CLINICAL STUDY PROTOCOL

Xplore: A Phase III Double-Blind, Parallel Group, Multicenter Study to Compare the Efficacy and Safety of Xlucane versus Lucentis® in Patients with Neovascular Age-Related Macular Degeneration

Protocol Number:	XBR1001
EudraCT Number:	2018-002930-19
Syneos Health Study Number:	1009980
Investigational Product:	Xlucane
Phase:	III
Sponsor:	Xbrane Biopharma Retzius väg 8 SE-171 65 Solna Sweden
Contract Research Organization:	Syneos Health 1030 Sync Street Morrisville, NC 27560 United States
Protocol Date:	24 Feb 2021
Protocol Version:	Amendment 5, Version 1.0

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: Xplore: A Phase III Double-Blind, Parallel Group, Multicenter Study to Compare the Efficacy and Safety of Xlucane versus Lucentis® in Patients with Neovascular Age-Related Macular Degeneration

EudraCT Number: 2018-002930-19

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This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

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3 SYNOPSIS

Protocol Number:

XBR1001

Title:

Xplore: A Phase III Double-Blind, Parallel Group, Multicenter Study to Compare the Efficacy and Safety of Xlucane versus Lucentis® in Patients with Neovascular Age-Related Macular Degeneration

Investigational Product:

Xlucane

Study Centers:

This study will be conducted at approximately 160 sites in approximately 15 countries in the United States, Europe, the Middle East, and Asia-Pacific.

Phase:

Phase III

Objectives:

Primary objective:

The primary objective of the study is to demonstrate that the proposed biosimilar candidate Xlucane is equivalent to Lucentis® in subjects with wet (ie, neovascular) age-related macular degeneration (wAMD) as assessed by the change in best corrected visual acuity (BCVA) from Baseline to Week 8.

Secondary objectives:

- Evaluate the efficacy of Xlucane vs Lucentis® in subjects with wAMD based on central foveal thickness measured by spectral domain optical coherence tomography (SD-OCT), area of choroidal neovascularization, and presence of leakage assessed by fundus fluorescein angiography (FA)
- Evaluate the safety of Xlucane vs Lucentis®
- Evaluate the systemic exposure of Xlucane vs Lucentis® in subjects participating in pharmacokinetics (PK) evaluation
- Evaluate immunogenicity (ie, anti-ranibizumab antibodies and neutralizing anti-drug antibodies [NAb]) of Xlucane vs Lucentis®

Study Design:

This is a phase III multicenter, double-blind (double-masked), randomized, parallel group study in subjects with wAMD. Approximately 580 subjects will be enrolled and randomized in a 1:1 ratio to receive either Lucentis® (0.05 mL of 10 mg/mL ranibizumab) or the investigational product, Xlucane (0.05 mL of 10 mg/mL ranibizumab), in the study eye once every 4 weeks (monthly) for 52 weeks (ie, 12 months).

The study eye will be defined as the eye meeting all of the inclusion criteria and none of the exclusion criteria (ie, the enrollment criteria).

The assigned study drug will be administered as an ophthalmic intravitreal (IVT) injection. Designated, unmasked study staff will prepare and administer the study drug, ensuring that the masking of the subject is maintained during the injection procedure.

Subjects will be randomized by interactive web response system (IWRS) to receive 13 doses of either Xlucane or Lucentis® in the study eye. The randomization scheme will automatically ensure that the study drug assignment for a given subject is random and that an overall 1:1 ratio of assignments to each of the 2 study drug treatments is approximated. In addition, the randomization scheme will include the following stratification parameters to ensure balanced distribution of assignment to the 2 treatments: eye color (light iris vs dark iris), geographical region where enrolled and the BCVA letters at Baseline (55 or lower, 56 to 65, 66 or higher). Subjects will be followed up for changes in efficacy variables and safety for 52 weeks. Each subject's involvement will last up to approximately 52 weeks (ie, 12 months).

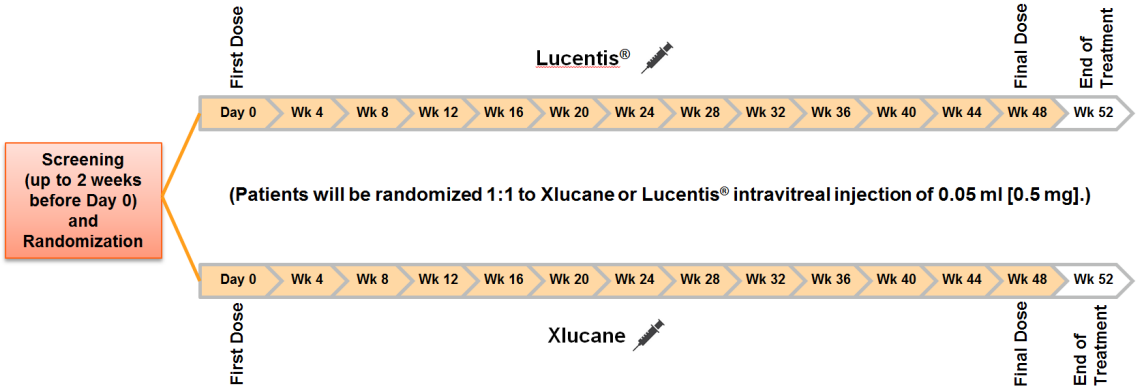
At the beginning of the study, a subgroup of 60 subjects at a select number of participating sites will be sequentially asked to participate in an evaluation of PK. This subgroup will be asked to provide blood samples for measurement of plasma ranibizumab immediately before administration of the first dose of Xlucane or Lucentis®. Additional samples will be collected at 23 hours (± 60 minutes) after the first dose (ie, Day 1) and at 23 hours (± 60 minutes) after the sixth dose (ie, Week 20) at expected time to maximum plasma concentration (T_{max}, which is around 22 hours).

An interim analysis will be performed on *unmasked* study data. After all of the randomized subjects have 6-month (ie, 24 weeks) data available, an *unmasked* analysis of efficacy and safety endpoints as well as PK and immunogenicity will be performed. The aim of the *unmasked* analysis is to initiate the submission of the application for marketing authorization as agreed with the European Medicines Agency.

This analysis will not affect the further conduct of the study. The site staff personnel will not receive details of patients' individual treatment assignment and therefore the blinding of patients' individual treatment and thereby the study will be maintained until completion of the study.

FA, CFP, and OCT will be performed at Screening. The images will be sent to the central reading center (CRC) for interpretation and confirmation of eligibility. The CRC will also grade images that are collected during the study.

Study Design



Number of Subjects:

It is anticipated that approximately 580 subjects will be enrolled and randomized.

Treatment:

Subjects will be randomized in a 1:1 ratio to receive Lucentis® (0.05 mL of 10 mg/mL ranibizumab), or the proposed biosimilar, Xlucane (0.05 mL of 10 mg/mL ranibizumab), once every 4 weeks (intravitreal injection) for 52 weeks (12 months).

Subjects will be randomized on Day 0. Only 1 eye (ie, the study eye) per subject will receive Xlucane or Lucentis®. Subjects will visit the site for study assessments after the first dose at Week 2 and every 4 weeks thereafter, for a total of 52 weeks. (Subjects participating in the PK sub-study will need to visit the site more often [ie, at least two more times].) Week 52 will be the End of Treatment visit.

Study Duration:

Each subject's involvement will last approximately 52 weeks (ie, 12 months), including follow-up.

Study Population:

Inclusion criteria

To be eligible for study entry, subjects must satisfy **all** of the following inclusion criteria:

1. Written and signed informed consent form obtained at screening before any study-related procedures are performed. Patients must be capable of providing their own consent (an impartial witness must be present in case of illiterate patients).
2. Willingness and ability to undertake all scheduled visits and assessments as judged by the investigator.
3. Newly diagnosed, active subfoveal choroidal neovascularization (CNV) lesion secondary to age-related macular degeneration (AMD) in the study eye. *Note*: active CNV indicates the presence of leakage as evidenced by fluorescein angiography (FA)

and intra- or subretinal fluid as evidenced by optical coherence tomography (OCT), which *must be confirmed by the central reading center during Screening:*

a. The area of CNV must be ≥ 50% of the total lesion area in the study eye, and

b. Total lesion area ≤ 9.0 disc areas (DA) in size (including blood, scars, and neovascularization) as assessed by FA in the study eye.

4. BCVA of ≤ 73 and ≥ 49 Early Treatment Diabetic Retinopathy Study (ETDRS) letter score in the study eye using the ETDRS chart (20/40 to 20/100 Snellen equivalent) at Screening.
5. Fellow eye should not be expected to need any anti-vascular endothelial growth factor (VEGF) treatment for the duration of study participation based on Investigator's decision.
6. Age ≥ 50 years at screening.
7. Male and female subjects of childbearing potential must be willing to completely abstain or agree to use an appropriate method of contraception from the time of signing informed consent form and for the duration of study participation through 3 months after the last dose of study drug. See Appendix 17.1 for examples of acceptable contraception. (The investigator and each subject will determine the appropriate method of contraception for the subject during the participation in the study.)

    a. A woman of childbearing potential is any woman, regardless of sexual orientation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).

    b. A man of sexual potential is any man who has not been surgically sterilized (eg, has not undergone bilateral orchiectomy).

Exclusion criteria

Subjects will be excluded from the study if **1 or more** of the following exclusion criteria is applicable:

1. Any previous intervention, including pharmacological treatment, laser, and/or surgery for wAMD in either eye; (Exception: Vitamin supplementation for AMD prevention). (In case of end stage wAMD in fellow eye where anatomical and functional status diagnosed on Screening, disqualifies subject from intravitreal anti-VEGF treatment according to local medical standards of care, the previous laser photocoagulation or PDT procedure in fellow eye performed for wAMD treatment is allowed). (This criterion is not applicable for fellow eye, in case of subjects who have only one eye or the fellow eye fulfills additional criteria specified in Section 8.3.4).
2. Any previous vitreoretinal surgery in the study eye for any cause.
3. Any previous IVT treatment, including any anti-VEGF medications, steroids, and/or any other investigational medication in either eye.

4. The use of long-acting steroids, either systemic or intraocular in any eye, in the 18 months before planned initiation of study treatment. (Note: Current or planned Iluvien® [fluocinolone acetonide intravitreal] implantation during the study is prohibited.)
5. Subfoveal fibrosis, subfoveal atrophy, and/or scarring extending > 50% of total lesion area in the study eye as assessed by the investigator at screening and confirmed by the central reading center prior to Randomization.
6. Choroidal neovascularization in either eye due to non-AMD causes (eg, diabetic macular edema, retinal vein occlusion, ocular histoplasmosis, trauma) as assessed by FA and confirmed by central reading center. (This criterion is not applicable for fellow eye, in case of subjects who have only one eye or the fellow eye optical media opacity prevents from taking the FA/OCT/FP images and the fellow eye fulfills additional criteria specified in Section 8.3.4).
7. Active or recent (within 28 days prior to Randomization) intraocular, extraocular, and periocular inflammation or infection in either eye.
8. History of idiopathic or autoimmune-associated uveitis in either eye.
9. Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
10. Unmedicated intraocular pressure (IOP) ≥ 30 mm Hg at Screening in either eye.
11. Topical ocular corticosteroids administered for ≥ 30 consecutive days in the study eye within 90 days prior to Screening.
12. Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia.
13. Corneal transplant or corneal dystrophy in the study eye.
14. History of rhegmatogenous retinal detachment in the study eye.
15. History of macular hole in the study eye.
16. Retinal pigment epithelial tear or rip involving the macula in the study eye as assessed by FA and confirmed by the central reading center.
17. Current vitreous hemorrhage in the study eye.
18. Subretinal hemorrhage that is ≥ 50% of the total lesion area in the study eye, or if the subretinal hemorrhage involves the fovea is 1 or more DA (≥ 2.54 mm^2) in size in the study eye, as assessed by FA and confirmed by the central reading center.
19. Other intraocular surgery (including cataract surgery) in the study eye within the 3 months prior to Baseline. The yttrium aluminum garnet [YAG] posterior capsulotomy is allowed no later than 4 weeks prior to screening.
20. Any concurrent intraocular condition in the study eye (eg, cataract or diabetic retinopathy) that, in the opinion of the investigator, could require treatment during the study period to prevent or treat loss of visual acuity.
21. Significant media opacities (including cataract) in the study eye interfering with BCVA assessment or fundus imaging (FA/fundus photography/OCT).

22. Aphakia or absence of the posterior capsule in the study eye, unless it occurred as a result of a YAG posterior capsulotomy in association with prior posterior chamber intraocular lens implantation.
23. Presence of advanced glaucoma or optic neuropathy that involves or threatens the central visual field in the study eye (as judged by the investigator).
24. History of glaucoma filtering surgery or argon laser trabeculoplasty in the study eye (Exception: Laser iridotomy and selective laser trabeculoplasty are allowed).
25. Uncontrolled ocular glaucoma or hypertension in the study eye, defined as IOP ≥ 25 mm Hg despite treatment with anti-glaucoma medication.
26. Any previous systemic anti-VEGF treatment (eg, bevacizumab).
27. Contraindication for Lucentis® (hypersensitivity to ranibizumab or to any of the study treatment excipients).
28. Current treatment for active systemic infection.
29. Females who are pregnant, nursing, planning a pregnancy during the study, or of childbearing potential and not using a reliable method of contraception (see Appendix 17.1) and/or not willing to use a reliable method of contraception during their participation in the study. A pregnancy test administered to women of childbearing potential at the Screening Visit (prior to treatment) must be negative for the patient to receive study medication.
30. Participation in another clinical trial within the previous 3 months or any other clinical trial of anti-angiogenic drugs.
31. Reasonable suspicion of other disease or condition that might render the subject at a high risk of treatment complications or otherwise confound interpretation of the study results (as judged by the investigator).
32. *PK subgroup only*: Contraindication for additional blood sampling (as judged by the investigator).

Primary Efficacy Endpoint:

- Change in BCVA letters at Week 8 compared to Baseline using the ETDRS protocol.

Secondary Efficacy Endpoints:

- Change in BCVA letters at Week 4, Week 12, Week 16, Week 24, Week 36 and Week 52 compared to Baseline using the ETDRS protocol
- Change in total size of choroidal neovascular leakage area in the study eye measured by FA at Week 24 and Week 52 compared to Baseline
- Change in total size of choroidal neovascularization in the study eye measured by FA at Week 24 and Week 52 compared to Baseline

- Change in Central Foveal Thickness (CFT) in the study eye measured by OCT at Week 2, Week 4, Week 8, Week 16, Week 24, Week 36 and Week 52 compared to Baseline
- Changes in the size and/or number of intraretinal cystoid space (cysts), subretinal fluid, and retinal pigment epithelium detachments in the study eye measured by qualitative morphology-based OCT
- Percentage of subjects with loss of < 15 letters using ETDRS, evaluated as change at Week 4, Week 8, Week 24, and Week 52 compared to Baseline in the study eye
- Percentage of subjects with a gain of ≥ 15 letters using ETDRS, evaluated as change at Week 4, Week 8, Week 24, and Week 52 compared to Baseline in the study eye
- Percentage of subjects without intra- or subretinal fluid in the study eye (ie, completely dry) at Week 24 and Week 52
- Percentage of subjects with retinal pigment epithelium detachments in the study eye
- Systemic ranibizumab concentrations

Safety Endpoint(s):

- Adverse events (AEs), including treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Injection site reactions (including endophthalmitis, vitritis, and hemorrhage)
- Immunogenicity (ie, anti-ranibizumab antibodies and NAb)
- Hematology and clinical chemistry (including analysis of alanine aminotransferase also known as serum glutamic-pyruvic transaminase [ALT/SGPT] and aspartate aminotransferase also known as serum glutamic-oxaloacetic transaminase [AST/SGOT], and creatinine)

Statistical Analysis:

For the primary estimand, the scientific question of interest is the between-group difference (Xlucane v Lucentis®) in the mean change from baseline in BCVA letter score at Week 8 in patients who fulfil the study eligibility criteria, have no Intercurrent Events up to and including the Week 8 BCVA assessment and complete 8 weeks of treatment of study drug (given as a single ophthalmic IVT injection every 4 weeks/monthly).

