations, and peer-reviewed publications; investigators should consult the primary sources and the ClinicalTrials.gov registry for the most current trial status and data. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.