MYL-1701P-3001 CLINICAL STUDY PROTOCOL

Protocol Title	A Multi Center, Randomized, Double-Masked, Active-Controlled, Comparative Clinical Study to Evaluate the Efficacy and Safety of MYL-1701P and Eylea® in Subjects with Diabetic Macular Edema
Product	MYL-1701P (M710)
Protocol Number	MYL-1701P-3001
Study Type	Comparative Safety and Efficacy
Version	Version 3.0
Protocol Date	09 Jun 2020
Legal/Filing Sponsor	Mylan [redacted]

SIGNATURE PAGE

Protocol Description	A Multi Center, Randomized, Double-Masked, Active-Controlled, Comparative Clinical Study to Evaluate the Efficacy and Safety of MYL-1701P and Eylea® in Subjects with Diabetic Macular Edema
Product Code	MYL-1701P
Protocol Version	Version 3.0
Protocol Version Date	09 Jun 2020

I have read this protocol and affirm that the information contained herein is complete and accurate.

Date: _____

Date: _____

Date: _____

Date: _____

Date: _____

PRINCIPAL INVESTIGATOR ACCEPTANCE FORM

SIGNATURE OF INVESTIGATOR

I, the undersigned, as Investigator for this study, have read this protocol numbered MYL-1701P-3001 and agree to conduct the study as outlined herein and in accordance with all applicable requirements of the country where the study is being conducted, the country where the study will be submitted, and the Sponsor's requirements. Applicable guidelines and regulations include, but are not limited to:

- Permission to allow the Sponsor and/or its agent or regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures subject confidentiality.
- Immediate notification of the Sponsor and/or its agent of any regulatory inspection related to this study.
- Submission of the proposed clinical investigation, including the protocol and consent form, to a duly constituted IRB/Ethics Committee for approval, and acquisition of written approval for each, prior to study initiation.
- Use of IRB/Ethics Committee-approved written informed consent that is obtained prior to study initiation for each subject.
- Submission of any proposed change in or deviation from the protocol to the IRB/Ethics Committee using a signed formal amendment document prepared by the Sponsor and/or its agent. Any proposed change(s) or deviation(s) from the protocol require that the informed consent also reflect such change(s) or deviation(s), and that the revised informed consent be approved by the IRB/Ethics Committee.
- Documentation and explanation of the individual protocol deviations on the appropriate CRF page or other Sponsor-approved document.
- Submission of written reports of serious AEs, as defined in the protocol, to the Sponsor within 24 hours.
- Adherence to ICH GCP guidelines.

Signature (Investigator) and Date

……..

Name

Contact Details

CLINICAL STUDY CONTACT LIST

Sponsor:

Mylan [redacted]
[redacted],
[redacted]

Sponsor GCRD Representative:

[redacted]

Sponsor Statistical Representative:

[redacted]

Sponsor GCO Representative:

[redacted]

Sponsor Bioanalytical Representative:

[redacted].

Sponsor Safety Reporting Hotline:

[redacted]

PROTOCOL SYNOPSIS

Protocol Title	A Multi Center, Randomized, Double-Masked, Active-Controlled, Comparative Clinical Study to Evaluate the Efficacy and Safety of MYL-1701P and Eylea® in Subjects with Diabetic Macular Edema
Protocol Number	MYL-1701P-3001
Background and Rationale	Diabetic retinopathy is an important cause of blindness worldwide. The International Diabetes Federation estimates that 285 million people worldwide have diabetes mellitus and that approximately 7% of these individuals are affected by diabetic macular edema. EYLEA® (aflibercept) injection, an anti-Vascular Endothelial Growth Factor (VEGF) agent, has been approved by the FDA and EMA for the treatment of Diabetic Macular Edema (DME). Eylea is being marketed by Regeneron Pharmaceuticals, Inc. in the US and Bayer AG in EU. Mylan Inc. and Momenta Pharmaceuticals, Inc. are developing MYL-1701P, a proposed biosimilar to Eylea, and this study will serve to demonstrate the clinical similarity of MYL-1701P and Eylea with regard to efficacy, safety, pharmacokinetics and immunogenicity in the treatment of patients with DME.
Primary Objectives	The primary objective is to demonstrate the clinical equivalence of MYL-1701P and Eylea over 8 weeks of treatment at doses and regimen recommended by the Eylea US Prescribing Information, as assessed by change from baseline to week 8 in best corrected visual acuity (BCVA).
Primary endpoints	The primary efficacy endpoint will be the mean change from baseline in BCVA as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 8.
Methodology and treatments	This is a multi-center, randomized, double-masked, active-controlled, comparative clinical study to demonstrate that no clinically meaningful differences exist between MYL-1701P and US-licensed Eylea in subjects with DME treated up to 52 weeks. Three hundred and twenty-four (324) eligible adult subjects with type 1 or 2 diabetes mellitus with central DME involvement and BCVA between 73 and 38 letters based on ETDRS letters (20/40 – 20/200 Snellen equivalent) in the study eye and central retinal thickness (CRT) ≥ 300 µm, as determined by spectral domain – optical coherence tomography (SD-OCT) in the study eye, will be randomized 1:1 to intravitreal treatment with MYL-1701P or Eylea. [redacted] Randomization will be stratified based on Baseline BCVA, i.e., ETDRS letter scores 73-55 vs. 54-38 and geographical region (US, EU, Japan and rest of the world). At study week 8, the primary endpoint will be assessed, and subjects will continue to receive the assigned treatment until Week 48. An end of study visit will be conducted at Week 52. Subjects will receive intravitreal injections of MYL-1701P or Eylea throughout the 52-week treatment period, with planned doses at Study Days 1, 29 (week 4), 57 (week 8), 85 (week 12), 113 (week 16), 169 (week 24), 225 (week 32), 281 (week 40) and 337 (week 48). Additional doses may be administered at Week 20, Week 28, Week 36 and Week 44 based on the visual acuity, and/or SD-OCT as per the protocol specified criteria for administering additional 4-weekly doses. It should be noted that in most subjects where Eylea was dosed every 4-weeks

	compared to every 8 weeks, no additional efficacy was observed. Hence, it is expected that most of the subjects may not require additional 4-weekly doses. All subjects will return to clinic every 4 weeks for assessment of visual acuity (BCVA based on ETDRS letters) and central retinal thickness (CRT by SD-OCT) to assess efficacy and to guide treatment. There will be additional visits during the study as specified in the study schedule for safety and pharmacokinetic evaluation. [redacted] Immunogenicity will be assessed for all the subjects participating in the study, through assessment of blood samples for anti-drug antibody and neutralizing antibody throughout the study. Along with immunogenicity, free aflibercept concentration in the blood samples from all subjects will be determined to evaluate drug tolerance status. Pharmacokinetic (PK) samples will be collected in patients identified for PK subpopulation (at least 32 in each study arm). Subjects in the PK subpopulation will have to visit the sites for 2 additional visits for sampling (visits V2 and V7A).
Investigational Products	**Test product:** MYL-1701P (a proposed biosimilar to Eylea) injection for intravitreal injection. **Reference Product:** Eylea for intravitreal injection, sourced from the United States.
Inclusion/ exclusion criteria	**Inclusion criteria** Each subject must meet all of the following criteria to participate in the study: 1. Male or female subjects age ≥ 18 years. For Japan, in case of a subject under 20 years old, his/her legally acceptable representative should provide the informed consent for the study participation. 2. Subjects have type 1 or type 2 diabetes mellitus who present with central DME involvement (defined as retinal thickening with a measurement of 300µm or more involving the 1 mm CRT by SD-OCT) in the study eye. 3. The cause of decreased vision in the study eye has been attributed primarily to DME by the Investigator. 4. Subjects must have BCVA at 4 m from 73 to 38 letters (ETDRS chart) equivalent to Snellen visual acuity of 20/40 to 20/200 in the study eye. 5. Subject is able to understand and voluntarily provide written informed consent to participate in the study. 6. If female of child bearing potential, the subject must have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test at baseline visit, and should not be nursing or planning a pregnancy. 7. If female, subject must be: a. Surgically sterilized via hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; or b. Of childbearing potential and practicing an acceptable form of birth control (defined as the use of an intrauterine device; a barrier method, like condom, with spermicide; any form of hormonal contraceptives; or abstinence from sexual intercourse) starting 60 days prior to dosing and continuing at