Before unmasking the data for subjects included in this trial, a statistical analysis plan (SAP), which will provide the technical details of the statistical analyses outlined here, will be prepared, finalized, and signed. In general, data will be summarized by means of summary statistics. Continuous data will be presented as the number of observations, mean, standard deviation (SD), minimum, Q1, median, Q3, and maximum. Categorical data will be presented as counts and percentages. The data will be presented for each treatment group by visit.

Efficacy data (ROW): Biosimilarity will be concluded if the two-sided 95% confidence interval (CI) for the difference in mean change in BCVA at Week 8 between the Xlucane and Lucentis® is confined within the equivalence margin of ± 3.5 letters.

Efficacy data (US FDA): Biosimilarity will be concluded if the two-sided 90% confidence interval (CI) for the difference in mean change in BCVA at Week 8 between the Xlucane and Lucentis® is confined within the equivalence margin of ± 3.5 letters.

The difference in the approach around the confidence interval is based on the regulatory requirement in the United States (90% CI) and the rest of the world (95% CI), as agreed with the relevant regulatory authorities.

The change in BCVA letters at Week 8 compared to Baseline using the ETDRS protocol will be analyzed using a mixed model for repeated measures (MMRM). An MMRM approach will be fitted with geographical region of the country where enrolled, visit, eye color (light iris vs dark iris), treatment, and treatment-by-visit interaction as fixed effects, with the Baseline BCVA letters and Baseline BCVA letters-by-visit interaction as covariates. The treatment differences from the model at Week 8 will be evaluated and a 95% or 90% two-sided CI for the least squares mean difference between groups will be calculated. To prove the 2 products to be biosimilar, the confidence limits for this difference have to be within the equivalence margin of ±3.5 letters. The primary analysis for assessment of biosimilarity will be based on the primary estimand.

Interim analysis: When all subjects have completed their 6-month assessments, an unmasked analysis of efficacy and safety endpoints as well as PK and immunogenicity will be performed. The aim of the *unmasked* analysis is to initiate the submission of the application for marketing authorization as agreed with the European Medicines Agency. This analysis will not affect the further conduct of the study.

PK data: The PK data (plasma levels of ranibizumab) will be compared between 2 groups of subjects receiving Xlucane and Lucentis® in a statistical non-confirmatory manner, for comparative purpose.

Safety data: AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be tabulated by system organ class (SOC) and preferred term (PT).

The total number of subjects with at least one TEAE and the total number of TEAEs will be presented. Number of subjects and number of TEAEs will be tabulated by SOC and PT. TEAEs will also be tabulated according to worst severity and relationship to treatment.

Sample Size: The sample size calculation was based on the primary efficacy endpoint: Change in BCVA between Baseline and Week 8.

A 95% or 90% two-sided CI for the difference between groups will be calculated. The difference in the approach around the confidence interval is based on the regulatory requirement in the United States (90% CI) and the rest of the world (95% CI), as agreed with the relevant regulatory authorities. To prove the 2 products to be biosimilar, the confidence limits for this difference have to be within the equivalence margin of ±3.5 letters.

For the purpose of sample size calculation, an SD of 10 letters will be assumed for this study. This is based on an analysis of the data from clinical trials of the originator product demonstrating a clear correlation between baseline BCVA and the SD of the change of BCVA at Week 8. Considering that a narrower inclusion criterion for BCVA is being

applied in this study compared to the studies of the originator product, it is expected that a baseline BCVA of around 60 letters will be observed. Therefore, an SD of 10 for the primary endpoint is well in the upper range of what is expected.

From 580 randomized patients there will be >90% power to show equivalence (ie, two-sided 95% CI for the mean difference between Xlucane and Lucentis® is confined within the equivalence margin of ± 3.5 letters) if the SD is no more than 10.

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ADA	anti-drug antibody
AE	adverse event
ALT	argon laser trabeculoplasty
ALT/SGPT	alanine aminotransferase/ serum glutamic-pyruvic transaminase
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APAC	Asia-Pacific (countries)
AST/SGOT	aspartate aminotransferase/ serum glutamic-oxaloacetic transaminase
ATE	arterial thromboembolic events
BCVA	best corrected visual acuity
BDRM	blinded data review meeting
β-HCG	beta-human chorionic gonadotropin
BP	blood pressure
BUN	blood urea nitrogen
CFP	color fundus photography
CFT	central foveal thickness
cGE	capillary gel electrophoresis
CH1	human constant heavy (domain)
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	human constant light (domain)
CLBA	competitive ligand binding assay
C_{max}	maximum plasma concentration
CNV	choroidal neovascularization
CORC	Coimbra Ophthalmology Reading Center
CRA	clinical research associate
CRC	central reading center
CRF	case report form
CRO	contract research organization
DA	disc area(s)
DME	diabetic macular edema
DP	drug product
DR	diabetic retinopathy
DS	drug substance
ECL	Electrochemiluminescence
eCRF	electronic case report form
EDC	electronic data capture
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERG	Electroretinogram
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiography
Fab	antigen binding fragment
FDA	Food and Drug Administration
GCP	Good Clinical Practice

HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IE	Intercurrent Event
IEC	independent ethics committee
IMP	investigational medicinal product
IOL	intraocular lens
IOP	intraocular pressure
IP	investigational product
IRB	institutional review board
ISR	injection site reaction
IUD	intrauterine device
IVT	Intravitreal
IWRS	interactive web response system
LC-MS	liquid chromatography-tandem mass spectrometry
LDH	lactate dehydrogenase
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
mCNV	myopic choroidal neovascularization
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mm Hg	millimeter(s) of mercury
MoA	mechanism of action
MW	molecular weight
N	number of subjects with an observation
NAb	neutralizing anti-drug antibody
N	number of subjects in the dataset or population
OCT	optical coherence tomography
PDT	photodynamic therapy
PK	pharmacokinetic(s)
PP	per protocol
PT	preferred term
RBC	red blood cell
RGA	reporter gene assay
rhuMAb	recombinant humanised monoclonal antibody
RPE	retinal pigment epithelium
RVO	retinal vein occlusion
ROW	Rest of the World
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SLE	slit lamp examination
SLT	selective laser trabeculoplasty
SOC	system organ class
SOP	standard operating procedure
SPR	surface plasmon resonance
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

T_{max}	time to maximum plasma concentration
USP	US Pharmacopoeia
VA	visual acuity
VEGF	Vascular Endothelial Growth Factor
VH	variable heavy (chain)
VL	variable light (chain)
wAMD	wet age-related macular degeneration
WBC	white blood cell
WFI	water for injection
WHO	World Health Organization
WMA	World Medical Association
YAG	yttrium aluminum garnet

6 INTRODUCTION

6.1 Background: Disease

Age-related macular degeneration (AMD) is a common eye condition that has been described as the leading cause of vision loss, affecting 10%–13% of adults over 65 years of age in North America, Europe, Australia, and Asia.[1] AMD is a progressive, degenerative disease affecting the macula, the region of the retina that is most important for visual acuity (VA). It causes damage to the macula, increasingly affecting sharp, central vision over time. While AMD by itself does not lead to complete blindness, the loss of central vision in AMD can interfere with simple everyday activities.[2] Age is a major risk factor for AMD, with the disease most likely occurring after age 60. Other risk factors include smoking, race, and family history and genetics.

Neovascular AMD is a major cause of loss of central vision in the elderly. While it does not cause complete blindness, it can make daily activities such as driving and reading difficult or impossible. Disease activity in neovascular AMD is lifelong. Even at late stages in the therapeutic course, exudative AMD patients remain at risk for substantial additional visual decline. AMD is a disease of the photoreceptors and the retinal pigment epithelium (RPE). In the aging eye, Bruch's membrane composition changes, RPE function diminishes, and drusen (containing lipofuscin and other toxic waste products of metabolism) is deposited. Vision loss results from the abnormal growth and leakage of blood vessels in the macula.

The main factor influencing AMD progression remains age, with genetics and smoking also having an impact. A meta-analysis of population-based AMD studies reported a global prevalence of 8.7% in people aged 45 to 85 years, with a higher prevalence in Europe and North America than in Asia.[3] The authors further predicted that the number of cases worldwide would increase from 170 million in 2014 to 196 million in 2020 and 288 million in 2040.

AMD is divided into "early," "intermediate," and "late" types based on severity, with the late type being the most severe.[2] The late type can be further divided into the dry (atrophic) and the wet (ie, neovascular or exudative) forms. The dry form is less aggressive and accounts for 90% of all AMD cases but only for 10% of cases of blindness due to AMD. Dry AMD may develop into wet AMD. Wet AMD (wAMD) affects 10% of the AMD patients and is the more aggressive form, which, if untreated, leads to rapid severe visual impairment and in many cases, legal blindness.[1] However, 80% to 90% of patients with severe vision loss due to AMD have wAMD.[1]

Wet AMD causes rupture of Bruch's membrane, an associated localized inflammatory response, and release of vascular endothelial growth factor (VEGF), which induces choroidal neovascularisation (CNV). The newly formed blood vessels grow through the ruptured membrane underneath the RPE and the retina. These new vessels are fragile and leak blood and proteins and may cause persistent edema below the macula, resulting in permanent damage to photoreceptors and the loss of central vision.

Treatment of wAMD includes photodynamic therapy (PDT) and laser coagulation, (although a recent Cochrane review found that laser coagulation is ineffective at preventing CNV and limiting loss of VA).[4]

To date, standard of care treatment for wAMD is intravitreal (IVT) anti-VEGF therapy, with the VEGF-antagonist pegaptanib (Macugen®; Bausch + Lomb) and the monoclonal antibody ranibizumab (Lucentis®; Genentech/Novartis). Another anti-VEGF treatment for wAMD is aflibercept (Eylea®; Regeneron), which is a VEGF-trap that interferes with the biological actions by binding to VEGF-A, preventing it from interacting with its receptors.

6.2 Xlucane

Xbrane Biopharma AB (referred to as Xbrane) is developing Xlucane as a proposed biosimilar candidate to the EU-licensed Lucentis® (ranibizumab). Lucentis was first approved as a treatment for wAMD in the United States in 2006 and the European Union/European Economic Area (EU/EEA) in 2007.[5]

The active ingredient in Xlucane and Lucentis® is ranibizumab. Ranibizumab belongs to the pharmacological class of VEGF inhibitors and is an antigen binding fragment (Fab) of a recombinant humanized monoclonal antibody (rhuMAb) that binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110}$. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular wAMD. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.[5]

Ranibizumab was originally developed from a murine monoclonal antibody produced using $VEGF_{165}$-immunized mice.[5] The variable light (VL) and variable heavy (VH) chain from the identified murine monoclonal antibody was fused to human constant light (CL) and human constant heavy (CH1) domains.[5] The affinity of the new construct for $VEGF_{165}$ was further optimized by phage display.[6] Crystallographic studies show that the mature Fab fragment binds specifically to VEGF-A and that this interaction occurs at the residues Met81, Gln89, and Gly92 on VEGF-A.[6,7] It should be noted that these residues are present in the 3 main VEGF-A isoforms in vivo ($VEGF_{121}$, $VEGF_{165}$, and $VEGF_{110}$) and that they are required for binding to the VEGF-A receptors (VEGFR-1 and VEGFR-2).[6,8]

Prevention of VEGF-A binding to its receptors VEGFR1 and VEGFR2 on the surface of endothelial cells precludes endothelial cell proliferation and neovascularisation, as well as vascular leakage. Ranibizumab contains a light chain with 214 residues and a heavy chain containing 231 residues. In the fully assembled product, the 2 polypeptide chains are linked via a disulfide bond. In addition to the interchain disulfide bond, there

are 2 intrachain disulfide bonds in each polypeptide chain. In a nonreduced environment, the fully assembled product has a molecular weight (MW) of approximately 48 kDa; after reduction, both polypeptide chains can be detected separately (light chain 23 kDa and heavy chain 25 kDa).

6.2.1 Quality Development

Xlucane has been developed with patented technology and deep knowledge and experience in protein production, resulting in a very high production yield—currently on average 8× what a standard system in *Escherichia coli* (BL21) would result in.

The manufacturing process for ranibizumab in Xlucane has been developed in-house by Xbrane (Stockholm, Sweden). As with Lucentis®, ranibizumab is produced in an *E coli* K-strain but with differences in the strain background and in the expression vector.

The formulation for Xlucane drug substance (DS) is being developed with a composition of 20 mg/mL ranibizumab, α,α-trehalose dihydrate, histidine hydrochloride monohydrate, histidine, polysorbate 20, and water for injection (WFI). All excipients are of pharmacopoeial grade.

The formulation for Xlucane drug product (DP) is being developed to replicate that of Lucentis® with a composition of 10 mg/mL ranibizumab, α,α-trehalose dihydrate, histidine hydrochloride monohydrate, histidine, polysorbate 20, and WFI. All excipients are of pharmacopoeial grade.

Batches of Xlucane DS, produced at 300 L scale, and Xlucane DP, using the DS material manufactured at the 300 L scale, have been analyzed extensively for comparative physiochemical and functional similarity assessment studies. Biosimilarity between the Xlucane and Lucentis® has been demonstrated in a stepwise procedure.

6.2.2 Summary of Nonclinical Development

Physicochemical characterization of Xlucane and Lucentis® was performed to enable comparison of the structural characteristics of the protein products (eg, the primary and higher order structures and protein variants). Functional in vitro assays representative of biological activity were part of the similarity assessment program. Protein and process related impurities were also characterized, quantified, and compared.

The methods used for the characterization of Xlucane were chosen to provide a thorough understanding of the similarity and potential differences between Lucentis® and Xlucane. In addition to the batches used, isolates from different purification steps were also used in initial studies for optimization of the analytical methods. Using these extra isolates, different forms of the target molecule were detected, further supporting the sensitivity of the methods used.

Extensive analyses show that the produced Xlucane lots and the analyzed Lucentis® batches were similar for the tests performed. Some analytical tests are ongoing and results are pending.

6.2.2.1 Primary and Higher Order Structures

The amino acid sequence of Xlucane was analyzed by liquid chromatography-tandem mass spectrometry (LC-MS) on protease degraded material, and was shown to be identical to that of Lucentis®. The primary structure for Lucentis® and Xlucane was analyzed using reduced/non-reduced conditions in combination with LC-MS for intact mass of the full Fab or for the individual subunits confirming expected mass in all samples tested. C-terminal sequence for light chain and heavy chain was confirmed in both Xlucane and Lucentis® using LC-MS/MS. Overall, the primary structure in Xlucane DS and DP is similar to the primary structure of Lucentis®.

Secondary and tertiary structure for Lucentis® and Xlucane material was analyzed and used to characterize the higher order structure. Overall methods showed that the higher order structure of Xlucane is similar to the higher order structure of Lucentis®.

6.2.2.2 Purity/Impurity Profile

Purity and impurities such as high molecular weight species, fragments, oxidized, deamidated, gluconoylated, pyroglutamated species were analyzed by size exclusion high performance liquid chromatography (HPLC), reversed phase HPLC, ion exchange HPLC, analytical ultra-centrifugation, reducing/non-reducing capillary gel electrophoresis (cGE), capillary isoelectric focusing (cIEF), and LC-MS. All methods showed that Xlucane and Lucentis® have a similar purity/impurity profile.

Process-related impurities such as host cell DNA, bacterial endotoxin, and sterility were analyzed by RT-PCR, LAL assay (Ph. Eur. 2.6.14, USP <85>), and membrane filtration (Ph. Eur. 2.6.1, USP <71>). Host cell DNA specifications have been set based on industry standards (there are no pharmacopoeial standards), and all results are below this limit. All other methods showed that Xlucane are within the specifications of EU and US Pharmacopoeial standards.

Host cell proteins (HCPs) have been analyzed with commercially available K12 HCP enzyme-linked immunosorbent assay (ELISA) kits. The method shows that levels of HCPs are within the specifications of industry standards (there are no pharmacopoeial standards). Xbrane is currently developing a specific HCP ELISA kit for the used process, and all clinical batches will be analyzed with this method prior to the start of the trial. Subvisible particles were also measured for Xlucane DP material, and the amount of subvisible particles is within the specifications of US Pharmacopoeial standards (USP <789>). Xbrane is currently developing an ELISA method for detection of Protein L from the first purification step. All clinical batches will be analyzed with this method prior to the start of the trial.

6.2.2.3 Potency and Binding

Xbrane has conducted surface plasmon resonance (SPR/BIAcore) and HEK293 reporter gene assay (RGA) with Xlucane and Lucentis® to evaluate potential differences in the content and functionality of ranibizumab. The HEK293/RGA will continue to be used in lot release and stability testing, and SPR/BIAcore will also be used for extended characterization.

Xlucane has been investigated for its binding capacity to $VEGF_{165}$, $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{189}$ and compared to that of Lucentis®. Specific interaction with VEGF-A is crucial for the action of Lucentis® and Xlucane and this mechanism of action (MoA) has been examined using BIAcore. BIAcore was used to provide quantitative data on the association rate constant for the binding of ranibizumab to each of the VEGF variants ($VEGF_{165}$, $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{189}$). Xbrane has demonstrated that the binding characteristics of Xlucane to $VEGF_{165}$, $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{189}$ by means of SPR/BIAcore are comparable to that of Lucentis®.

The HEK293/RGA assay was also used to assess similarity with respect to potency between batches of Xlucane DS and Xlucane DP, formulated as described in Section 6.2.1, and Lucentis® batches. The RGA was used to represent a relevant signal transduction pathway ($VEGF_{165}$, $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{189}$). The interaction between $VEGF_{165}$, $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{189}$ and the VEGF-AR2 (KDR) receptor in HEK293 cells (GloResponse™ Cell Line) was quantified. Results from the RGA show that the potency is similar for Xlucane and Lucentis for all isoforms. The assay has been fully validated for $VEGF_{165}$ and qualified for all other isoforms.

6.2.2.4 Pharmacokinetic Study in Rabbits

In addition, to support the development of Xlucane for registration in India and Japan as well as other regions such as China, an in vivo pharmacokinetic (PK) study was conducted in New Zealand White rabbits (data on file; forthcoming).[9] The main objective of the study was to compare the PK characteristics of 2 formulations of ranibizumab (biosimilar [Xlucane] and Lucentis®) at a dose level of 0.5 mg (per eye) following a single bilateral intravitreal injection. The study design is shown in Table 1.

Table 1: Experimental Design of Rabbit PK Study

Group No.	Test Material	Dose Level (mg/eye)	Dose Volume (µL/eye)	Dose Concentration (mg/mL)	No. of Males		
					PK/Termination Time Point		
					Day 2[a]	Day 14	Day 28
1	Lucentis®	0.5	50	10	2 (4 eyes for PK)	2 (4 eyes for PK)	4 (4 eyes for PK; 4 eyes for histo)
2	Xlucane	0.5	50	9.8	2 (4 eyes for PK)	2 (4 eyes for PK)	4 (4 eyes for PK; 4 eyes for histo)

Abbreviation(s): h = hour; histo = histology; No. = number; PK = pharmacokinetic.
[a] Day 2, at 24 h ± 1 h postdose.

During the course of the study, the animals were monitored for mortality/moribundity, abnormal clinical signs, inappetence, body weights, ophthalmology, and electroretinograms (ERGs). Serum and ocular tissues were collected for measurement of ranibizumab concentration and pharmacokinetics. At scheduled termination, ocular tissues (right eye) were collected from microscopic evaluation.

There was no mortality during the course of the study. There were no abnormal clinical signs/appetence nor changes in the body weights/body weight gains or ERG parameters that could be attributed to a single bilateral IVT of biosimilar Xlucane or Lucentis® at dose level of 0.5 mg/eye. Ocular changes attributed to the administration of Lucentis® were limited to a transient inflammation of the anterior chamber in 2/16 eyes (2/8 animals) on Day 14. By Day 28, signs of anterior uveitis were not observed in any of the 4 surviving animals, but changes in the posterior segment, notably the presence of cell-like opacities in the anterior portion of the vitreous, and deeper, larger vitreal opacities were present in 1/8 Lucentis®-treated animals (both eyes). The administration of Xlucane was well tolerated, with no ocular inflammation observed in any of the eyes treated.

A comparable exposure (C_{max} and $AUC_{(0-t)}$) in serum and ocular tissues was observed in animals that received Xlucane compared to Lucentis®. T_{max} was generally observed at the last time point collected (24 hours postdose) or at the last quantifiable value (48 hours postdose) for serum. T_{max} was observed at 24 hours postdose in ocular tissues (vitreous humour and sensory retina). At 24 hours postdose, the highest exposure (C_{max} and $AUC_{(0-t)}$) was found in vitreous humor, followed by the sensory retina and then the serum. When estimated for vitreous humor, the $T_{1/2}$ was 71.9 hours for Lucentis® and 72.4 hours for Xlucane.

Microscopic changes of the right eye of animals treated with Xlucane or Lucentis® were limited to mononuclear cell infiltration. The incidence and severity of this change was generally higher in the Lucentis® group (minimal to moderate severity; 7 ocular tissues affected) when compared to the Xlucane group (minimal severity; 3 ocular tissues affected).

In conclusion, a single bilateral IVT injection of 1 of 2 formulations of ranibizumab (biosimilar Xlucane or Lucentis®) to New Zealand white rabbits was well tolerated,

with no compound-related clinical signs or changes in the body weights, appetite, or ERGs. The systemic exposure (C_{max} and $AUC_{(0-t)}$) in serum and local exposure in ocular tissues in animals treated with Xlucane 0.5 mg/eye (or 1 mg/total) was comparable to animals treated with Lucentis® 0.5 mg/eye (or 1 mg/total). Microscopic changes of the right eye of animals treated with Xlucane or Lucentis® were limited to mononuclear cell infiltration. The incidence and severity of this change was generally higher in the Lucentis® group (minimal to moderate severity; 7 ocular tissues affected) when compared to the Xlucane group (minimal severity; 3 ocular tissues affected).

6.2.3 Planned Clinical Study

Xlucane has not yet been tested in any clinical study. The planned clinical development includes this pivotal phase III study to evaluate the efficacy, equivalence, PK, immunogenicity, and safety of Xlucane and Lucentis®. The clinical study is planned to be conducted in the EU, US, APAC, and other regions to confirm the biosimilarity of Xlucane to Lucentis®.

The clinical phase III study is a double-blind (double-masked), multicenter, parallel group study in patients with wAMD. The patients will be randomized 1:1 to receive Lucentis® or Xlucane. The patients will receive 13 doses of Xlucane or Lucentis® and be followed for changes in efficacy and safety for 52 weeks. The primary endpoint is change in best corrected visual acuity (BCVA) letters at Week 8 compared to Baseline using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Approximately 580 patients will be randomized in the study. Refer also to Section 8.2 of the protocol for study design discussion.

Immunogenicity will be evaluated by anti-drug antibody (ADA) formation and neutralizing anti-drug antibody (NAb) up to Week 52 after Randomization. An electrochemiluminescence (ECL) bridging assay format that uses labelled (biotinylated and ruthenylated) Xlucane will be employed for screening, with confirmatory and titration tiers for ADA performed. The characterization of NAb will be performed using a Competitive Ligand Binding Assay format (CLBA) that will measure the capacity of the test samples to inhibit binding of Xlucane to biotinylated VEGF-165 immobilized on streptavidin-coated plates.

A PK substudy is incorporated in the proposed phase III clinical trial to permit an assessment for similarity in systemic exposure following Xlucane and Lucentis® administration. It is anticipated that the systemic exposure should be low, given the dose and route of administration. Between approximately 40 and 60 patients will be included in the PK sub-study. The collection of PK samples is proposed for immediately before the first dose, at 23 hours after the first dose (Day 1), and at 23 hours after the sixth dose (Week 20); T_{max} is around 22 hours.

6.3 Lucentis® (ranibizumab injection)

Lucentis® (ranibizumab injection) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Lucentis® is indicated for

the treatment of patients with: wAMD; macular edema following RVO; DME; diabetic retinopathy (DR); and myopic CNV (mCNV). The active substance of Lucentis® is ranibizumab, a monoclonal antibody fragment.[5]

The mode of action of ranibizumab is to bind to the vascular endothelial growth factor A (VEGF-A) present in the eyes of the affected patients. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, mCNV, DR, DME and macular edema following RVO. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

Ranibizumab, which lacks an Fc region, has a molecular weight of approximately 48 kilodaltons and is produced by an *E coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product.

6.3.1 Nonclinical Studies

Animal studies have not been conducted to determine the carcinogenic potential of ranibizumab. Based on the anti-VEGF mechanism of action of ranibizumab, treatment with Lucentis® may pose a risk to reproductive capacity.

6.3.1.1 Infertility

No studies on the effects of ranibizumab on fertility have been conducted and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with Lucentis® may pose a risk to reproductive capacity.

6.3.2 Clinical Studies in wAMD

The safety and efficacy of Lucentis® were assessed in three randomized, double-masked, sham- or active-controlled studies in patients with wAMD. A total of 1323 patients (Lucentis® 879, control 444) were enrolled in the three studies.

In studies AMD-1 and AMD-2 the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared with Baseline. Visual acuity was measured at a distance of 2 meters. Almost all Lucentis®-treated patients (approximately 95%) maintained their visual acuity. Among Lucentis®-treated patients, 31% to 37% experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not significantly affect the results. Further, patients in the group treated with Lucentis® had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1-0.3 disc areas (DA) for Lucentis® versus 2.3-2.6 DA for the control arms. At Month 24, the mean

change in the total area of the CNV lesion was 0.3-0.4 DA for Lucentis® versus 2.9-3.1 DA for the control arms.

In study AMD-3, the primary efficacy endpoint was the mean change in visual acuity at 12 months compared with Baseline. Visual acuity was measured at a distance of 4 meters. After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every 3 months with Lucentis® lost visual acuity, returning to Baseline at Month 12. In study AMD-3, almost all Lucentis®-treated patients (90%) lost fewer than 15 letters of visual acuity at Month 12.

In study AMD-4, clinical results at Month 24 remain similar to that observed at Month 12. From Month 3 through Month 24, visual acuity decreased by 0.3 letters in the 0.5 mg less frequent dosing arm and increased by 0.7 letters in the 0.5 mg monthly arm. Visual acuity was measured at a distance of 4 meters.

7 STUDY OBJECTIVES

7.1 Primary Objective

The primary objective of the study is to demonstrate that the biosimilar candidate Xlucane is equivalent to Lucentis® in subjects with wAMD as assessed by the change in BCVA from Baseline to Week 8.

7.2 Secondary Objectives

The secondary objectives of the study are as follows:

- Evaluate the efficacy of Xlucane vs Lucentis® in subjects with wAMD based on central foveal thickness (CFT) measured by spectral domain optical coherence tomography (SD-OCT), area of choroidal neovascularization, and presence of leakage assessed by fundus fluorescein angiography (FA)
- Evaluate the safety of Xlucane vs Lucentis®
- Evaluate the systemic exposure of Xlucane vs Lucentis® in subjects participating in pharmacokinetics (PK) evaluation
- Evaluate immunogenicity (ie, anti-ranibizumab antibodies and NAb) of Xlucane vs Lucentis®

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan: Description

This is a phase III multicenter, double-blind (double-masked), randomized, parallel group study in subjects with wAMD. Approximately 580 subjects will be enrolled and randomized in a 1:1 ratio to receive either Lucentis® (0.05 mL of 10 mg/mL ranibizumab) or the investigational product (IP), Xlucane (0.05 mL of 10 mg/mL ranibizumab), in the study eye once every 4 weeks for 52 weeks (ie, 12 months).

The study eye will be defined as the eye meeting all of the inclusion criteria and none of the exclusion criteria (ie, the enrollment criteria).

The assigned study drug will be administered as an ophthalmic intravitreal (IVT) injection. Designated, unmasked study staff will prepare and administer the study drug, ensuring that the masking of the subject is maintained during the injection procedure. See Section 8.4.6.

Subjects will be randomized by interactive web response system (IWRS) to receive 13 doses of either Xlucane or Lucentis® in the study eye. The randomization scheme will automatically ensure that the study drug assignment for a given subject is random and that an overall 1:1 ratio of assignments to each of the 2 study drug treatments is approximated. In addition, the randomization scheme will include the following stratification parameters to ensure balanced distribution of assignment to the 2 treatments: eye color (light iris vs dark iris), geographical region where enrolled and the BCVA letters at Baseline (55 or lower, 56 to 65, 66 or higher). Subjects will be followed up for changes in efficacy variables and safety for 52 weeks. Each subject's involvement will last up to approximately 52 weeks (ie, 12 months).

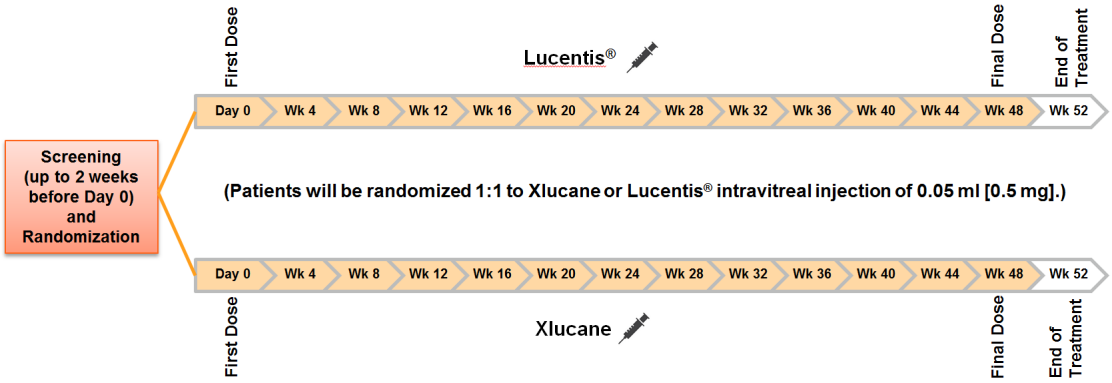
At the beginning of the study, a subgroup of between approximately 40 and 60 subjects at a select number of participating sites will be sequentially asked to participate in an evaluation of PK. This subgroup will be asked to provide blood samples for measurement of plasma ranibizumab immediately before administration of the first dose of Xlucane or Lucentis®. Additional samples will be collected 23 hours after the first dose (ie, Day 1) and 23 hours after the sixth dose (ie, Week 20) at expected time to maximum plasma concentration (T_{max}, which is around 22 hours). The primary analysis set will be the Per-Protocol population.