	least 90 days following the last treatment. c. Of non-childbearing potential (i.e., postmenopausal for at least 1 year). For Japan: If female, subject must be • Of non-childbearing potential (i.e., surgically sterilized via hysterectomy, bilateral oophorectomy, or bilateral tubal ligation, or postmenopausal* for at least 1 year); * definition: she is not menstruating for at least 12 months without any other medical reason. • Of childbearing potential and practicing an acceptable form of birth control (defined as the use of an intrauterine device; a barrier method, like condom, with spermicide; any form of hormonal contraceptives; or abstinence from sexual intercourse) starting 60 days prior to dosing and continuing at least 90 days following the last treatment For Czech Republic: If female, must be permanently sterile or subject must be using a birth control method, which is considered as highly effective (described in detail in Section 4.4.2), starting 60 days prior to dosing and continuing at least 90 days following the last treatment 8. If male, subject must be surgically or biologically sterile. If not sterile, the subject must agree to use an acceptable form of birth control with sexual partner (as described in inclusion criteria #7b) or abstain from sexual relations during the study period and up to 90 days following the last treatment dose. For Czech Republic: If male, subjects should use highly effective method of contraception starting 60 days prior to dosing and continuing at least 90 days following the last treatment (described in detail in Section 4.4.3). 9. Subject is willing to comply with the study duration, study visits and study related procedures. **Exclusion Criteria** Subjects who meet any of the following criteria will be excluded from the study: 1. Subjects with known hypersensitivity to aflibercept or any of the excipients in MYL-1701P and Eylea 2. Known hypersensitivity to fluorescein 3. Ocular media of insufficient quality to obtain fundus and OCT images 4. Subjects will be excluded if any of the following conditions are met in the study eye: a. Subjects with a history of vitreoretinal surgery in study eye and/or including scleral buckling b. Subjects who have had panretinal or macular laser photocoagulation within 3 months of randomization c. Subjects with history of use of intraocular corticosteroids anytime in the past or periocular (subconjunctival, intra-scleral, sub-tenon or retrobulbar) corticosteroids within 4 months of randomization d. Subjects who have reduced vision due to causes other than DME, with the exception of requirement for spherical correction, or mild cataract assessed by the Investigator as not

	interfering with assessment of BCVA or CRT e. Subjects with active proliferative diabetic retinopathy f. Subjects with active ocular inflammation g. Subjects who have had cataract or other intraocular surgery within 3 months of randomization or expected to undergo cataract surgery or capsulotomy during the study duration h. Subjects who have had laser capsulotomy within 3 months of randomization i. Subjects with aphakia, whether congenital or surgical j. Subjects with vitreous hemorrhage k. Subjects with visually significant vitreomacular traction or epiretinal membrane evident biomicroscopically or on OCT that is thought to affect central vision l. Subjects with myopia of spherical equivalent of ≥ - 8 diopters, prior to any possible refractive or cataract surgery m. Subjects with any other disease that might compromise visual acuity or require medical or surgical intervention during the study period, or could confound interpretation of the results (including retinal vascular occlusion, retinal detachment, macular hole or choroidal neovascularization of any cause) n. Structural damage to the center of the macula that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates based on the Investigator's discretion with help of FA/FP and OCT. o. Subjects with uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication); subjects with controlled glaucoma may participate in the study. For India, subjects with a clinical diagnosis of glaucoma (controlled or uncontrolled). p. Surgery for glaucoma in the past or likely to be needed in the future q. Intraocular pressure ≥25 mm of Hg in the study eye r. Prior treatment with verteporfin (photodynamic therapy) 5. Subjects will be excluded if any of the following conditions are met in either eye: a) Subjects with active iris neovascularization b) Subjects with preretinal fibrosis involving the macula c) Subjects with history of idiopathic or autoimmune uveitis d) Subjects with active or suspected ocular or peri-ocular infection including but not limited to infectious blepharitis, keratitis, scleritis, or conjunctivitis 6. Subjects who received previous therapy with antiangiogenic drugs for either eye (pegaptanib, bevacizumab, ranibizumab, aflibercept). 7. Subjects who have received previous systemic antiangiogenic drugs (bevacizumab, aflibercept). 8. Subjects with current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and

	ethambutol. 9. Subjects who plan to participate in another clinical study while enrolled in this study and/or who have received an investigational drug and/or device within 30 days or 5 half-lives, whichever is longer, prior to screening. 10. Subject receiving treatment for a serious systemic infection. 11. Subjects with uncontrolled diabetes mellitus as defined by HbA1c ≥10% at screening 12. Subjects with uncontrolled hypertension defined as systolic blood pressure > 160 mm Hg or diastolic blood pressure > 95 mm of Hg. 13. Subjects with a history of cerebrovascular accident or myocardial infarction within 6 months of randomization. 14. Subjects with renal failure requiring dialysis or renal transplant. 15. Subjects who have only one functional eye, even if the eye met all other study requirements, or who have an ocular condition on the fellow eye with a poorer prognosis than the study eye. 16. Presence or history of malignant neoplasm (including lymphoproliferative disease), except for adequately treated basal cell carcinoma and cervical carcinoma in situ; or any malignancy with complete remission of more than 5 years. 17. Subjects with a history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, psychiatric disease, or any other condition, that in the opinion of the Investigator would jeopardize the safety of the subject or the validity of the study results.
Sample size	[redacted] A total of 324 subjects will be randomized at 1:1 ratio to each arm after allowing for approximately 10% drop-outs. [redacted]
Statistical Methods	For the primary endpoint of change from baseline in BCVA at Week 8, the primary analysis will be based on a mixed model repeated measures analysis with terms for treatment, visit, treatment by visit interaction, and region, together with baseline BCVA as a covariate. The within subject variance-covariance matrix will be assumed to be unstructured; estimation will use restricted maximum likelihood, and the denominator degrees of freedom will use the Kenward-Roger estimate. This model will provide an estimate, standard error, and 90% as well as 95% two-sided CIs for the treatment difference at Week 8. If these CIs are fully contained within the interval (-3, 3) then equivalence will have been demonstrated. The primary analysis will be performed on the Full Analysis Set and will include data from all visits regardless of whether the subject is still receiving study medication. Additionally, sensitivity analysis of the primary endpoint will be conducted, in which BCVA values after discontinuing study medication will be excluded. Supportive analyses of the primary endpoint will also be produced based on the

	Per Protocol Population.
Reporting Strategy	[redacted] Complete efficacy, safety, pharmacokinetics and immunogenicity data through Week 52 will be included in the 52-Week CSR. Study will continue to be double-masked until Week 52.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF COMMONLY USED ABBREVIATIONS

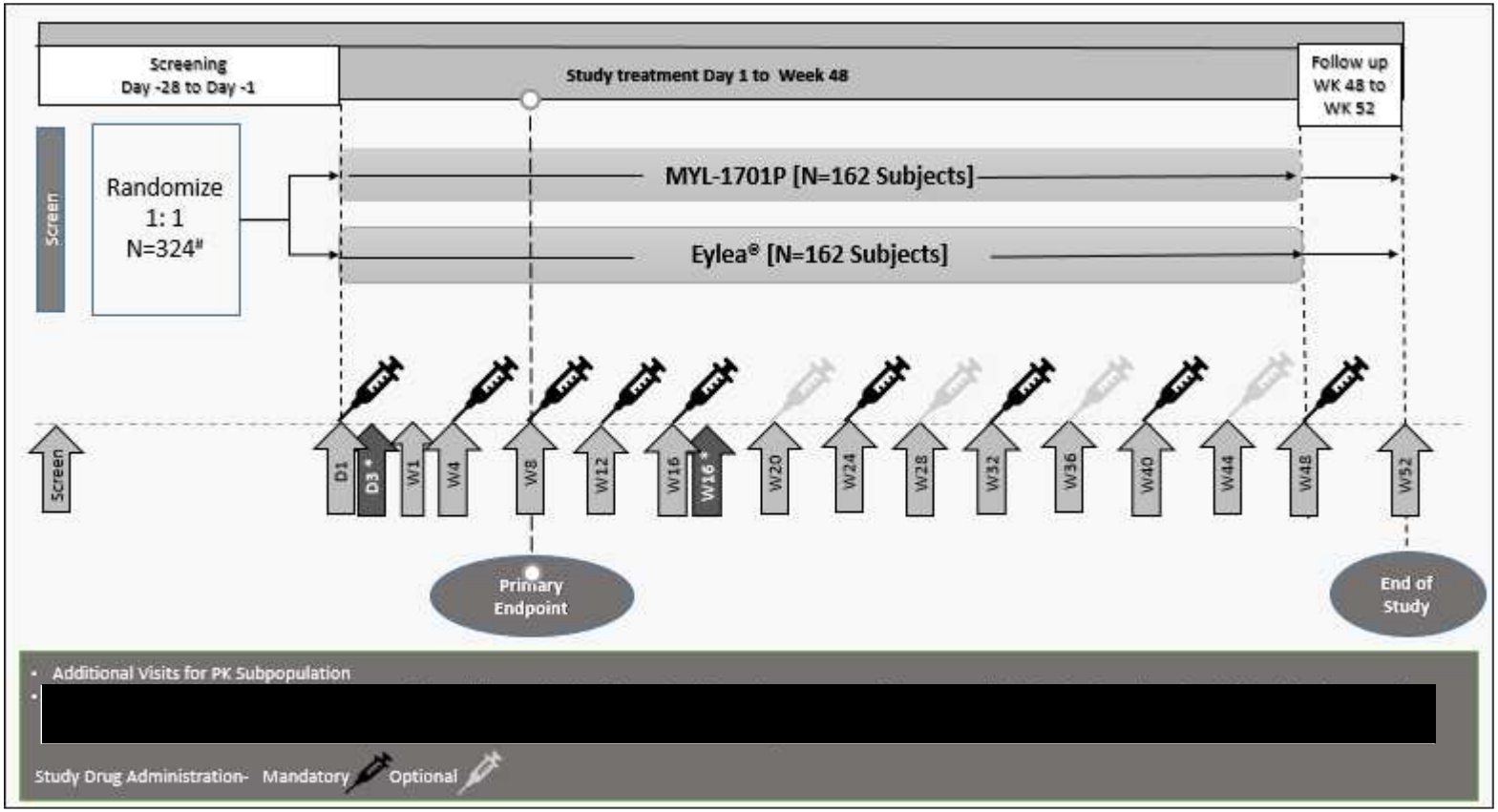
AE	Adverse event
ADR	Adverse drug reactions
ALT	Alanine transaminase
AMD	Age-related macular degeneration
AST	Aspartate transaminase
BCVA	Best corrected visual acuity
BP	Blood Pressure
CI	Confidence interval
C_{max}	maximum plasma concentration
COVID-19	Corona virus disease - 2019
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Central retinal thickness
CSR	Clinical Study Report
CTAD	Buffered citrate, theophylline, adenosine, and dipyridamole
DME	Diabetic Macular Edema
ECG	Electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study
EMA	European Medicines Agency
FA	Fluorescein angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FP	Fundus photography
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent ethics committee
IFU	Instructions For Use
IRB	Institutional Review Board
IOP	Intraocular pressure
IXRS	Interactive response system
kg	kilogram
MedDRA	Medical dictionary for regulatory activities
mg	milligram
mL	milliliter
mmHg	millimeter of mercury
MMRM	Mixed Model Repeated Measures
NIAID/ FAAN	National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network
PI	Prescribing Information
PK	Pharmacokinetic
PP	Per Protocol
PSRM	Product safety and risk management
QC	Quality Control
QTc	QT corrected
QTcF	QT corrected (Fredericia's correction)
RVO	Retinal vein occlusion

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	spectral domain – optical coherence tomography
SID	Subject Identification
SPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
US	United States
VEGF	Vascular Endothelial Growth Factor
WoCBP	Women of Child-Bearing Potential

1 STUDY DIAGRAM AND STUDY SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Study Conduct Section (6) for detailed information on each procedure and assessment required for compliance with the protocol.

Figure 1: Study Diagram



The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Study Conduct Section (Section 6) for detailed information on each procedure and assessment required for compliance with the protocol.

Table 1: Study Schedule

Assessment	**Period**	**Screening**	**Treatment period**																
	Visit	Screening Visit	V1/ BL	V2[q]	V3	V4	V5	V6	V7	V7A[p]	V8	V9	V10	V11	V12	V13	V14	V15	V16
	Day or week:	D -28 to D -1	D1	D3 (±0 d)	W1 (±2d)	W4 (±3d)	W8 (±3d)	W12 (±7d)	W16 (±7 d)	W16 +2d (±0 d)	W20 (±7d)	W24 (±7d)	W28 (±7d)	W32 (±7d)	W36 (±7d)	W40 (±7d)	W44 (±7d)	W48 (±7d)	W52 (±7d) EOS/ ET
Informed Consent[a]		x																	
Demography		x																	
Medical, Surgical and Ophthalmic history[b]		x																	
Inclusion/Exclusion criteria		x	x																
Height/weight		x	x[c]																x[c]
Pregnancy test[d]		x	x			x	x	x	x		x	x	x	x	x	x	x	x	x
Clinical Safety Laboratory[e]		x	x		x			x				x							x
PT, aPTT and INR		X																	
PT, aPTT and INR for patients in Czech Republic only		x						x				x			x			x	
Targeted Physical Examination[f]		x	x		x							x							x
Vital Signs[g]		x	x		x	x	x	x	x		x[h]	x	x[h]	x	x[h]	x	x[h]	x	x
12- Lead Electrocardiogram[i]		x	x		x							x							x
Complete Ophthalmologic Examination[j]		x	x	x[r]	x	x	x	x	x		x	x	x	x	x	x	x	x	x
Best Corrected		x	x			x	x	x	x		x	x	x	x	x	x	x	x	x