An interim analysis will be performed on *unmasked* study data. After all of the randomized subjects have 6-month (ie, 24 weeks) data available, an *unmasked* analysis of efficacy and safety endpoints as well as PK and immunogenicity will be performed.

The aim of the *unmasked* analysis is to initiate the submission of the application for marketing authorization as agreed with the European Medicines Agency. This analysis will not affect the further conduct of the study.

FA, CFP, and OCT will be performed at Screening. The images will be sent to the central reading center (CRC) for interpretation and confirmation of eligibility. The CRC will also grade images that are collected during the study.

Figure 1 Study Design



8.1.1 Schedule of Assessments

Assessment(s)	Pre-treatment	Treatment Period									End of Treatment[21]
Visit(s)	1	2	3	4	5	6	7	8	9	10 to 15[19]	16
Time point	Screening	Day 0/ BL	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28 to Week 48[19]	Week 52
Window (± days)	≤ 21 days before start of treatment		± 2 days	± 2 days	±2 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days
Informed consent	X										
Eligibility criteria	X										
Demographic data (such as, ethnic origin, date of birth, and sex)	X										
Medical history[1]	X										
Physical examination[2]	X[2]										X[2]
Body mass index (height and weight measured)	X										
SLE[3]	X	X		X	X	X	X	X	X	X	X
Dilated fundus examination[4]	X	X		X	X	X	X	X	X	X	X
IOP measurement[5]	X	X		X	X	X	X	X	X	X	X
CFP[6]	X[8]								X		X
FA[7]	X[8]								X		X
OCT[9]	X[8]	X	X	X	X	X	X	X	X	X	X
BCVA by ETDRS (including manifest refraction)[10]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[11]	X	X		X	X	X	X	X	X	X	X

Assessment(s)	Pre-treatment	Treatment Period									End of Treatment[21]
Visit(s)	1	2	3	4	5	6	7	8	9	10 to 15[19]	16
Time point	Screening	Day 0/ BL	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28 to Week 48[19]	Week 52
Window (± days)	≤ 21 days before start of treatment		± 2 days	± 2 days	±2 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days
Hematology[12]	X			X	X	X			X	(X)[20]	X
Clinical chemistry[13]	X			X	X	X			X	(X)[20]	X
Urine pregnancy test[14] *Country specific requirements exist (see notes)*	X										X
Randomization		X									
Subgroup ONLY: PK sampling[15]		X[15]						X[15]			
Blood sample collection for immunogenic evaluation[16]		X[17]		X[17]	X[17]	X[17]		X[17]	X[17]	(X)[17]	X[17]
Study drug administration[18]		X		X	X	X	X	X	X	X	
Adverse event reporting	X (including BL events)	X----------X									
Injection site reactions		X		X----------X							
Concomitant medications	X	X	X----------X								

Abbreviations: BCVA = best corrected visual acuity; BL = Baseline; CFP = color fundus photography; CRC = central reading center; EOT = end of treatment; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; IOP = intraocular pressure; IVT = intravitreal; NAb = neutralizing anti-drug antibody; OCT = optical coherence tomography; PE = physical examination; PK = pharmacokinetic; SLE = slit lamp examination.

Notes:

1. Collect full medical history, historical disease data, diagnostic information, and concomitant illnesses/diseases, adverse events (including Baseline events), and concomitant medications.
2. A PE will consist of a routine evaluation of organ systems (including head, ears, eyes, nose, throat, neck, cardiovascular, pulmonary, abdomen, skin, extremities, neurological, lymph nodes, and musculoskeletal). At the Screening Visit, the PE will include the collection of the subject's eye color (ie, light iris or dark iris). At the Week 52/EOT Visit, the PE will also include a query of the patient to determine if changes in his/her physical condition have occurred since the PE at Screening.
3. SLE of the anterior segment is conducted in both eyes at Screening and prior to Randomization on Day 0. At all other scheduled visits, SLE is conducted in the study eye only.
4. Dilated fundus examination of the posterior segment is conducted in both eyes at Screening and prior to Randomization on Day 0. At all other scheduled visits dilated fundus examination is conducted in the study eye only.
5. IOP is measured in both eyes at Screening, prior to Randomization on Day 0, and at Week 52 (or EOT visit). At all other scheduled visits, IOP is measured in the study eye only. At pre-injection, IOP should be measured using the Goldmann tonometry method. After IVT injection (eg, 30 minutes post injection), non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer) within the next 30 minutes.
6. CFP assessment is conducted in both eyes at Screening. At Week 24 and 52 (or EOT visit), CFP assessment is conducted in the study eye only. Images should be sent to the CRC.
7. FA assessment is conducted at Screening, Week 24 and 52 (or EOT visit), Images of both eyes should be sent to the CRC for these visits. FA Grading by CRC is conducted on both eyes at Screening Visit and in the study eye only at Week 24 and 52 (or EOT visit).
8. Assessments to be confirmed by the CRC during Screening and prior to Randomization.
9. OCT assessment is conducted in both eyes at Screening and BL. At all other visits, including Week 52 (or EOT visit), OCT assessment is conducted in the study eye only. Images should be sent to the CRC.
10. BCVA assessment by ETDRS at 4 meters, including manifest refraction.
11. Vital signs measurements to include heart rate and blood pressure. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.
12. Hematology panel evaluations will be sent to a central laboratory. See also Section 10.1.4.2.3. Results from Screening visit must be reviewed by the investigator before patient is randomized

13. Clinical chemistry panel evaluations will be sent to a central laboratory. See also Section 10.1.4.2.3. Results from Screening must be reviewed by the investigator before patient is randomized
14. Urine pregnancy test for females of childbearing potential (only), must be negative for the patient to receive study medication. ***Country specific requirement:*** *It must be noted that sites in Czech Republic must perform urine pregnancy test every 2 months in addition to Screening and Week 52 (EOT visit)- This includes Week 8, Week 16, Week 24, Week 32, Week 40 and Week 48. (Please refer to CRF completion guidelines for documenting these visits)*
15. See Schedule in Section 8.1.2 for details on timing of PK sampling relative to study drug injection.
16. Additional samples for monitoring immunogenicity testing are collected from subjects with any sign(s) of intraocular inflammation, as these may indicate an immune reaction.
17. Blood sampling for immunogenic (ie, anti-ranibizumab antibodies and NAb) testing must be performed before dosing on Day 0, Week 4, Week 8, Week 12, Week 20, Week 24, Week 36, and Week 52.
18. Study drug administration in study eye only, per randomized assignment. After the injection, monitor the subject for any signs or symptoms for at least 60 minutes.
19. Visits 10, 11, 12, 13, 14, and 15 (Week 28, 32, 36, 40, 44, and 48) should each continue to occur monthly (ie, every 4 weeks).
20. During Visits 10 to 15 (Week 28 to Week 48), hematology and clinical chemistry panel evaluations should occur at Visit 12 (Week 36).
21. EOT assessments may also be performed for early discontinuation or withdrawal from the study.

8.1.2 Schedule of Additional Assessments for PK Subgroup ONLY

Visit(s)	2	2b[2]	8b[3]
Time point	Day 0	Day 1[2]	(Week 20)[3]
Blood Sampling Window (±)	≤ 60 minutes ***Predose***	23 hours ± 60 minutes ***Postdose***	23 hours ± 60 minutes ***postdose***
Blood sample(s) for PK evaluation	X[1]	X	X[3]
IOP measurement[4]		X	X
SLE[5]		X	X
Adverse event reporting		X	X

Abbreviations: IOP = intraocular pressure; PK = pharmacokinetic; SLE = slit lamp examination.

Notes:
1. Day 0 PK blood sampling must be performed ≤ 60 minutes before the first IVT injection of study medication.
2. Day 1 PK blood sampling must be performed 23 hours (± 60 minutes) after the IVT injection (ie, first dose of study medication).
3. Week 20 PK blood sampling must be performed 23 hours (± 60 minutes) after the IVT injection (ie, sixth dose of study medication).
4. IOP is measured by tonometry in the study eye only. Non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer) within the next 30 minutes.
5. Slit lamp examination of the anterior segment is conducted in the study eye only.

8.2 Discussion of Study Design

8.2.1 Study Design

The objectives of this study are to demonstrate the equivalence[11] of Xlucane to Lucentis® and to evaluate the safety and efficacy of Xlucane as compared to Lucentis® (ranibizumab injection). This will be done through a multicenter, randomized, double-blind (double-masked), parallel group study. The rationale for the design of this trial is to appropriately evaluate Xlucane as compared to Lucentis®, the reference standard for wAMD.

The selected endpoints for demonstrating equivalence of Xlucane to Lucentis® are in accordance with current standards, as are the safety endpoints of the trial. Masking subjects and designated study team members to the treatment assignment(s) ensures objectivity and minimizes bias. Randomization through the IWRS guards against selection bias.

The selected dosing schedule of the 2 study drugs is based upon clinical studies with Lucentis®, whereby monthly dosing is expected to maintain visual acuity and to result in an additional average 1 to 2 letter gain. Furthermore, prespecified safety evaluations will monitor subjects for any adverse events and injection site reactions (ISRs) during and after treatment.

Biosimilarity will be concluded if the two-sided 90% (US FDA) or 95% (ROW) confidence interval (CI) for the difference in mean change in BCVA at Week 8 between the Xlucane and Lucentis® is confined within the equivalence margin of ± 3.5 letters. The difference in the approach around the confidence interval is based on the regulatory requirement in United States (90% CI) and the rest of the world (95% CI), as agreed with the relevant regulatory authorities.

A meta-analysis of ANCHOR[18] and MARINA[10] studies was done in order to focus on Week 8 BCVA data and ensure that the proposed equivalence margin will preserve at least 50% of the lower limit of the 95% confidence interval for the difference in mean change in BCVA between treatment and placebo which was 7.7 (Table 2).

Table 2 Meta-analysis wAMD Ranibizumab Studies using BCVA change at 8 weeks

Study	Experimental			Control			95% CI			Weight (fixed)
	N	Mean	SD	N	Mean	SD	MD	lower	upper	
MARINA	240	5.4	9.3	238	-2.2	8.4	7.6	6.09	9.11	62.9%
ANCHOR	139	9.8	11.83	143	-1.8	15	11.6	8.08	15.12	37.1%
	379			**381**						

	95% CI		
	MD	**lower**	**upper**
Fixed effects model	9.08	7.70	10.47

An equivalence margin of ±3.5 letters represents at least 55% of the lower limit of the 95% confidence interval of treatment benefit (7.7 letters) demonstrated above.

Considering this and that the minimal clinically important difference in VA has previously been set to or estimated to be 5 to 10 letters,[12,13,14] an equivalence margin of ±3.5 letters is deemed adequate and supported by EMA/FDA in recent scientific advice.

As the primary objective of the study is to demonstrate equivalence of Xlucane versus Lucentis®, a symmetrical equivalence region of ±3.5 letters will be used. Biosimilarity will be concluded if the two-sided 95% or 90% CI for the difference between Xlucane and Lucentis in the BCVA change from Baseline at Week 8 is confined within the equivalence margin of ± 3.5 letters.

The study is also aimed to detect any notable differences in plasma ranibizumab levels between the 2 products, Xlucane and Lucentis®. Systemic ranibizumab exposure is very low after IVT injection, and there are potential issues in detecting such low levels by an assay. Further considering the approach that any notable differences are more easily detectable at steady-state, when ranibizumab concentrations are higher (ie, near the expected T_{max} after dosing, which is around 22 hours), the current study has PK measurements at Baseline, Day 1 (23 hours [± 60 minutes] after the first dose), and at Week 20 (23 hours [± 60 minutes] after the sixth dose) to possibly detect any differences in peak systemic exposure between the 2 products.

The rationale for the design of this trial is to appropriately evaluate Xlucane as compared to Lucentis®, the current standard of care for wAMD. The clinical relevance for selecting the endpoints of BCVA (using ETDRS) and changes in CFT, area of CNV,

and leakage from CNV lesion(s) is founded upon multiple studies.[5] Similarly, in Lucentis® clinical studies, VA was measured at a distance of 4 meters (or less) relative to ETDRS. Increased retinal thickness (ie, CFT) and leakage from CNV are well associated with wAMD. All are common causes of severe vision loss and thus changes in these measures can be considered objective endpoint evaluations for wAMD.

Refer also to Section 6.2 of the protocol.

8.3 Selection of Study Population

8.3.1 Number of Planned Subjects

It is anticipated that approximately 580 subjects will be enrolled and randomized.

There are approximately 160 sites anticipated to participate in approximately 15 countries in the United States, Europe, the Middle East, and Asia-Pacific.

Refer also to the statistical considerations in Section 11.4, on which the numbers are based.

Rescreening will be allowed for subjects previously determined as screen failures due to inclusion and/or exclusion criteria that could transiently change and do not compromise the subject's safety. Only one rescreen will be allowed per subject. When a rescreen is authorized by the Sponsor or its designee, the subject is to be reconsented, and all screening procedures (ie, laboratory testing, OCT, and color fundus photography [CFP]) should be repeated/completed and provided to the CRC, **with the exception of the FA procedure**. **Based on the CRC's determination, screening FA may *not* need to be repeated. Thus, if the CRC deems it appropriate/acceptable, prior FA performed at the time of the screen failure, may therefore be used for eligibility assessment. However if more than 30 days have passed since subject was screen failed, all procedures including FA must be repeated.** Subjects who discontinue the study after Randomization and after receiving study medication are not eligible for rescreening.

8.3.2 Inclusion Criteria

To be eligible for study entry, subjects must satisfy **all** of the following inclusion criteria:

1. Written and signed informed consent form obtained at Screening before any study-related procedures are performed. Patients must be capable of providing their own consent (an impartial witness must be present in case of illiterate patients).
2. Willingness and ability to undertake all scheduled visits and assessments as judged by the investigator.

3. Newly diagnosed, active subfoveal choroidal neovascularization (CNV) lesion secondary to age-related macular degeneration (AMD) in the study eye. *Note*: active CNV indicates the presence of leakage as evidenced by fluorescein angiography (FA) and intra- or subretinal fluid as evidenced by optical coherence tomography (OCT), which *must be confirmed by the central reading center during Screening:*
    a. The area of CNV must be ≥ 50% of the total lesion area in the study eye, and
    b. Total lesion area ≤ 9.0 disc areas (DA) in size (including blood, scars, and neovascularization) as assessed by FA in the study eye
4. BCVA of ≤ 73 and ≥ 49 ETDRS letter score in the study eye using the ETDRS chart (20/40 to 20/100 Snellen equivalent) at Screening.
5. Fellow eye should not be expected to need any anti-VEGF treatment for the duration of study participation based on Investigator´s decision.
6. Age ≥ 50 years at Screening.
7. Male and female subjects of childbearing potential must be willing to completely abstain or agree to use an appropriate method of contraception from the time of signing the informed consent form and for the duration of study participation through 3 months after the last dose of study drug. See Appendix 17.1 for examples of acceptable contraception. (The investigator and each subject will determine the appropriate method of contraception for the subject during the participation in the study.)
    a. A woman of childbearing potential is any woman, regardless of sexual orientation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).
    b. A man of sexual potential is any man who has not been surgically sterilized (eg, has not undergone bilateral orchiectomy).