Assessment	Period	Screening	Treatment period																
	Visit	Screening Visit	V1/ BL	V2[q]	V3	V4	V5	V6	V7	V7A[p]	V8	V9	V10	V11	V12	V13	V14	V15	V16
	Day or week:	D -28 to D -1	D1	D3 (±0 d)	W1 (±2d)	W4 (±3d)	W8 (±3d)	W12 (±7d)	W16 (±7 d)	W16 +2d (±0 d)	W20 (±7d)	W24 (±7d)	W28 (±7d)	W32 (±7d)	W36 (±7d)	W40 (±7d)	W44 (±7d)	W48 (±7d)	W52 (±7d) EOS/ ET
Visual Acuity (Bilateral)																			
Spectral Domain – Optical Coherence Tomography / Central Retinal Thickness (Bilateral)		x	x			x	x	x	x		x	x	x	x	x	x	x	x	x
Fluorescein Angiography/ Fundus Photography (Bilateral) [k]		x																	x
Randomization[l]			x																
Study Drug administration			x			x	x	x	x		x[h]	x	x[h]	x	x[h]	x	x[h]	x	
Pharmacokinetic blood sampling[m]			x	x	x	x	x		x	x		x		x		x			x
Immunogenicity blood sampling[n]			x		x	x	x		x			x		x		x			x
Drug Tolerance blood sampling[n]			x		x	x	x		x			x		x		x			x
Adverse events[o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Record Concomitant medication		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study Diary Issue/Review[S]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: aPTT = activated partial thromboplastin time; BL = baseline visit; EOS = end of study; ET = Early Termination; INR = International Normalized Ratio
PT = Prothrombin Time
Note: An unscheduled visit may be necessary and can occur at any time if the Investigator believes it is essential for any reason

a. Written informed consent will be obtained prior to the initiation of any study related procedures
b. Medical, surgical, ophthalmic and smoking history, and current medical conditions and medications
c. Weight only
d. Female subjects of child bearing potential will have a serum pregnancy test at screening and at the EOS visit (Study Week 52) and urine pregnancy test at other identified visits
e. Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be obtained before study drug administration
f. A targeted physical examination will be performed. If indicated, based on report of adverse events or result of safety laboratory test, directed physical exam will be performed at additional visits
g. Vital signs include blood pressure (BP), pulse rate and temperature. BP will be measured after the subject is sitting for 5 mins
h. Additional doses may be administered at Week 20, Week 28, Week 36 and Week 44 based on the visual acuity, and/or SD-OCT at that visit and in accordance with protocol specified criteria for administering additional 4-weekly doses. If an additional dose is administered, collect vital signs before the study drug administration
i. 12-lead Electrocardiogram will be conducted before study drug administration
j. Ophthalmologic examination includes slit lamp examination, indirect ophthalmoscopy and intraocular pressure measurement in study eye. Slit lamp examination, indirect ophthalmoscopy and intraocular pressure (IOP) measurement will be done before study drug administration and measurement of IOP and finger counting will be done approximately 30 minutes after study drug administration
k. Fluorescein Angiography/Fundus Photography will be done after BCVA testing and other investigations including blood and urine samples are collected
l. On Day 1 prior to study drug administration, subjects will be randomized 1:1 to receive either MYL-1701P or Eylea
m. Pharmacokinetic blood samples will be taken only in patients that are part of the PK subpopulation, before study drug administration. The blood sampling collected for drug tolerance on visits (V1, V3, V4, V5, V7, V9, V11, V13, V16) will be used for PK evaluation
n. Immunogenicity (ADA/NAb) and drug tolerance blood samples will be taken before study drug administration whenever applicable. Additional immunogenicity samples will be collected if subject has signs of intraocular inflammation suggesting immune reaction
o. Ocular Adverse Events (AEs) and non-ocular AEs will be collected and analyzed separately. Ocular AEs for the study eye and the fellow eye will be collected and analyzed separately
p. Week 16+2 days visit will be conducted only for subjects participating in subset PK evaluation
q. Visit 2 (Day 3) will be performed at clinic only for the subjects in sentinel cohort and subjects in PK subset. For all other subjects, it will be a telephonic visit
r. Ophthalmological examination on Visit 2 (Day 3) will be conducted only for subjects in the sentinel cohort
s. Study Diary will be issued during V1/BL, reviewed during subsequent visits, and returned during the V16/EOS or ET visit. Study diary will be used by subjects to record the AEs and concomitant medications in between the study visits

2 INTRODUCTION

2.1 Indication

Mylan Inc., in collaboration with Momenta Pharmaceuticals, Inc. is developing a proposed biosimilar version of Eylea® (aflibercept). Eylea was first approved in 2011 by US FDA for treatment of wet Age-Related Macular Degeneration.

Eylea (aflibercept) is a vascular endothelial growth factor (VEGF) inhibitor indicated for the following treatments in the US and EU:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)

Additionally, it is indicated for Diabetic Retinopathy in Patients with DME in the US and visual impairment due to myopic choroidal neovascularization in the EU.

This study is being conducted by Mylan to demonstrate the clinical similarity of MYL-1701P (a proposed biosimilar to Eylea, also referred to as M710) and Eylea with regard to efficacy, safety, pharmacokinetics and immunogenicity in the treatment of patients with DME.

2.2 Background and Rationale

Diabetic retinopathy is a common cause of blindness worldwide. The International Diabetes Federation estimates that 285 million people worldwide have diabetes mellitus and that 7% of these individuals are affected by diabetic macular edema (Whiting DR, 2011; Ding J et al., 2012).

Anti-VEGF drugs are effective at improving vision in people with DME. Eylea (aflibercept) confers some advantage over ranibizumab and bevacizumab in people with DME, at one year in both visual and anatomic terms. (Virgili G et al., 2017).

MYL-1701P is being developed as a proposed biosimilar to Eylea (aflibercept). Eylea is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Eylea is being marketed by Regeneron Pharmaceuticals, Inc. in the US and Bayer AG in EU.

Complete information of the investigational medicinal product for MYL-1701P-3001 is available in the Single Reference Safety Document, which for this study is the MYL-1701P Investigator's Brochure.

Throughout this study protocol, "Eylea" refers to US-licensed Eylea.

2.2.1 Rationale for Study

MYL-1701P is currently being developed by the sponsor (Mylan Inc.) in collaboration with Momenta Pharmaceuticals, that is being formulated as a proposed biosimilar to Eylea in accordance with European Union (EU) and US Biosimilar guidelines. (EMA 2014, FDA 2015)

This is a multi-center, randomized, double-masked, active-controlled, comparative clinical study to demonstrate that no clinically meaningful differences exist between MYL-1701P and US-licensed Eylea in subjects with DME treated up to 52 weeks.

It is part of the overall registration package to support the regulatory approval of MYL-1701P as a proposed biosimilar to Eylea.

2.2.1.1 Rationale for Study Population- Diabetic Macular Edema

The active pharmacologic agent, in Eylea (aflibercept), is understood to act as a soluble decoy receptor that binds to VEGF-A and PlGF, and thereby inhibits the binding and activation of their cognate receptors VEGFR-1 and VEGFR-2, which are expressed on the surface of endothelial cells. Activation through VEGFR-1 and VEGFR-2 is associated with neovascularization and vascular permeability, while inhibition of activation by Eylea (aflibercept) has been demonstrated to reduce both processes, with clinical benefit in the indicated disorders. (Eylea US Package Insert, 2017).

[redacted]

2.2.1.2 Rationale for Subject Selection and Study Endpoints

[redacted]

It is recognized that baseline visual acuity can be a factor in treatment response. In Dugel PU et al., 2016, treatment response was analyzed by categories of baseline BCVA for several anti-VEGF treatments, but with greatest focus on trials of Lucentis. It was demonstrated that change in BCVA increased as baseline BCVA decreased. Therefore, to reduce variability, randomization will be stratified based on Baseline BCVA, i.e., ETDRS letter scores 73-55 vs. 54-38 and geographical region (US, EU, Japan and rest of the world). (Dugel PU et al., 2016) In addition, baseline BCVA is included as a covariate in the primary analysis.

Change from baseline in BCVA is a clinically relevant endpoint and being a continuous variable is adequately sensitive to detect any clinically meaningful differences between study treatments. Hence mean change in BCVA is considered as the primary endpoint for the current study. Central retinal thickness is being evaluated as a key secondary endpoint. CRT assesses the pharmacodynamic aspects of aflibercept and is supportive in detecting differences between study treatments (MYL-1701P and Eylea).

2.3 Study Design

This is a multi-center, randomized, double-masked, active-controlled, comparative clinical study between MYL-1701P and US-licensed Eylea in subjects with DME treated up to 52 weeks.

A total of 324 eligible adult subjects with type 1 or 2 diabetes mellitus with central DME involvement and BCVA between 73 and 38 letters based on ETDRS letters (20/40 – 20/200 Snellen equivalent) in the study eye with CRT $\geq$ 300 µm, as determined by SD-OCT, in the study eye will be randomized 1:1 to intravitreal treatment with MYL-1701P or Eylea. [redacted]

At study week 8, the primary endpoint will be assessed, and subjects will continue to receive the assigned treatment until Week 48. An end of study visit will be conducted at Week 52.

Subjects will receive intravitreal injections of either MYL-1701P or Eylea throughout the 52-week treatment period, with planned doses at Study Day 1, Day 29 (week 4), Day 57 (week 8), Day 85 (week 12), Day 113 (week 16), Day 169 (week 24), Day 225 (week 32), Day 281 (week 40) and Day 337 (week 48).

In addition to the nine planned doses, study drug may also be administered at Week 20, Week 28, Week 36 and Week 44 based on the current visual acuity, and or SD-OCT at that visit and in accordance with the "criteria for administering additional 4-weekly doses" outlined in Section 5.1.2.

Both US Package Insert (USPI) and EU Summary of Product Characteristics (SPC) for Eylea recommends intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by intravitreal injection once every 8 weeks (2 months), USPI also allows additional every 4-week (monthly) dosing in some subjects based on the need. However, SPC does not make any such recommendations for 4 weekly dosing after 5 injections.

The current study allows for additional optional doses after 5 initial monthly injections if deemed necessary as per the prespecified criteria. Additional efficacy was not demonstrated in most subjects when Eylea was dosed every 4 weeks compared to every 8 weeks. Hence, most of the subjects may not require additional 4-weekly doses. Whenever the Investigator decides to administer additional doses, they must satisfy the criteria outlined in Section 5.1.2 and should also weigh the procedural risks related to intravitreal injection versus potential benefit.

All subjects will return to clinic every 4 weeks for assessment of visual acuity (BCVA based on ETDRS letters) and central retinal thickness (CRT by SD-OCT) to assess efficacy and to guide treatment. There will be additional visits during the study as specified in the study visit schedule for safety and pharmacokinetic evaluation.

Randomization will be stratified by BCVA at baseline (ETDRS Letter Scores 73-55 vs 54-38) and geographical region (US, EU, Japan and Rest of the World).

Immunogenicity will be evaluated for all the subjects participating in the study, through assessment of blood samples collected prior to study drug administration for anti-drug antibodies and neutralizing antibodies. Along with immunogenicity, free drug concentration in the blood samples from all subjects will be determined to evaluate drug tolerance status.

2.3.1 Pharmacokinetic Subpopulation

At least 32 subjects in each study arm will be included in the pharmacokinetic (PK) subset and PK sampling will be done in these subjects as per the Study Schedule (Table 1). These subjects will be enrolled from identified participating Investigator sites after voluntary consent for the same. These subjects will be required to visit the study site for PK sampling for 2 additional visits V2 and V7A, scheduled 48 hours after the first dose and fifth dose of study drug administration respectively.

[redacted]

2.3.3 Reporting Strategy

[redacted] Complete efficacy, safety, pharmacokinetics and immunogenicity data through Week 52 will be included in the 52-week CSR.

[redacted]

2.4 Potential Risks

There are no clinical data available on MYL-1701P in humans or animals. Although MYL-1701P has not yet been used in a clinical setting, comparative physiochemical characterization and biological characterization conducted to date showed a high degree of similarity between MYL-1701P and Eylea.

The adverse reactions available for the reference product, Eylea, could be reasonably assumed to be associated with MYL-1701P, and therefore considered expected for the purposes of expedited reporting to regulatory authorities and investigators. The excipients in the formulation of MYL-1701P are different from that of the Eylea formulation. Investigator should consider this difference between MYL-1701P and Eylea, while evaluating history of hypersensitivity to any of the excipients.

However, because MYL-1701P has not yet been evaluated in clinical studies, investigators should carefully monitor for all adverse events, including those not described as associated with Eylea and should promptly document and report the adverse events as per the protocol.

2.4.1 Safety Profile of Eylea

A complete overview of the undesirable effects of Eylea can be found in the Eylea SPC and Eylea USPI. (Eylea SPC, 2017 and Eylea US Package Insert, 2017).

The adverse events of particular concern include but are not limited to:

- Endophthalmitis and retinal detachment following intravitreal injections: In such an event subject, should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- Increases in intraocular pressure after intravitreal injection.
- Potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors; these events will be classified according to Hicks et al, 2018 by an Independent Cardiovascular Adjudication Committee

The most common adverse reactions (≥5%) reported in patients receiving Eylea were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

As this is a therapeutic protein, there is a potential for immunogenicity with Eylea/MYL-1701P. Subjects should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.

For any potential allergic reaction after administration of study drug, diagnosis and assessment of anaphylaxis will be done using National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria of anaphylaxis; the management of anaphylaxis should follow the standard institutional practices (Appendix 11.1).

2.4.2 Intravitreal injections

The drugs used to anesthetize the eye before injections can cause an allergic reaction, seizures and irregular cardiac rhythm.

Subconjunctival hemorrhage or floaters may occur because of intra-vitreal injection. Mild discomfort, ocular hyperemia, increased lacrimation, discharge or itching may occur which may last for few days.

There may be an elevation of intraocular pressure immediately following the injection. It usually returns to normal spontaneously but may need treatment with topical drugs or a paracentesis to lower the pressure.

As a result of the injection, endophthalmitis can develop and it is treated by intravitreal injection of antibiotics, but there is a risk of permanent loss of vision including blindness. Retinal detachment can also occur as a result of the injection. If this occurs, surgical intervention may be required. The injection could also cause a vitreous hemorrhage. This usually resolves spontaneously, although surgical intervention may be required.

2.4.3 Eye examination and Investigations

There is a rare risk of an allergic response to the topical medications used to anesthetize the eye or dilate the pupil. There may be other adverse events related to the topical medications used, for which respective prescribing information should be referred.

There are no known risks associated with SD-OCT or fundus photographs. The bright flashes used to take the photographs may be annoying but are not painful and cause no damage.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary objective

The primary objective is to demonstrate the clinical equivalence of MYL-1701P and Eylea over 8 weeks of treatment at doses and regimen recommended by the Prescribing Information for Eylea, as assessed by change from baseline to week 8 in BCVA.

3.1.2 Secondary objectives

The key secondary objective is:

- To compare the efficacy of MYL-1701P and Eylea as measured by change in CRT over time

The other secondary objectives are:

- To compare the efficacy of MYL-1701P and Eylea as measured by change in BCVA over time
- To compare safety, tolerability, pharmacokinetics, and immunogenicity over time of MYL-1701P and Eylea
- To compare the number of administrations of study drug required over the treatment period
- To compare impact of immunogenicity on efficacy and safety

3.2 Endpoints

3.2.1 Primary Endpoints

The primary efficacy endpoint will be the mean change from baseline in BCVA as assessed by ETDRS letters at week 8.