8.3.3 Exclusion Criteria

Subjects will be excluded from the study if **1 or more** of the following exclusion criterion is applicable:

1. Any previous intervention, including pharmacological treatment, laser, and/or surgery for wAMD in either eye; (Exception: Vitamin supplementation for AMD prevention). (In case of end stage wAMD in fellow eye where anatomical and functional status diagnosed on Screening, disqualifies subject from intravitreal anti-VEGF treatment according to local medical standards of care, the previous laser photocoagulation or PDT procedure in fellow eye performed for wAMD treatment is allowed). (This

criterion is not applicable for fellow eye, in case of subjects who have only one eye or the fellow eye fulfills additional criteria specified in Section 8.3.4).

2. Any previous vitreoretinal surgery in the study eye for any cause.
3. Any previous IVT treatment, including any anti-VEGF medications, steroids, and/or any other investigational medication in either eye.
4. The use of long-acting steroids, either systemic or intraocular in any eye, in the 18 months before planned initiation of study treatment. (Note: Current or planned Iluvien® [fluocinolone acetonide intravitreal], implantation during the study is prohibited.)
5. Subfoveal fibrosis, subfoveal atrophy, and/or scarring extending > 50% of total lesion area in the study eye as assessed by the investigator at Screening and confirmed by the central reading center prior to Randomization.
6. Choroidal neovascularization in either eye due to non-AMD causes (eg, DME, RVO, ocular histoplasmosis, trauma) as assessed by FA and confirmed by central reading center. (This criterion is not applicable for fellow eye, in case of subjects who have only one eye or the fellow eye optical media opacity prevents from taking the FA/OCT/FP images and the fellow eye fulfills additional criteria specified in Section 8.3.4).
7. Active or recent (within 28 days prior to Randomization) intraocular, extraocular, and periocular inflammation or infection in either eye.
8. History of idiopathic or autoimmune-associated uveitis in either eye.
9. Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
10. Unmedicated intraocular pressure (IOP) ≥ 30 mm Hg at Screening in either eye.
11. Topical ocular corticosteroids administered for ≥ 30 consecutive days in the study eye within 90 days prior to Screening.
12. Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia.
13. Corneal transplant or corneal dystrophy in the study eye.
14. History of rhegmatogenous retinal detachment in the study eye.
15. History of macular hole in the study eye.
16. Retinal pigment epithelial tear or rip involving the macula in the study eye as assessed by FA and confirmed by the central reading center.
17. Current vitreous hemorrhage in the study eye.
18. Subretinal hemorrhage that is ≥ 50% of the total lesion area in the study eye, or if the subretinal hemorrhage involves the fovea is 1 or more DA (≥ 2.54 mm^2) in size in the study eye, as assessed by FA and confirmed by the central reading center.

19. Other intraocular surgery (including cataract surgery) in the study eye within the 3 months prior to Baseline. The yttrium aluminum garnet [YAG] posterior capsulotomy is allowed no later than 4 weeks prior to Screening.
20. Any concurrent intraocular condition in the study eye (eg, cataract or diabetic retinopathy) that, in the opinion of the investigator, could require treatment during the study period to prevent or treat loss of visual acuity.
21. Significant media opacities (including cataract) in the study eye interfering with BCVA assessment or fundus imaging (FA/FP/OCT).
22. Aphakia or absence of the posterior capsule in the study eye, unless it occurred as a result of a YAG posterior capsulotomy in association with prior posterior chamber intraocular lens (IOL) implantation.
23. Presence of advanced glaucoma or optic neuropathy that involves or threatens the central visual field in the study eye (as judged by the investigator).
24. History of glaucoma filtering surgery or ALT in the study eye (Exception: Laser iridotomy and SLT are allowed).
25. Uncontrolled ocular glaucoma or hypertension in the study eye, defined as IOP ≥ 25 mm Hg despite treatment with anti-glaucoma medication.
26. Any previous systemic anti-VEGF treatment (eg, bevacizumab).
27. Contraindication for Lucentis® (hypersensitivity to ranibizumab or to any of the study treatment excipients).
28. Current treatment for active systemic infection.
29. Females who are pregnant, nursing, planning a pregnancy during the study, or of childbearing potential and not using a reliable method of contraception (see Appendix 17.1) and/or not willing to use a reliable method of contraception during their participation in the study. A pregnancy test administered to women of childbearing potential at the Screening Visit (prior to treatment) must be negative for the patient to receive study medication.
30. Participation in another clinical trial within the previous 3 months or any other clinical trial of anti-angiogenic drugs.
31. Reasonable suspicion of other disease or condition that might render the subject at a high risk of treatment complications or otherwise confound interpretation of the study results (as judged by the investigator).
32. *PK subgroup only*: Contraindication for additional blood sampling (as judged by the investigator).

8.3.4 Optic media opacity in one eye (fellow eye)

There may be circumstances where subjects with only one eye or with the fellow eye with opaque optical media preventing from obtaining FA/OCT/FP images, could be considered for study participation. In those cases it is required that: the subject fulfills all study eligibility criteria; fellow eye suffers from visual impairment of BCVA less than 20/200 Snellen equivalent (<50 ETDRS letters); the fellow eye has a known medical history leading to visual impairment; the fellow eye is not expected to be treated during study in any way and the inclusion of the subject in the study is approved by the study Medical Monitor. It must be noted that in such cases the images from the fellow may not be obtained due to optical media opacity, and therefore they do not need to be graded by the central imaging center.

8.3.5 Removal of Subjects From Therapy or Assessments

Subjects may stop study drug for any of the following reasons:

- Subject request (ie, withdrawal of consent)
- Use of nonpermitted concurrent therapy
- Noncompliance with the study drug or study schedule
- Lost to follow-up (defined as at least 2 missed study visits without any medical reason and without any contact with the study subject, despite the documented investigator's efforts)
- Occurrence of adverse events (AEs) not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue
- Investigator request
- Intercurrent illness
- Sponsor request
- Treatment failure, as assessed by the treating investigator

Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

Subjects withdrawing from the study will be encouraged to complete the same final evaluations (ie, End of Treatment/ Week 52) as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The Sponsor has the right to terminate the study at any time in case of serious adverse events (SAEs) or if special circumstances concerning the study drug or the company

itself occur, making further treatment of subjects impossible. In this event, the investigator will be informed of the reason for study termination.

Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study, in subjects or female partners of male subjects, should be immediately confirmed and reported to the investigator, who will then withdraw the pregnant female subject from the study without delay. Subjects should also immediately notify investigators of any pregnancy occurring during the study but which was confirmed only after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

Full details will be recorded on the withdrawal page of the eCRF, or an SAE report will be completed if the subject has completed the study. Details of the procedures to be followed if a pregnancy occurs are provided in Section 10.1.4.2.1.

8.4 Study Medications

In this study, Xlucane 0.5 mg (0.05 mL of 10 mg/mL ranibizumab) will be administered by ophthalmic IVT injection (only) once every 4 weeks (approximately 28 days/ monthly) in the study eye for 12 months in subjects with wAMD who are randomized to receive Xlucane.

Lucentis® 0.5 mg (0.05 mL of 10 mg/mL ranibizumab) will also be administered by ophthalmic IVT injection (only) once every 4 weeks (approximately 28 days/monthly) in the study eye for 12 months in subjects with wAMD who are randomized to receive Lucentis®.

The study medication (Xlucane & Lucentis®, respectively) should be administered only by qualified ophthalmologists experienced in IVT injections.

The IVT injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Approximately 30 minutes following the IVT injection, subjects should also be monitored for elevation in IOP using Goldmann tonometry. Noncontact tonometry is allowed but if IOP is greater than 30 mm Hg, the result should be confirmed by applanation tonometry (eg, Goldmann, Tonopen, Icare) within the next 30 minutes. Subjects should also be monitored onsite for (at least 60 minutes) and instructed to report any symptoms suggestive of endophthalmitis without delay following the injection.

Each vial should only be used for the treatment of a single eye (ie, the study eye). Lucentis® prefilled syringes may be used if needed (eg, if vials are not available).

8.4.1 Identity of Study Medication

Based on the design of this protocol, the Principal Investigator (PI) **MUST** oversee proper separation and delegation of unmasked study roles and responsibilities. To ensure the masking of each randomized subject, the PI must delegate tasks to an unmasked treating investigator and ample unmasked support staff to execute protocol instructions.

Xlucane/ Lucentis® for IVT injection is supplied as single-use vial designed to deliver 0.05 mL of 10 mg/mL ranibizumab. (Lucentis® prefilled syringes may be used if needed [eg, if vials are not available].) The details of the study medications are given in Table 3. All study drug will be imported according to the relevant regulatory requirements. It must be noted that EU-Lucentis® is not FDA approved and is therefore considered an investigational new drug in the United States.

Table 3 Study Medication Details

Study Medication	Dosage Form and Strength	Manufacturer
Xlucane	Supplied as single-use, 2-cc glass vial containing 2.3 mg of proposed ranibizumab biosimilar in 0.23 mL solution designed to deliver 0.05 mL of 10 mg/mL proposed ranibizumab biosimilar, by intravitreal injection.	Xbrane Biopharma Retzius väg 8 SE-171 65 Solna Sweden
EU-licensed Lucentis®	Supplied as single-use, 2-cc glass vial containing 2.3 mg of ranibizumab in 0.23 mL solution designed to deliver 0.05 mL of 10 mg/mL ranibizumab, by intravitreal injection.	Novartis Pharma Stein AG Schaffhauserstrasse 4332 Stein Switzerland

8.4.1.1 Xlucane

Xlucane is a sterile, colorless solution in a single-use glass vial. Xlucane is supplied as a sterile solution in a single-use container designed to deliver a 0.05 mg mL of 10 mg/mL ranibizumab.

Xlucane is for IVT injection only. Keep vial(s) refrigerated at 2º-8ºC (36º-46ºF). Do not freeze. Protect vial(s) from direct sunlight.

There are no human- or animal-derived materials used in the Xlucane DS and Xlucane DP manufacturing process. A Master Cell Bank (MCB) has also been established for the DS manufacturing process.

8.4.1.2 Lucentis® (ranibizumab injection)

Xbrane has made a thorough physiochemical assessment, of Lucentis® to provide information for defining the quality target product profile. The choice of analytical methods is based on FDA Guidance, the EMA guideline, ICH Q5E, advice from the CHMP, and data available in the public domain for the reference product.[5,15,16,17]

The quality target product profile (QTPP), has been determined by analysis and characterization of Lucentis® lots (SL732 expiry date 09-2019; ST601 expiry date 11-2019; SR124 expiry date 01-2020; 3179575 expiry date 01-2020; SJ836 expiry date 06-2019; SK351 expiry date 08-2019; SX444 expiry date 08-2020; and B0014801 expiry date 08-2020). The QTPP is continuously updated with data from sourced and analyzed Lucentis® batches and it will serve as a basis for similarity evaluation of Xlucane GMP batches (manufactured for the phase III clinical study) to Lucentis®.

Lucentis® is a sterile, colorless to pale yellow solution in a single-use prefilled syringe or a single-use glass vial. Lucentis® is supplied as a preservative-free, sterile solution in a single-use container designed to deliver 0.05 mL of 10 mg/mL Lucentis® (0.5 mg dose prefilled syringe or vial) aqueous solution with 10 mM histidine HCl, 10% α,α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5.

Lucentis® should be refrigerated at 2º-8ºC (36º-46ºF). DO NOT FREEZE. Do not use beyond the date stamped on the label. Protect Lucentis® prefilled syringes and vials from light and store in the original container until time of use. Do not open Lucentis® prefilled syringe sealed tray until time of use.

8.4.2 Packaging and Labeling

All investigational products provided by the Sponsor are supplied as individual kits. Study medication will be packaged and labeled at a central packaging facility. All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Each study kit (1x white cartons) will contain either one 2-cc glass vial of Xlucane or one 2-cc glass vial of Lucentis®. The Xlucane and Lucentis® single-use containers will be appropriately labeled. A clinical label will be placed on cartons and rendered tamper evident. Each kit will have unique identification number.

Sites are to dispense the appropriate kit per IWRS information upon subject randomization and at each subsequent visit. Each study kit will have appropriate labeling information according to regulatory requirements.

Site must contact the CRA in case of any questions.

The study medication kits must be stored under refrigeration at 2º-8ºC (36º-46ºF) at all times. The product should be kept in the original carton to protect from light until the time of use. Do Not Freeze. Do not use beyond the expiry date which is stated on the carton/vial. Do not use any kit if it is damaged. Study medication vials should be used once only and any unused portion left in the vials/syringes should not be considered for use.

In case prefilled syringes are used as a contingency, additional documentation will be provided to investigators/sites and regulatory authorities as needed in compliance with country regulatory requirements.

8.4.3 Randomization

The receipt and review of the lab report is necessary before randomizing a subject. Upon confirmation of eligibility for a given subject to participate in the study, a unique randomization number for that subject will be assigned via an IWRS. The IWRS will be accessed immediately by study site personnel after confirmation of the subject's eligibility has been recorded. The randomization number for a given subject will be used to identify the study drug that will be administered to that subject.

The randomization scheme will automatically ensure that the study drug assignment for a given subject is random and that an overall 1:1 ratio of assignments to each of the 2 study drug treatments is approximated.

In addition, the randomization scheme will include the following stratification parameters to ensure balanced distribution of assignment to the 2 treatments: eye color (light iris vs dark iris), geographical region where enrolled and the BCVA letters at Baseline (55 or lower, 56 to 65, 66 or higher). Permuted random blocks within each stratification combination will be used to ensure the 1:1 ratio within each combination.

An independent biostatistician will create the randomization scheme, which will remain unavailable to all other masked individuals, until after study completion and subsequent locking of the study database.

Once a randomization number has been assigned, that number must not be used again for any other subject (eg, when a subject is withdrawn from the study, that subject's randomization number must not be used again for any other subject).

8.4.4 Selection of Doses in the Study

The dose and route of administration for Xlucane will be identical to that of Lucentis®. The recommended dose for Lucentis® is 0.5 mg (0.05 mL of 10 mg/mL ranibizumab) given as a single IVT injection every 4 weeks/monthly.

8.4.5 Selection and Timing of Dose for Each Subject

Subjects will be randomized by IWRS to receive 13 doses of either Xlucane or Lucentis® in the study eye, once every 4 weeks/monthly over 52 weeks. Proper aseptic injection technique should always be used when administering the IVT injections.

The minimum interval between 2 consecutive injections/doses should not be less than 4 weeks minus the visit window interval of the scheduled visit.

For example, Visit 3 (Week 2) to Visit 5 (Week 8) allow -2 day window, therefore the minimum interval between two consecutive injections between these visits can be 26 days.