3.2.2 Secondary Endpoints

3.2.2.1 Efficacy

The key secondary efficacy endpoint is

- The mean change from baseline in CRT as determined by spectral-domain-optical coherence tomography (SD-OCT) over time

The other secondary efficacy endpoints will include:

- The mean change in BCVA over time
- Proportion of subjects who gained ≥15 letters from Baseline in BCVA, assessed in change from baseline in ETDRS letters over time
- Number of administrations of study drug required

3.2.2.2 Safety

Safety and tolerability will be assessed over time, based on the following evaluations:

- Ocular (study eye and fellow eye) and non-ocular adverse events (AE)
- Vital signs
- Physical examinations performed
- Complete ophthalmological examination (OE)
- Safety labs (serum chemistry, hematology, and urinalysis)
- Twelve-lead electrocardiograms (ECGs)

3.2.2.3 Immunogenicity

Anti-Drug Antibodies to aflibercept: occurrence, titer, and neutralizing capacity

3.2.2.4 Pharmacokinetics

Concentration of aflibercept (free drug)

4 STUDY POPULATION

4.1 Study Population

A total of 324 subjects are planned to be randomized into the study to ensure to have 290 subjects complete the study. One extra subject will be randomized for each subject who meets any of the pre-specified criteria related to missed/delayed dosing or study assessments because of the COVID-19 pandemic. The maximum number of these extra subjects will be 70.

Study duration from screening to end of study can be up to 13 months/56 weeks approximately.

4.2 Sample Size Considerations

[redacted] A total of 324 subjects will be randomized to each arm after allowing for approximately 10% drop-outs. [redacted]

4.3 Inclusion and Exclusion Criteria

4.3.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible to participate in the study:

1. Male or female subjects age ≥ 18 years. For Japan, in case of a subject under 20 years old, his/her legally acceptable representative should provide the informed consent for the study participation.
2. Subjects have type 1 or type 2 diabetes mellitus who present with central DME involvement (defined as retinal thickening with a measurement of 300µm or more involving the 1 mm CRT by SD-OCT) in the study eye.
3. The cause of decreased vision in the study eye has been attributed primarily to DME by the Investigator.
4. Subjects must have BCVA at 4 m from 73 to 38 letters (ETDRS chart) equivalent to Snellen visual acuity of 20/40 to 20/200 in the study eye.
5. Subject is able to understand and voluntarily provide written informed consent to participate in the study.
6. If female of child bearing potential, the subject must have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test at baseline visit, and should not be nursing or planning a pregnancy.
7. If female, subject must be:
    a. Surgically sterilized via hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; or

b. Of childbearing potential and practicing an acceptable form of birth control (defined as the use of an intrauterine device; a barrier method, like condom, with spermicide; any form of hormonal contraceptives; or abstinence from sexual intercourse) starting 60 days prior to dosing and continuing at least 90 days following the last treatment.

c. Of non-childbearing potential (i.e., postmenopausal for at least 1 year).

For Japan: If female, subject must be:

- Of non-childbearing potential (i.e., surgically sterilized via hysterectomy, bilateral oophorectomy, or bilateral tubal ligation, or postmenopausal* for at least 1 year);
  * definition: she is not menstruating for at least 12 months without any other medical reason.
- Of childbearing potential and practicing an acceptable form of birth control (defined as the use of an intrauterine device; a barrier method, like condom, with spermicide; any form of hormonal contraceptives; or abstinence from sexual intercourse) starting 60 days prior to dosing and continuing at least 90 days following the last treatment

For Czech Republic: If female, must be permanently sterile or subject must be using a birth control method, which is considered as highly effective (described in detail in Section 4.4.2), starting 60 days prior to dosing and continuing at least 90 days following the last treatment

8. If male, subject must be surgically or biologically sterile. If not sterile, the subject must agree to use an acceptable form of birth control with sexual partner (as described in inclusion criteria #7b) or abstain from sexual relations during the study period and up to 90 days following the last treatment dose.

   For Czech Republic: If male, subjects should use highly effective method of contraception starting 60 days prior to dosing and continuing at least 90 days following the last treatment (described in detail in Section 4.4.3).

9. Subject is willing to comply with the study duration, study visits and study related procedures.

4.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Subjects with known hypersensitivity to aflibercept or any of the excipients in MYL-1701P and Eylea
2. Known hypersensitivity to fluorescein
3. Ocular media of insufficient quality to obtain fundus and OCT images
4. Subjects will be excluded if any of the following conditions are met in the study eye:
   a. Subjects with a history of vitreoretinal surgery in study eye and/or including scleral buckling
   b. Subjects who have had panretinal or macular laser photocoagulation within 3 months of randomization

c. Subjects with history of use of intraocular corticosteroids anytime in the past or periocular (subconjunctival, intra-scleral, sub-tenon or retrobulbar) corticosteroids within 4 months of randomization

d. Subjects who have reduced vision due to causes other than DME, with the exception of requirement for spherical correction, or mild cataract assessed by the Investigator as not interfering with assessment of BCVA or CRT

e. Subjects with active proliferative diabetic retinopathy

f. Subjects with active ocular inflammation

g. Subjects who have had cataract or other intraocular surgery within 3 months of randomization or expected to undergo cataract surgery or capsulotomy during the study duration

h. Subjects who have had laser capsulotomy within 3 months of randomization

i. Subjects with aphakia, whether congenital or surgical

j. Subjects with vitreous hemorrhage

k. Subjects with visually significant vitreomacular traction or epiretinal membrane evident biomicroscopically or on OCT that is thought to affect central vision

l. Subjects with myopia of spherical equivalent of ≥ - 8 diopters, prior to any possible refractive or cataract surgery

m. Subjects with any other disease that might compromise visual acuity or require medical or surgical intervention during the study period, or could confound interpretation of the results (including retinal vascular occlusion, retinal detachment, macular hole or choroidal neovascularization of any cause)

n. Structural damage to the center of the macula that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates based on the Investigator's discretion with help of FA/FP and OCT.

o. Subjects with uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication); subjects with controlled glaucoma may participate in the study. [For India - Subjects with a clinical diagnosis of glaucoma (controlled or uncontrolled)].

p. Surgery for glaucoma in the past or likely to be needed in the future

q. Intraocular pressure ≥25 mm of Hg in the study eye

r. Prior treatment with verteporfin (photodynamic therapy)

5. Subjects will be excluded if any of the following conditions are met in either eye:

a. Subjects with active iris neovascularization

b. Subjects with preretinal fibrosis involving the macula

c. Subjects with history of idiopathic or autoimmune uveitis

d. Subjects with active or suspected ocular or peri-ocular infection including but not limited to infectious blepharitis, keratitis, scleritis, or conjunctivitis

6. Subjects who received previous therapy with antiangiogenic drugs for either eye (pegaptanib, bevacizumab, ranibizumab, aflibercept).
7. Subjects who have received previous systemic antiangiogenic drugs (bevacizumab, aflibercept).
8. Subjects with current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol.
9. Subjects who plan to participate in another clinical study while enrolled in this study and/or who have received an investigational drug and/or device within 30 days or 5 half-lives, whichever is longer, prior to screening.
10. Subject receiving treatment for a serious systemic infection.
11. Subjects with uncontrolled diabetes mellitus as defined by HbA1c ≥10% at screening
12. Subjects with uncontrolled hypertension defined as systolic blood pressure > 160 mm Hg or diastolic blood pressure > 95 mm of Hg.
13. Subjects with a history of cerebrovascular accident or myocardial infarction within 6 months of randomization.
14. Subjects with renal failure requiring dialysis or renal transplant.
15. Subjects who have only one functional eye, even if the eye met all other study requirements, or who have an ocular condition on the fellow eye with a poorer prognosis than the study eye.
16. Presence or history of malignant neoplasm (including lymphoproliferative disease), except for adequately treated basal cell carcinoma and cervical carcinoma in situ; or any malignancy with complete remission of more than 5 years.
17. Subjects with a history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, psychiatric disease, or any other condition, that in the opinion of the Investigator would jeopardize the safety of the subject or the validity of the study results.

4.3.3 Criteria for study drug termination, withdrawal from the study and study termination

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study center.
Every effort should be made to retain subjects in the study. When available, a reason for not completing the study will be recorded in the electronic case report form (eCRF).
If, a subject discontinues from the study prematurely, due to any reason as provided in the below withdrawal criteria, the site should request the subjects' consent for being followed-up during further study visits or at least until the Week 8 to perform safety and efficacy assessments as per the Study Schedule (Table 1).

A subject may be required to terminate study drug for reasons including the following:

- The subject withdraws consent.
- For female subjects, diagnosis of pregnancy or stated intention to become pregnant. All efforts should be made by the site to obtain consent from the pregnant women, so that they are followed until delivery or termination.

- At the investigator's discretion (it is recommended that the investigator discusses with medical monitor prior to decision), if it is in the subject's best interest due to occurrence of an AE and/or other findings considered to present a safety concern to continued dosing with study drug, which include but not limited to:
    - Development of hypersensitivity reaction suspected to be attributable to study drug which may contraindicate the continued dosing with the study drug
    - Development of ocular or periocular infection, active intraocular inflammation which may contraindicate the continued dosing with the study drug
- Despite education/reinforcement, the subject shows persistent inadequate compliance with required study visits/procedures, potentially compromising safety monitoring while on study drug based on investigator's discretion.
- The subject takes prohibited treatment presenting a safety concern to continued dosing with study drug
- At the investigator's discretion (it is recommended that the investigator discusses with medical monitor prior to decision), in certain situations such as disease flare, progression, or nonresponse that requires treatment with a prohibited medication or procedure, which in the opinion of the investigator warrants treatment withdrawal.
- If the mask is broken for a subject by the Investigator

Subjects who prematurely terminate study will have an Early Termination (ET) visit scheduled as soon as possible.
The Principal Investigator and/or Mylan reserves the right to terminate the study for any reason.
The study will be terminated early if there are significant safety concerns.

4.4 Contraception

4.4.1 Females - Non-Childbearing Potential

Female subjects of non-childbearing potential must meet at least one of the following criteria:

1. Postmenopausal females, defined as females, 45 years of age or more, and who have been amenorrheic for at least 1 year.
2. Females who have a documented hysterectomy and/or bilateral oophorectomy.

All other females will be considered to be of childbearing potential.

For patients in <u>Czech Republic</u>, following are applicable:

Females - Non-Childbearing Potential (Permanently sterile)

Female subjects of non-childbearing potential (permanently sterile) must meet at least one of the following criteria:

1. Postmenopausal females, defined as females, 45 years of age or more, and who have been amenorrheic for at least 1 year, without an alternative medical cause.
2. Females who have a documented hysterectomy, bilateral salpingectomy and/or bilateral oophorectomy.

All other females will be considered to be of childbearing potential.

4.4.2 Females - Childbearing Potential

Female subjects of child-bearing potential must use an acceptable, highly effective method of contraception (i.e., a method with a failure rate <1% when used consistently and correctly)

starting 60 days prior to dosing and continuing at least 90 days following the last treatment, such methods include at least one of the following:

- Abstinence (periodic abstinence is not acceptable)
- Tubal ligation*
- Intrauterine device of intrauterine system*
- Barrier method, like condom*, with spermicide*
- Male partner who has had a vasectomy for at least 6 months. Male partners with vasectomies of <6 months are NOT considered protected
- Hormonal contraceptives (oral*, injected, transdermal or implanted) with the exception of low dose gestagens, i.e. only containing lynestrenol or norethisterone, since they do not inhibit ovulation and are therefore not considered as highly-effective. The subject must remain on the hormonal contraceptive throughout the study and must have been using hormonal contraceptives for an adequate period prior to the study to ensure effectiveness (e.g., 3 months)
  *: For patients in Japan, it must be approved or certified in Japan

For patients in <u>Czech Republic</u>, following are applicable:

Females - Childbearing Potential

Female subjects of child-bearing potential must use an acceptable, highly effective method of contraception (i.e., a method with a failure rate <1% per year when used consistently and correctly) starting 30 days prior to dosing and continuing at least 90 days following the last treatment, such methods include at least one of the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner (Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)

4.4.3 Male subjects (only for patients in <u>Czech Republic)</u>

Male subjects should use highly effective method of contraception starting 30 days prior to dosing and continuing at least 90 days following the last treatment, such methods include at least one of the following:

- Vasectomy with confirmation of success from the doctor
- Consistent use of condom
- Absolute sexual abstinence (refrain from vaginal intercourse)

4.5 Pregnancy Testing

Serum or urinary pregnancy testing will be performed on all females of childbearing potential as described in the schedule of activities (results will be reviewed and must be negative prior to dosing). In the event of a positive test, the subject will be withdrawn from the study (or will not enter the study if during screening).

Any pregnancy occurring after randomization to study drug will be followed up and reported to the sponsor as per Section 9.4.1.

5 STUDY DRUG

5.1 Investigational Drug

Test Product, Dose, and Mode of Administration:

MYL-1701P (a proposed biosimilar to Eylea) injection for intravitreal injection is a sterile, clear, and colorless to pale yellow solution. It is supplied as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 µL) of proposed aflibercept (40 mg/mL) [redacted]

Reference Therapy, Dose, and Mode of Administration:

Eylea is a sterile, clear, and colorless to pale yellow solution. It is supplied as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 µL) of Eylea (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose). Eylea will be sourced from the United States.

5.1.1 Administration of Study Drugs

All subjects are planned to receive study drug as an intravitreal injection at a dose of 2 mg every 4 weeks for a total of 5 injections, and then every 8 weeks through the remainder of the 52-week treatment period, with the last dose at 48 weeks.

Subjects will receive intravitreal injections of MYL-1701P or Eylea throughout the 52-week treatment period, with planned doses at Study Day 1, Day 29 (week 4), Day 57 (week 8), Day 85 (week 12), Day 113 (week 16), Day 169 (week 24), Day 225 (week 32), Day 281 (week 40) and Day 337 (week 48).

In addition to the nine planned doses, study drug may also be administered at Week 20, Week 28, Week 36 and Week 44 based on the visual acuity, and/or SD-OCT at that visit and in accordance with the "criteria for administering additional 4-weekly doses" outlined in Section 5.1.2.

5.1.2 Criteria for administering additional 4-weekly doses

[redacted]

Additional efficacy has not been demonstrated in most subjects when Eylea was dosed every 4 weeks compared to every 8 weeks. Hence, most of the subjects may not require additional 4-weekly doses.

5.1.3 Delayed and Missed Visits and/or Dose

Every attempt should be done to complete the visits and/or dosing with in the given window period for each scheduled visit. The out of window drug administration should be recorded as a protocol deviation.