Visit 6 (Week 12) to Visit 16 (Week 52) allow a -5 day window, therefore the minimum interval between two consecutive injections between these visits can be 23 days.

If a visit is outside the protocol defined visit window, should be considered as 'Late Visit or Out Of Window visit' and must be entered in the CRF as a protocol deviation (PD). Visits that are delayed for more than 14 days from the scheduled visit date, should be considered as 'missed' visits. The next visit should be scheduled in consideration of the protocol defined interval as much as possible and as per medical judgement of the investigator.

The study is expected to complete no later than one year or 12 months (+7 days) from the date of the last patient randomized into the study. This will be considered as the study end date and will be communicated once the last patient has been randomized.

Patient visits should be scheduled as per the protocol and within stipulated visit windows to ensure all patients complete the study and have the EOT (Visit 16) scheduled within the study end date.

If due to any reason it is not possible to complete all remaining visits for any patient within the study end date, an early termination visit must be scheduled and EOT procedures completed as per Section 8.1.1

8.4.6 Masking

Due to the study objectives, the identity of the study treatment assignments will not be known to subjects. Additionally, except for the site designees who are unmasked for the purpose of preparing and administering the study treatments, other research staff will also be masked. Masked study team members will perform efficacy assessments.

There will be no overlap between the masked and unmasked staff members. Access to the randomization codes will be strictly controlled.

The study medications will have caps/stoppers of differing colors and length; however, they will be packaged and labeled in identical outer cartons. Therefore, sites must have the following unmasked team members and their designated back-ups:

- Unmasked personnel to prepare syringes for IVT injection and provide to the unmasked injector, and complete study drug accountability.

- Unmasked injector to perform injection and safety assessments immediately after the injections (but not to participate in the efficacy assessments).

- There will also be masked and unmasked clinical research associates (CRAs) available for the same site. Unmasked CRAs will monitor study drug accountability.

Randomization information for any particular subject may be made available to the investigator only in the event of a medical emergency or an AE that necessitates identification of the study drug for the welfare of that participant. Masking codes should only be broken in emergency situations for reasons of participant safety. Whenever possible, the investigator(s) should always consult with the medical monitor and the Sponsor prior to breaking the masking.

When the masking code is broken, the reason must be fully documented. The reporting requirements for unmasking are the same for reporting an SAE. See also Section 10.1.4.2.1 Serious Adverse Events.

When all subjects have completed their 6-month assessments, an *unmasked* analysis of efficacy (ie, equivalence) and safety endpoints as well as PK and immunogenicity will be performed. The aim of the *unmasked* analysis is to initiate the submission of the application for marketing authorization as agreed with the European Medicines Agency. This analysis will not affect the further conduct of the study.

8.4.7 Prior and Concomitant Therapy

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding electronic data capture form (eg, eCRF) along with the reason the medication was taken.

Drug interaction studies have not been conducted with Lucentis®.

During the study, subjects may **not** receive any standard or investigational agents for treatment of their AMD in the study eye other than study treatment until they have completed the final or early termination visit assessments. This includes medications administered locally (eg, IVT by juxtascleral or periorbital routes), as well as those administered systemically with the intent of treating the fellow eye. Vitamins and dietary supplements are allowed.

In case the fellow eye develops AMD or other medical condition during the study, it is expected that the fellow eye may be treated locally (eg, IVT by juxtascleral or periorbital routes), with standard of care therapy per local clinical practice first.

If anti-VEGF therapy is necessary, it is recommended to start it no earlier than after the last PK assessment and to perform the fellow eye IVT procedures in the interval between the study drug injections.

Any other medications that are considered necessary for the subject's welfare and that are not expected to interfere with the evaluation of the study medication may be given at the discretion of the Investigator, with the **exceptions** noted below:

- Any systemic treatment or ocular treatment with an investigational agent
- Systemic anti-VEGF therapy

If the permissibility of any medication/treatment is in question, please contact the medical monitor. Ocular surgery to the study eye should be delayed until the subject completes the study, if possible and safe.

8.4.7.1 Rescue Medication

No rescue treatment is allowed. Any subject who is in need of rescue treatment, in the judgement of the Principal Investigator, may be removed from the study. Early termination procedures will be completed as per Section 8.1.1.

8.4.8 Known Contraindications

8.4.8.1 Ocular or Periocular Infections

Lucentis® is contraindicated in patients with ocular or periocular infections.

8.4.8.2 Hypersensitivity

Lucentis® is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in Lucentis®. Hypersensitivity reactions may manifest as severe intraocular inflammation.

8.4.9 Warnings and Precautions

Subjects should be monitored prior to and following each injection (for at least 60 minutes) to permit any early treatment and appropriate management if needed.

8.4.9.1 Endophthalmitis and Retinal Detachments

IVT injections, including those with Lucentis®, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering study medication. In addition, patients should be monitored following the injection to permit early treatment should an infection occur.

Subjects should also be advised that in the days following study medication administration, they are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the subject to seek immediate care from the local investigator (ie, an ophthalmologist).

8.4.9.2 Increases in Intraocular Pressure

Increases in IOP have been noted both before and after injection (at 60 minutes) while being treated with Lucentis®. Monitor IOP prior to and following IVT injection with study medication and manage appropriately.

8.4.9.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the Lucentis® clinical trials, there is a potential risk of ATEs following IVT use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The ATE rate in the 3 controlled wAMD studies (AMD-1, AMD-2, and AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg Lucentis® compared with 1.1% (5 of 441) in patients from the control arms. In the second year of studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of Lucentis®-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of Lucentis® used adjunctively with verteporfin photodynamic therapy [PDT), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg Lucentis® compared to 1.1% (5 of 435) in patients in the control arms (odds ratio: 2.2 [95% CI: 0.8,7.1]).

8.4.10 Treatment Compliance

All study drug doses will be administered by trained staff at study centers.

As study drug is administered in the clinic, treatment compliance will be overseen and documented by the investigator and study staff using the treatment records (and drug accountability records). At a minimum, date, time, and dose should be accurately recorded in real-time to confirm that each dose of study treatment was administered per the protocol.

9 TIMING OF STUDY PROCEDURES

The planned study assessments are in Section 8.1.1 and 8.1.2.

The BCVA will be quantified using the ETDRS method. The BCVA assessment will be performed by qualified study personnel following manifest refraction and precede any examination requiring contact with the study eye.

It is recommended that IOP is measured prior to pupil dilation as the IOP values may be influenced by the pupil dilation. Also the elevated IOP may alert the investigator that the pupil should not be dilated and additional examinations may have to be undertaken. Every effort should be made to have IOP measurements performed at approximately the same time of day and using the same type of instrument for a given subject throughout the study, whenever possible. For the pre-injection IOP measurements have to be performed using the Goldmann tonometry method.

In case the sequence of procedures is different at any site due to their local SOPs, and IOP measurement is not performed as above, then the process should be kept the same for all study subjects at the site. However even in such cases the protocol requirement of IOP measurement using Goldmann applanation tonometer and prior to injection procedure must be followed.

It also recommended that at the visits where both IOP measurement and FA is performed- IOP measurement is done first followed by fluorescein angiography test. It is expected that between IOP measurement and FA test photographs taken, there should be adequate time to wash-out all topical fluorescein.

Subjects should be monitored onsite prior to and following each injection (for at least 60 minutes) to permit any early treatment and appropriate management if needed. Investigators may use their clinical judgement to determine if any additional IOP lowering medications or any unscheduled assessments may be needed during the study.

Subjects should also be advised that in the days following study medication administration, they are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the subject to seek immediate care from the study doctor or an ophthalmologist.

9.1 Pre-treatment

9.1.1 Screening Visit (Visit 1)

- Subjects will provide written informed consent before any study-related procedures may be performed.
- Assess for eligibility (against the inclusion and exclusion criteria).
- Collect full medical history, historical disease data, diagnostic information, and concomitant illnesses/diseases, adverse events (including Baseline events), and concomitant medications.
- Record demographic data, such as ethnic origin, date of birth, and sex.
- Perform a physical examination (PE), including body mass index (height and weight measured). A PE will consist of a routine evaluation of organ systems (including head, ears, eyes, nose, throat, neck, cardiovascular, pulmonary, abdomen, skin, extremities, neurological, lymph nodes, and musculoskeletal).

  - At the Screening Visit, the PE will include the collection of the subject's eye color (ie, light iris or dark iris).
- Perform BCVA assessment using the ETDRS at 4 meters, including manifest refraction.
- Perform FA and OCT in both eyes, in which results should be submitted to and confirmed by the central reading center *prior* to Randomization.
- Perform CFP in both eyes.
- Perform SLE of the anterior segment in both eyes.
- Perform dilated fundus examination of the posterior segment in both eyes.
- Measure IOP in both eyes. Goldmann tonometry should be used for pre-injection IOP.
- Record vital signs including blood pressure and heart rate. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.
- Collect blood sample for hematology and clinical chemistry tests.
- For females of childbearing potential only, collect urine sample for pregnancy test.
- Record any Baseline events and concomitant medications.

9.2 Treatment Period

9.2.1 Day 0 Visit (Visit 2) - Baseline

The Day 0 Visit (Visit 2) will take place after the Screening Visit (Visit 1). The following procedures will be performed before injection:

- Reassess/confirm eligibility against the inclusion and exclusion criteria.
- Confirm receipt of the central reading center's interpretation(s) of FA and OCT from Screening.
- Perform BCVA assessment using the ETDRS at 4 meters, including manifest refraction.
- Perform SLE of the anterior segment in both eyes.
- Perform dilated fundus examination of the posterior segment in both eyes.
- Measure IOP in both eyes, using the Goldmann tonometry method.
- Perform OCT in both eyes.
- Record vital signs including blood pressure and heart rate. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.
- Collect blood sample(s) for immunogenic (ie, anti-ranibizumab antibodies and NAb) evaluations.
- ***PK subgroup only***: Collect additional blood sample(s) for PK evaluations ≤ 60 minutes before the first dose.
- Record any changes in adverse events and concomitant medications.

- Randomization will take place for eligible subjects, and each will receive a subject number. The receipt and review of the lab report is necessary before randomizing a subject.

When all the above Day 0 (Visit 2) procedures have been performed/confirmed, the study drug will be administered as an IVT injection to the subject in the study eye only. The following shall be performed after injection:

- Monitor the subject (after injection) for at least 60 minutes.
- Measure IOP in the study eye. After IVT injection (eg, 30 minutes post injection), non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer) within the next 30 minutes.
- Record any AEs, including any ISRs.

9.2.1.1 Day 1 (Visit 2b) for PK subgroup ONLY

Only for the PK subgroup of subjects who agree to additional PK evaluations. At 23 hours (± 60 minutes) after the first dose, subgroup subjects will be asked to return to the site for the following:

- Record any changes in adverse events and concomitant medications.
- Perform SLE of the anterior segment in the study eye.
- Measure IOP in the study eye by Goldmann tonometry method. Non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer) within the next 30 minutes.
- Adverse event reporting, if any.
- Additional blood sample(s) to be collected for PK evaluations.

9.2.2 Week 2/ Visit 3 (± 2 days)

The Week 2 Visit will take place 14 days/ 2 weeks (± 2 days) after Visit 2. The following procedures will be performed:

- Record any changes in adverse events and concomitant medications.
- Perform BCVA assessment using the ETDRS at 4 meters, including manifest refraction.
- Perform OCT in the study eye.
- Record any AEs.

9.2.3 Week 4/ Visit 4 (± 2 days)

The Week 4 Visit will take place 14 days/ 2 weeks (± 2 days) after Visit 3. The following procedures will be performed before injection:

- Record any AEs and any changes in concomitant medication.
- Perform BCVA assessment using the ETDRS at 4 meters, including manifest refraction.
- Perform OCT in the study eye.
- Perform SLE of the anterior segment in the study eye.
- Measure IOP in the study eye by Goldmann tonometry method.
- Perform dilated fundus examination of the posterior segment in the study eye.
- Record vital signs including blood pressure and heart rate. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.
- Collect blood sample for hematology and clinical chemistry tests.
- Collect blood sample(s) for immunogenic (ie, anti-ranibizumab antibodies and NAb) evaluations.

When all of these procedures have been performed, the study drug will be administered. Immediately, after the injection, the following shall be performed:

- Measure IOP in the study eye. After IVT injection (eg, 30 minutes post injection), non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer) within the next 30 minutes.
- Monitor the subject for any signs or symptoms at least 60 minutes after the injection.
- Record any AEs, including any ISRs.

9.2.4 Week 8/ Visit 5 (± 2 days)

The Week 8 Visit will take place 28 days/ 4 weeks (± 2 days) after Visit 4. The following procedures will be performed before injection:

- Record any AEs and any changes in concomitant medication.
- Perform BCVA assessment using the ETDRS at 4 meters, including manifest refraction.
- Perform OCT in the study eye.
- Perform SLE of the anterior segment in the study eye.
- Measure IOP in the study eye by Goldmann tonometry method.
- Perform dilated fundus examination of the posterior segment in the study eye.

- Record vital signs including blood pressure and heart rate. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.
- Collect blood sample for hematology and clinical chemistry tests.
- Collect blood sample(s) for immunogenic (ie, anti-ranibizumab antibodies and NAb) evaluations.

When all of these procedures have been performed, the study drug will be administered. Immediately, after the injection, the following shall be performed:

- Measure IOP in the study eye. After IVT injection (eg, 30 minutes post injection), non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer) within the next 30 minutes.
- Monitor the subject for at least 60 minutes after the injection.
- Record any AEs, including any ISRs.

9.2.5 Week 12/ Visit 6 (± 5 days)

The Week 12 Visit will take place 28 days/ 4 weeks (± 5 days) after Visit 5. The following procedures will be performed before injection:

- Record any AEs and any changes in concomitant medication.
- Perform BCVA assessment using the ETDRS at 4 meters, including manifest refraction.
- Perform OCT in the study eye.
- Perform SLE of the anterior segment in the study eye.
- Measure IOP in the study eye by Goldmann tonometry method.
- Perform dilated fundus examination of the posterior segment in the study eye.
- Record vital signs including blood pressure and heart rate. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.
- Collect blood sample for hematology and clinical chemistry tests.
- Collect blood sample(s) for immunogenic (ie, anti-ranibizumab antibodies and NAb) evaluations.

When all of these procedures have been performed, the study drug will be administered. Immediately, after the injection, the following shall be performed:

- Measure IOP in the study eye. After IVT injection (eg, 30 minutes post injection), non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with

Goldmann, Tonopen or ICare (applanation tonometer) within the next 30 minutes.
- Monitor the subject for at least 60 minutes after the injection.
- Record any AEs, including any ISRs.

9.2.6 Week 16/ Visit 7 (± 5 days)

The Week 16 Visit will take place 28 days/ 4 weeks (± 5 days) after Visit 6. The following procedures will be performed before injection:

- Record any AEs and any changes in concomitant medication.
- Perform BCVA assessment using the ETDRS at 4 meters, including manifest refraction.
- Perform OCT in the study eye.
- Perform SLE of the anterior segment in the study eye.
- Measure IOP in the study eye by Goldmann tonometry method.
- Perform dilated fundus examination of the posterior segment in the study eye.
- Record vital signs including blood pressure and heart rate. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.
- ***For subjects with any prior or present signs of intraocular inflammation:*** Collect blood sample(s) for immunogenic evaluations.

When all of these procedures have been performed, the study drug will be administered. Immediately, after the injection, the following shall be performed:

- Measure IOP in the study eye. After IVT injection (eg, 30 minutes post injection), non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer) within the next 30 minutes.
- Monitor the subject for at least 60 minutes after the injection.
- Record any AEs, including any ISRs.

9.2.7 Week 20/ Visit 8 (± 5 days)

The Week 20 Visit will take place 28 days/ 4 weeks (± 5 days) after Visit 7. The following procedures will be performed before injection:

- Record any AEs and any changes in concomitant medication.
- Perform BCVA assessment using the ETDRS at 4 meters, including manifest refraction.
- Perform OCT in the study eye.
- Perform SLE of the anterior segment in the study eye.

- Measure IOP in the study eye by Goldmann tonometry method.
- Perform dilated fundus examination of the posterior segment in the study eye.
- Record vital signs including blood pressure and heart rate. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.
- Collect blood sample(s) for immunogenic (ie, anti-ranibizumab antibodies and NAb) evaluations.

When all of these procedures have been performed, the study drug will be administered. Immediately, after the injection, the following shall be performed:

- Measure IOP in the study eye. After IVT injection (eg, 30 minutes post injection), non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer) within the next 30 minutes.
- Monitor the subject for at least 60 minutes after the injection.
- Record any AEs, including any ISRs.

9.2.7.1 Week 20 (Visit 8b) for PK subgroup ONLY

Only for the PK subgroup of subjects who agree to additional PK evaluations. At 23 hours (± 60 minutes) after the Visit 8 dose, subgroup subjects will be asked to return to the site for the following:

- Record any changes in adverse events and concomitant medications.
- Perform SLE of the anterior segment in the study eye.
- Measure IOP in the study eye by Goldmann tonometry method. Non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer) within the next 30 minutes.
- Adverse event reporting, if any.
- Additional blood sample(s) to be collected for PK evaluations.

9.2.8 Week 24/ Visit 9 (± 5 days)

The Week 24 Visit will take place 28 days/ 4 weeks (± 5 days) after Visit 8. The following procedures will be performed before injection:

- Record any AEs and any changes in concomitant medication.
- Perform BCVA assessment using the ETDRS at 4 meters, including manifest refraction.
- Perform FA (images of both eyes should be sent to CRC, grading of study eye only will be done by CRC)

- Perform OCT in the study eye.
- Perform CFP in the study eye.
- Perform SLE of the anterior segment in the study eye.
- Measure IOP in the study eye by Goldmann tonometry method.
- Perform dilated fundus examination of the posterior segment in the study eye.
- Record vital signs including blood pressure and heart rate. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.
- Collect blood sample for hematology and clinical chemistry tests.
- Collect blood sample(s) for immunogenic (ie, anti-ranibizumab antibodies and NAb) evaluations.

When all of these procedures have been performed, the study drug will be administered. Immediately, after the injection, the following shall be performed:

- Measure IOP in the study eye. After IVT injection (eg, 30 minutes post injection), non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer) within the next 30 minutes.
- Monitor the subject for at least 60 minutes after the injection.
- Record any AEs, including any ISRs.

9.2.9 Week 28 to Week 48 (every 28 days or every 4 weeks; monthly) [Visits 10 to 15] (± 5 days)

The monthly (ie, every 28 days or every 4 weeks) Week 28 to Week 48 Visits (Visits 10 to 15) will take place 28 days/ 4 weeks (± 5 days) after the prior visit(s). The following procedures will be performed before injection at each visit:

- Record any AEs and any changes in concomitant medication.
- Perform BCVA assessment using the ETDRS at 4 meters, including manifest refraction.
- Perform OCT in the study eye.
- Perform SLE of the anterior segment in the study eye.
- Measure IOP in the study eye by Goldmann tonometry method.
- Perform dilated fundus examination of the posterior segment in the study eye.
- Record vital signs including blood pressure and heart rate. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.
- **For Week 36 (Visit 12) ONLY:** Collect blood sample for hematology and clinical chemistry tests. Collect blood sample(s) for immunogenic (ie, anti-ranibizumab antibodies and NAb) evaluations.

- ***For subjects with any prior or present signs of intraocular inflammation:*** Collect additional blood sample(s) for immunogenic evaluations.

When all of these procedures have been performed, the study drug will be administered. Immediately, after the injection, the following shall be performed (at each visit):

- Measure IOP in the study eye. After IVT injection (eg, 30 minutes post injection), non-contact tonometry may be used, but in the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer) within the next 30 minutes.
- Monitor the subject for at least 60 minutes after the injection.
- Record any AEs, including any ISRs.

9.2.10 Week 52/ End-of-treatment or Early Withdrawal Visit/ Visit 16 (± 5 days)

The End-of-treatment Visit (Week 52/ Visit 16) will take place 28 days (± 5 days) after the last injection of study drug *or* at the time of early discontinuation/withdrawal (if applicable). The following procedures will be performed:

- Record any AEs and any changes in concomitant medication since the previous visit.
- Perform a PE. A PE will consist of a routine evaluation of organ systems (including head, ears, eyes, nose, throat, neck, cardiovascular, pulmonary, abdomen, skin, extremities, neurological, lymph nodes, and musculoskeletal). At the Week 52/End of Treatment Visit, the PE will also include a query of the patient to determine if changes in his/her physical condition have occurred since the PE at Screening.
- Perform BCVA assessment using the ETDRS at 4 meters, including manifest refraction.
- Perform FA(images of both eyes should be sent to CRC, grading of study eye only will be done by CRC).
- Perform OCT in the study eye.
- Perform CFP in the study eye.
- Perform SLE of the anterior segment in the study eye.
- Perform dilated fundus examination of the posterior segment in the study eye.
- Record vital signs including blood pressure and heart rate. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.
- Collect blood sample for hematology and clinical chemistry tests.
- Collect blood sample(s) for immunogenic (ie, anti-ranibizumab antibodies and NAb) evaluations.

- For females of childbearing potential only, collect urine sample for pregnancy test.
- Measure IOP in **both** eyes, using the Goldmann tonometry method. In the event IOP is greater than 36 mm Hg, it is recommended to perform another IOP measurement with Goldmann or Tonopen or ICare (applanation tonometer).

9.3 Duration of Treatment

The duration of treatment will be approximately 52 weeks, including follow-up. Pre-treatment screening assessments shall occur within 21 days before the start of treatment.

10 EFFICACY, PHARMACOKINETICS, IMMUNOGENICITY, AND SAFETY VARIABLES

The planned schedule of assessments is in Section 8.1.1. The planned schedule of correlative assessments is in Section 8.1.2.

10.1 Efficacy, Pharmacokinetics, Immunogenicity, and Safety Measurements Assessed

10.1.1 Efficacy Variables

The following methods will be used for assessing and recording efficacy.

10.1.1.1 Best Corrected Visual Acuity Assessment

- BCVA will be assessed at all visits by ETDRS and the following:
  - Mean change in BCVA
  - Percentage of subjects who lose <15 letters
  - Percentage of subjects who gain ≥15 letters

10.1.1.2 Central Foveal Thickness

- CFT will be assessed at all visits by OCT.

10.1.1.3 Morphological Changes in the Neovascular Membrane

- Changes in the size and/or number of intraretinal cystoid space (cysts), subretinal fluid, and retinal pigment epithelium detachments measured by qualitative morphology-based OCT data (in the study eye).

10.1.1.4 Choroidal Neovascularization

- Leakage and size from the choroidal neovascularization.

10.1.2 Pharmacokinetic Variables

10.1.2.1 Pharmacokinetic Assessment(s)

- One or more PK variables based on plasma concentration of ranibizumab (primarily expected C_{max}).

10.1.3 Immunogenicity Variables

- Immunogenicity (ie, anti-ranibizumab antibodies and NAb)

10.1.4 Safety Variables

10.1.4.1 Safety Assessments

- AEs, as detailed in the following section
- ISRs (including endophthalmitis, vitritis, and haemorrhage)
- Hematology and clinical chemistry (including analysis of alanine aminotransferase also known as serum glutamic-pyruvic transaminase [ALT/SGPT] and aspartate aminotransferase also known as serum glutamic-oxaloacetic transaminase [AST/SGOT] and creatinine) as detailed in the following section.

10.1.4.2 Adverse Events

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the subject a nonleading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?” AEs should be reported on the appropriate page of the eCRF.

Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

Mild:	An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
Moderate:	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
Severe:	An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug. Causality should be assessed using the categories presented in the following table:

Unrelated:	Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
Related:	Clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

Action Taken

The investigator will describe the action taken with the study treatment in the appropriate section of the eCRF, as follows:

- Dose not changed
- Study drug permanently withdrawn
- Study drug temporarily interrupted
- Not applicable
- Unknown

Other Specific Treatment of Adverse Events

The investigator will describe the other treatment(s) for the AE/SAE in the appropriate section of the eCRF, as follows:

- None
- Concomitant medication

- Other, specify.

Follow-up of Adverse Events

All investigators should follow up with subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

Subjects should be followed up for 28 days (± 5 days) after receiving the last dose of study drug, and any AEs that occur during this time should be reported according to the procedures outlined above.

Documentation and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study (from the time of receiving written informed consent to 28 days [± 5 days] of receiving last dose of study drug) must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of "serious" or "not serious"
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

10.1.4.2.1 Serious Adverse Events

Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and [are] SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or PE page of the eCRF).

- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

Reporting of Serious Adverse Events

Any SAE must be reported by the investigator if it occurs during the clinical study, from the time of receiving written informed consent to 28 days (± 5 days) of receiving last dose of study drug, whether or not the SAE is considered to be related to the investigational product. All SAEs must be reported by the investigator within 24 hours of becoming aware of the SAE. An SAE report consists of the SAE form, the medical history form, and the concomitant medication form. A copy of these forms must be sent **within 24 hours** of becoming aware to the attention of the product safety scientist at:

Fax No.: 001-877-464-7787
e-mail: SafetyReporting@SyneosHealth.com

The investigator should not wait to receive additional information to document fully the event before notification of an SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

The Sponsor and/or Syneos Health will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects or the conduct of the study or alter the independent ethics committee (IEC)/institutional review board (IRB) approval/favorable opinion of the study. In addition, Syneos Health, on behalf of the Sponsor, will expedite the reporting to all concerned investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Details of the procedures to be followed if a pregnancy occurs are provided as follows.

Pregnancy Reporting

Pregnancies occurring in female subjects and female partners of male subjects during the study (from the time of first dose of study drug to 3 months after the last dose of study drug) should be reported by the investigator using the Pregnancy Report Form via email and fax (Section 10.1.4.2.1) immediately or within 24 hours of acknowledgement.

The investigator will (1) notify the subject's physician that the subject was being treated with an investigational drug (Xlucane) or approved control (Lucentis®/ranibizumab) and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to the Sponsor.

If a female partner of a male study subject becomes pregnant during the study, the investigator will also notify the Sponsor immediately after the pregnancy is confirmed. The investigator will (1) obtain a consent from the female partner for pregnancy follow-up and (2) follow the progress of the pregnancy to term. The investigator should document the outcome of the pregnancy and provide a copy of the documentation to the Sponsor.

Any pregnancy will be followed to term and the status of mother and child will also be reported to the Sponsor after delivery. Newborns should be followed up for at least 30 days for any potential congenital anomalies.

Any SAE experienced during pregnancy must be reported on the SAE Report Form. Spontaneous abortions should always be reported as SAEs.

10.1.4.2.2 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (eg, investigator's brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

All suspected unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The Sponsor and/or Syneos Health shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB within 7 days after knowledge by the Sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC/IRB within 15 days after knowledge by the Sponsor of such a case. All investigators should follow up SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Post

study SUSARs that occur after the subject has completed the clinical study must be reported by the investigator to the Sponsor.

10.1.4.2.3 Clinical Laboratory Evaluation

The hematology and clinical chemistry laboratory analyses will be performed at a central laboratory (Q^2 Solutions). Reference ranges will be supplied and used by the investigator to assess the laboratory data for clinical significance and pathological changes. The following laboratory safety tests will be performed at Screening, during treatment, and at the end of treatment. **Results from Screening visit must be reviewed by the investigator before patient is randomized.**

Hematology

The following will be evaluated: hemoglobin, hematocrit, white blood cell (WBC) count (total and differential), red blood cell (RBC) count, platelet count, mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC).

Clinical Chemistry

The following will be evaluated: creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, total cholesterol, triglycerides, calcium, and phosphorus.

10.1.4.2.4 Other Laboratory Variables

Screening for pregnancy will be performed (urine beta-human chorionic gonadotropin [β-HCG]) at Screening, for females only. Kits will be provided by the central laboratory.

Blood samples will be collected for PK and immunogenic (ie, anti-ranibizumab antibodies and NAb) testing, at Baseline, during treatment and, at the end of treatment; PK and immunogenicity assessments will be done by Syneos Health laboratory.

10.1.4.2.5 Vital Signs

Vital signs (blood pressure and heart rate) will be recorded at Screening, during treatment (except Week 2 [Visit 3]), and at the end of treatment in a standardized manner. Systolic and diastolic blood pressure and pulse rate will be measured after patients have been at rest (seated) for at least 5 minutes.

10.1.4.2.6 Ophthalmological Examination

At Screening, during treatment, and at the end of treatment, an ophthalmological examination will be performed. Any changes from Screening to end of treatment/study will be recorded.

IOP measurements will be conducted at all visits (except Visit 3 [Week 2]).

10.1.4.2.7 Other Safety Assessments

A PE will be performed at Screening (with body mass index) and at the End of Treatment/Early Termination Visit. A PE will consist of a routine evaluation of organ systems (including head, ears, eyes, nose, throat, neck, cardiovascular, pulmonary, abdomen, skin, extremities, neurological, lymph nodes, and musculoskeletal). At the Week 52/End of Treatment Visit, the PE will also include a query of the patient to determine if changes in his/her physical condition have occurred since the PE at Screening.

10.1.5 Appropriateness of Measurements

The efficacy and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

10.1.6 Drug Concentration Measurements

The plasma levels of ranibizumab will be evaluated at Baseline, on Day 1 at 23 hours (± 60 minutes) after the first dose, and at steady-state at Week 20 at 23 hours (± 60 minutes) after the sixth dose to detect any notable differences in systemic exposure between the 2 products, Xlucane and Lucentis®. The assay will be developed with sufficient sensitivity to be able to detect the differences at such low plasma levels.

10.2 Stopping Rules

The estimated duration of the study is contingent on safety and the number of injections evaluated. The study will be stopped in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship that would render continuation of the study unjustifiable. Study treatment will be halted, and the appropriate individuals from the Sponsor and Syneos Health will determine if the study should be terminated for any safety concerns.

The Sponsor may also end the study for administrative reasons.

Should the study be terminated prematurely, the Sponsor will provide written notification to all investigators and regulatory authorities specifying the reason(s) for early termination. The investigator must inform the Independent Ethics Committees

(IECs)/Institutional Review Board (IRB) promptly and provide the reason(s) for the termination. Previously dosed subjects will be assessed through all planned study visits.

11 STATISTICAL METHODS

11.1 General Considerations

Before unmasking the data for subjects included in this trial for the interim analysis, a statistical analysis plan (SAP), which will provide the technical details of the statistical analyses outlined here, will be prepared, finalized, and signed.

In general, data will be summarized by means of summary statistics. Continuous data will be presented as the number of observations, mean, standard deviation (SD), minimum, Q1, median, Q3, and maximum. Categorical data will be presented as counts and percentages. The data will be presented for each treatment group by visit. All data summarized will be presented in patient listings.

11.2 Analysis Sets

The **Enrolled Set** will consist of all patients enrolled in the study, ie, all patients who signed the informed consent form. This set will be used for summaries of disposition for all patients enrolled.

The **Full Analysis Set (FAS)** will include all patients for whom treatment regimen has been assigned. The FAS will be used for all analyses of efficacy endpoints. Patients will be analyzed according to the randomized treatment. Different strategies will be applied for handling data following intercurrent events (IE) (see Section 11.3.3.1). Unless stated otherwise, all subject listings will be presented using this set.

The **Safety Set (SS)** will include all patients who receive at least 1 dose of study drug. Patients will be analyzed according to treatment received. The SS will be used for analyses of safety endpoints.

The **Pharmacokinetic Set (PKS)** will include patients in the SS who have at least 1 postdose evaluable plasma ranibizumab concentration value. Patients will be analyzed according to treatment received. For cases in which a PD is identified to potentially affect plasma level, the identified concentration values will be flagged as non-evaluable and excluded from the analyses.

A blinded data review meeting (BDRM) will be held prior to database lock and unblinding of the interim analysis to agree upon the PKS, PK samples/parameters to be included in the analyses, and any data to be excluded from the FAS analyses due to IEs. All patients for whom data were impacted due to the COVID-19 pandemic will be identified as well as the data points affected. Such data will be recorded as a protocol deviation and will be assessed at the BDRM along with all other PDs with respect to

potential to affect the efficacy results. Attendees will include appropriate individuals from the Sponsor and Syneos Health. Details regarding the data to be reviewed at the meeting will be documented in the SAP and a separate BDRM plan.

11.3 Planned Analyses

11.3.1 Patient Disposition

Screen failures (with reasons), randomization, and dosing with study drug will be summarized for the Enrolled Set.

Study completion and early termination (with reasons) as well as attendance at each visit will be summarized for the FAS.

Inclusion in each analysis set will be summarized, along with reasons for exclusion.

11.3.2 Demographic and Other Baseline Characteristics

Demographics and key baseline characteristics will be summarized.

11.3.3 Efficacy Endpoints

11.3.3.1 Primary Efficacy Endpoint

The primary endpoint of the study is the change in BCVA letters at Week 8 compared to Baseline using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol for the study eye.

Due to the increase in protocol deviations related to the COVID-19 pandemic and following the recent ICH E9 (R1) Addendum[19], the primary and secondary estimands of the study related to efficacy are detailed in this section. These estimands were not explicitly defined in earlier versions of the protocol (see Section 18) but the estimand framework provides a more comprehensive approach to show the impact of Covid-19 in the analysis[20]. The presence of such IEs in a biosimilarity study may introduce potential bias and a dilution of treatment differences (i.e. increasing the chance of proving equivalence), as such the ordering of the estimands described below (in terms of primary and secondary) are chosen.

For the primary estimand, the scientific question of interest is the between-group difference (Xlucane v Lucentis®) in the mean change from baseline in BCVA letter score at Week 8 in patients who fulfil the study eligibility criteria, have no IEs up to and including the Week 8 BCVA assessment and complete 8 weeks of treatment of study drug (given as a single ophthalmic IVT injection every 4 weeks/monthly).

IEs are defined as:

- Early discontinuation of study treatment. Subsequent missing data (missing or collected) will be imputed in the analysis with a hypothetical strategy.
- Non-adherence with the protocol which would potentially affect the efficacy results. Such identified data at the BDRM (missing or collected) will be imputed in the analysis with a hypothetical strategy.
- Start of anti-VEGF treatment in the fellow eye. Subsequent data (missing or collected) will be imputed in the analysis with a hypothetical strategy.

The secondary estimand of the study for the primary endpoint will use alternate methods of handling data following IEs compared to the primary estimand. This approach will use a treatment policy with respect to IEs such that any data collected following the IE will be used in the analysis. So the scientific question of interest is the between-group difference (Xlucane v Lucentis®) in the mean change from baseline in BCVA letter score at Week 8 in patients who fulfil the study eligibility criteria and complete 8 weeks of treatment of study drug, regardless of any other IEs. However, because the study design does not plan for assessments following early treatment discontinuation, a true treatment policy strategy is not possible to apply. As such, any missing data following early treatment discontinuation will be imputed using a hypothetical strategy.
Assumptions for imputing missing data due to IEs and analysis methods for each estimand are detailed in Section 11.3.7.

The change in BCVA letters at Week 8 compared to Baseline using the ETDRS protocol will be analyzed using a mixed model for repeated measures (MMRM). An MMRM approach will be fitted with geographical region of the country where enrolled, visit, eye color (light iris vs dark iris), treatment, and treatment-by-visit interaction as fixed effects, with the baseline BCVA letters and baseline BCVA letters-by-visit interaction as covariates. The treatment differences from the model at Week 8 will be evaluated and a 95% or 90% two-sided CI for the least squares mean difference between groups will be calculated. To prove the 2 products to be biosimilar, the confidence limits for this difference have to be within the equivalence margin of ± 3.5 letters for the primary estimand. The secondary estimand analysis will be supportive of the primary estimand analysis.

11.3.3.2 Secondary Efficacy Endpoints

The same properties of the primary and secondary estimand of the primary endpoint will be considered for each of the secondary endpoints. For responder analyses, the between-group difference in proportions (Xlucane v Lucentis®) will be of interest.

The following continuous secondary endpoints will be analyzed in a similar fashion to the primary efficacy endpoint:

- Change in BCVA letters at Week 4, Week 12, Week 16, Week 24, Week 36 and Week 52 compared to Baseline using the ETDRS protocol
- Change in total size of choroidal neovascular leakage area in the study eye measured by FA at Week 24 and Week 52 compared to Baseline
- Change in total size of choroidal neovascularization in the study eye measured by FA at Week 24 and Week 52 compared to Baseline
- Change in Central Foveal Thickness (CFT) in the study eye measured by OCT at Week 2, Week 4, Week 8,Week 16, Week 24, Week 36 and Week 52 compared to Baseline
- Changes in the size and/or number of intraretinal cystoid space (cysts), subretinal fluid, and retinal pigment epithelium detachments in the study eye measured by qualitative morphology-based OCT

The following secondary endpoints will be analysed (stratified by randomization stratification group) using a Cochran-Mantel-Haenzel test and Miettinen-Nurminen methods to obtain the difference in proportions between groups and corresponding 90% and 95% CIs.

- Percentage of subjects with loss of <15 letters using ETDRS, evaluated as change at Week 4, Week 8, Week 24, and Week 52 compared to Baseline in the study eye
- Percentage of subjects with gain of ≥15 letters using ETDRS, evaluated as change at Week 4, Week 8, Week 24, and Week 52 compared to Baseline in the study eye
- Percentage of subjects without intra- or subretinal fluid in the study eye (ie, completely dry) at Week 24 and Week 52
- Percentage of subjects with retinal pigment epithelium detachments in the study eye

11.3.4 Safety Endpoints

11.3.4.1 Adverse Events

Events that occur after a patient provides informed consent but before the time of the first dose of study drug will be considered non-treatment-emergent adverse events (AEs). Treatment-emergent AEs (TEAEs) are defined as events that are newly occurring or worsening from the time of the first dose of study drug.

Reported AE terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and system organ classes (SOCs).

The percentage of patients with TEAEs together with the number of the respective TEAEs overall, by SOC, and by preferred terms within each SOC will be presented. Separate summaries will be provided for overall TEAEs, TEAEs by severity,

treatment-related TEAEs, serious TEAEs, and TEAEs leading to treatment discontinuation.

All AEs will be presented in patient listings.

11.3.4.2 Other Safety Endpoints

The following endpoints (as well as the change from Baseline when applicable) will be summarized:

- Injection site reactions
- Vital signs (heart rate, systolic blood pressure, diastolic blood pressure)
- Clinical chemistry (creatinine, AST/SGOT, ALT/SGPT, alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, total cholesterol, triglycerides, calcium, and phosphorus)
- Immunogenicity (ie, anti-ranibizumab antibodies and NAb)

11.3.5 Pharmacokinetics

The PK data analysis will be performed using the PK Set.

The ranibizumab PK concentrations will be summarised by treatment and listed individually. Descriptive statistics on the PK parameters (*C0*, predose; *C1*, time point 23 hours [± 60 minutes] after the first dose on Day 1; and *C6*, time point 23 hours [± 60 minutes] after the sixth dose on Week 20) will be presented. If a difference in ranibizumab protein concentration between Xlucane and Lucentis® batches is detected, additional descriptive statistics will be presented taking such difference into account. Further details will be defined in the statistical analysis plan.

11.3.6 Interim Analyses

When all subjects have completed their 6-month assessments, an *unmasked* analysis of efficacy and safety endpoints as well as PK and immunogenicity will be performed. The aim of the *unmasked* analysis is to initiate the submission of the application for marketing authorization as agreed with the European Medicines Agency. This analysis will not affect the further conduct of the study.

11.3.7 Handling of Missing Data

Any data following an IE, which is deemed to have been impacted by the IE, may be treated as missing data in the analysis in accordance with Section 11.3.3.1.

For the primary analysis of each endpoint/estimand, a missing at random (MAR) approach will be assumed for missing data (ie, the probability of an observation being missing depends only on observed measurements). Sensitivity analyses will be conducted using different missing data assumptions such as missing not at random (MNAR) and missing completely at random (MCAR) within each endpoint/estimand.

For continuous endpoints, a MMRM model will be used (using only evaluable data) to adopt a MAR assumption for the primary analysis. Patients with missing data at a particular time point still contribute to the analysis at that time point based on their other observed data used in the MMRM (ie, visit, treatment, baseline BCVA letter score, geographical region of the country where enrolled, eye color (light iris vs dark iris), and BCVA letter score at other visits) and the known covariance structures between these factors. The sensitivity analyses will use alternate methods (to be detailed in the SAP) of imputing missing data such as multiple imputation with pattern mixture modelling and using evaluable data only. ANCOVA models will be used to analyze such data at the respective visit.

For non-continuous endpoints, alternate methods will be specified in the SAP to impute missing data, although the same mechanisms will be assumed as for continuous endpoints (ie, primary analysis assumes MAR, sensitivity analyses to assess MNAR and MCAR).

Due to the indication under evaluation in this study, it is considered that most missing data due to COVID-19 can be treated as MAR, but this will be evaluated and agreed at the BDRM. Additional subgroup and sensitivity analyses relating to the potential bias from missing data and/or deviations from the protocol during the COVID-19 pandemic will be considered for analysis of all endpoints and added to the SAP prior to database lock.

11.4 Determination of Sample Size

The change in BCVA after 8 weeks was evaluated from previous studies based on similar patient populations. There was a wide range of SD across the studies, ranging from 8.58 letters to 11.83 letters.

For the purpose of sample size calculation, an SD of 10 letters will be assumed for this study. This is based on an analysis of the data from clinical trials of the originator product demonstrating a clear correlation between baseline BCVA and the SD of the change of BCVA at Week 8. Considering that a narrower inclusion criterion for BCVA is being applied in this study compared to the studies of the originator product, it is expected that a baseline BCVA of around 60 letters will be observed. Therefore, an SD of 10 for the primary endpoint is well in the upper range of what is expected.

From 580 randomized patients there will be >90% power to show equivalence (ie, two-sided 95% CI for the mean difference between Xlucane and Lucentis® is confined within the equivalence margin of ± 3.5 letters) if the SD is no more than 10.

The power calculations were performed using SAS® (Version 9.3, SAS Institute Inc., Cary, NC, USA).

11.5 Protocol Deviations

All protocol deviations related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessment will be identified, evaluated, and closed prior to the respective database lock (interim or final analysis) and will be described in the final SAP/clinical study report.

12 QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

12.2 Monitoring

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an informed consent form (ICF) and is administered study drug.

In accordance with current GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

12.3 Data Management and Coding

Syneos Health will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures (SOPs) of the data management and biostatistics departments of Syneos Health.

Study centers will enter data directly into an electronic data capture (EDC) system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and WHO Drug Dictionary for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

12.4 Quality Management and Risk Evaluation

Details will be provided in a separate Integrated Quality Risk Management (IQRM) Plan.

13 RECORDS AND SUPPLIES

13.1 Drug Accountability

On receipt of the study drug, the investigator (or designee) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts before completing a supplies receipt. The investigator will retain a copy of this receipt at the study center and return the original receipt to the unmasked study monitor. The unmasked monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the unmasked study monitor to ensure that the investigator (or designee) has correctly documented the amount of study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

13.2 Financing and Insurance

Financing and insurance for this study will be outlined in a separate agreement between Syneos Health and the Sponsor.

14 ETHICS

14.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

14.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

14.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

14.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points that he/she does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept

and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

14.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the locally and/or nationally recognized authorities, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with any required authorizations, applicable to national and/or local laws and regulations on personal data protection.

15 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the Sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The Sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

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20. Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials (Adopted by CHMP 26 June 2020)

17 APPENDICES

17.1 Examples of Acceptable Contraception

For females:

a. Complete abstinence, defined as complete avoidance of heterosexual intercourse
b. Bilateral tubal ligation or salpingectomy
c. Partner underwent vasectomy
d. Hormonal methods of contraception, including combined oral contraceptive pills, injectables, implants, and intrauterine devices (IUDs)
e. Nonhormonal IUDs (ie, copper)
f. Condom or occlusive cap (diaphragm, sponge, or cervical/vault caps) with spermicide combined with a hormonal method

For males:

a. Complete abstinence, defined as complete avoidance of heterosexual intercourse
b. Bilateral orchiectomy
c. Vasectomy
d. Condom with spermicide if female partner uses a hormonal method

17.2 Investigator Signature Page

Protocol Title: Xplore: A Phase III Double-Blind, Parallel Group, Multicenter Study to Compare the Efficacy and Safety of Xlucane versus Lucentis® in Patients with Neovascular Age-Related Macular Degeneration

Protocol Number: XBR1001

Confidentiality and GCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the independent ethics committee/institutional review board (IEC/IRB), I will not modify this protocol without obtaining prior approval of Xbrane Biopharma and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Xbrane Biopharma and the IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Xbrane Biopharma, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

18 PROTOCOL AMENDMENT SUMMARY OF CHANGES

18.1 Summary of Changes

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized. Key additions are in **bold** and underlined.

Protocol Section	Summary of Changes	Rationale for Changes
Title page	Update of Sponsor address.	Change of address.
2 Study Personnel	Updated contact details of Project Manager.	Change of Project Manager.
2 Other Personnel	Physical address of central laboratory in North America has been specified. Telephone and fax number updated accordingly.	Clarification. The central laboratory vendor in North America has not changed.
3 Synopsis – Study design	Clarification regarding the maintenance of blinding in connection to interim analysis.	Text was added to clarify that subjects´treatment assignment will not be revealed in connection to Interim Analysis and thereby the blinding of the study will be maintained.
8.4.2 Packaging and Labeling	Central provision of BD needles and syringes is suspended until further notice. Should this change, the sites will be informed via an official letter.	Company decision.