If dose is given late for unavoidable reasons, the next scheduled dose should occur no sooner than three weeks after the previous dose. The next dose should be scheduled such that it is as

close as possible to the original scheduled date of visit and at least 3 weeks apart from the previous dose. Investigators should ensure that the subjects' general clinical and the ocular conditions are suitable for dosing prior to every dosing.

If the visit is delayed until the start of the window period of the next dose, the visit will be considered as a missed visit.

The reasons for the delayed or missed visits and/or doses must be documented in the patient's study records and appropriate section of the eCRF and all efforts should be taken to administer the subsequent scheduled doses on time.

5.1.4 Administration Procedure

MYL-1701P must only be administered by a qualified person and the dosing regimen is expected to be the same as the current labeling for Eylea. Intravitreal injections should not be performed if the pre-dose intra-ocular pressure is more than 30 mm Hg. (Eylea EU SPC, 2017)

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent).

Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection. The choice of the anesthetic agent and the microbicide can follow institutional practices. The details of the pre-medication administered should be documented.

Immediately following the intravitreal injection, subjects should be monitored for elevation in intraocular pressure. If required, a sterile paracentesis needle should be available. Additionally, vision will be assessed post-injection by hand movements or counting fingers.

Following intravitreal injection, subjects should be instructed to report any symptoms suggestive of intraocular inflammation, endophthalmitis and/or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

If the subject reports any of these symptoms, Investigator will perform OE and appropriate investigations to confirm the diagnosis. Additional immunogenicity samples will be collected if subject has signs of intraocular inflammation, suggesting immune reaction.

Each vial should only be used for the treatment of a single eye. After injection, any unused product must be discarded.

In the event of any significant dosing errors, the CRO Medical Monitor, or designee should be contacted immediately.

5.2 Drug Inventory

Mylan will supply MYL-1701P and US-reference Eylea to the study sites packaged and labeled per all local legal requirements.

Clinical Supplies will provide prepackaged supplies for each subject. A kit will be assigned at randomization using the IXRS.

A label will be attached to the outside of each kit. The text will be compliant with local regulatory requirements and may include some of the following information:

- Protocol number
- Subject number/study center number
- Contents and quantity
- Lot number

- Randomization code/kit number
- Investigator name
- Storage instructions
- Caution statement (for clinical study use only)
- Expiry date
- Sponsor's name and address

5.3 Study Medication Complaints

In the event of a complaint/concern during study participation, regarding the supplied study medication, the site should contact the sponsor. Additional information and potentially the return of study medication may be requested by Mylan to investigate the complaint. The details of the complaint handling will be provided in an appropriate study manual.

5.4 Storage, Disposition of Unused Study Drug and Drug Accountability

The Investigator, or an approved representative, e.g., pharmacist, will ensure that all investigational products are stored in a secured area under recommended storage conditions and in accordance with applicable regulatory requirements while at the investigator site.

Study drug should be stored in accordance with the drug label. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.

Temperature of storage facilities should be monitored and recorded daily using validated devices that record maximum and minimum temperatures. Should the storage facility experience any excursion of temperature outside of the labelled storage condition this must be reported immediately to Mylan or designee. At sites where daily monitoring and recording is not possible at weekends, then on the next working day after the weekend the temperature record (e.g., max/min thermometers) should be checked immediately for any temperature excursions. Devices used for temperature monitoring should be regularly calibrated. Affected material must be placed into quarantine until the impact of the excursion has been assessed and confirmed by Mylan.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the study drug. If Mylan or CRO supplies drug accountability forms, these must be used. Alternatively, Mylan may approve use of standard institution forms. In either case, the forms must identify the study drug, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Mylan or designee.

At the end of the study, Mylan will provide instructions as to disposition of any unused investigational product. If Mylan authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Mylan. Destruction must be adequately documented.

5.5 Masking

Considering the ophthalmology indication, the term "masking" has been used instead of "blinding" throughout the protocol.

The study drug will be provided as glass vials and syringes.

<u>Masked personnel</u>

Investigator will be masked throughout the study. Investigator/designee will perform all study assessments prior to and following study drug administration. Investigator will also decide on the requirement of optional injections as necessary.

Unmasked Personnel

If an alternate ophthalmologist is available at the site:

An alternate ophthalmologist will be identified to be responsible for preparation and administration of the study drug. Ophthalmologist administering the study drug will perform the post injection procedures like measurement of IOP and any safety assessments up to 30 minutes after the study drug administration. However, the ophthalmologist administering the study drug will not perform any other study assessments including safety and efficacy assessments. If the unmasked ophthalmologist is not available at 30 minutes after dosing, the masked ophthalmologist may perform post-dose safety assessments.

An unmasked site personnel, may be identified to be responsible for the receipt, tracking, preparation and destruction of study drug.

If an alternate ophthalmologist is not available at the site; and a qualified unmasked Pharmacist or Physician Assistant is available at site:

Incases, where the site does not have an alternate ophthalmologist, a qualified unmasked study personnel, i.e., unmasked pharmacist, physician assistant, will be identified to be responsible for the receipt, tracking, preparation and destruction of study drug. The identified qualified pharmacist/physician assistant will prepare the drug and hand over the syringe to the masked Investigator for intravitreal administration. Every effort should be taken to avoid any accidental unmasking of masked study personnel during the process. The detailed instructions will be given in a separate masking and unmasking plan.

Every effort will be made to ensure that all other study site personnel other than those designated as unmasked, remain masked to treatment assignment.

Masked and unmasked roles will be assumed for the entire study and, switching from an unmasked to a masked role after the first subject is randomized at a site is not permitted. Any deviation to the roles above must be approved by the sponsor, and properly documented before any subjects are treated. The Site Signature and Delegation Log are required to be maintained as new personnel are added to the study team.

The central SD-OCT assessment, and central laboratory assessment, including safety, PK and immunogenicity, will be performed by the masked personnel. The complete details of the study personnel with their masking status will be maintained in the Masking and Unmasking plan.

The responsibilities of the Masked personnel are as follows:

- Perform all screening procedures up until randomization
- Assess inclusion/exclusion criteria
- Obtain medical, surgical, ophthalmic and smoking history
- Obtain informed consent
- Collect and process samples for laboratory testing
- Acquire SD - OCT, fundus photography (FP), and fluorescein angiography (FA) images and transfer them to reading centers
- Acquire ECGs
- Perform study drug administration (when preparation of study drug is done by an identified unmasked pharmacist, physician assistant at the site)

- Perform post-treatment safety assessments (except for post injection procedures like measurement of IOP and any safety assessments up to 30 minutes after the study drug administration).
- Decide on need for additional treatment, if any
- Assess AEs, including severity and relationship
- Perform complete OE at all study visits
- Evaluate all safety, including review of images for safety concerns at the site
- Evaluate vital signs and ECGs; perform physical examinations
- Test refraction and BCVA
- Check IOP
- Assess SD - OCT, FP/FA.

Responsibilities of the Unmasked Personnel are as follows:

- Receipt, tracking, and destruction of study drug
- Prepare study drug
- Study drug administration and post injection procedures like measurement of IOP and any safety assessments up to 30 minutes after the study drug administration (*when unmasked ophthalmologist is identified at the site*)

Note: For patients in Czech Republic, additionally, the masked or unmasked ophthalmologist can monitor the patient for clinical signs and symptoms suggestive of adverse events for at least 60 minutes after the study drug administration.

5.6 Randomization

Assignment of Subject Identification number (SID), randomization number and study medication, as well as site drug inventory control will be managed by an automated IXRS. A manual containing complete instructions for Web or telephone access and use will be provided to each site prior to study start. At their first clinic visit, the IXRS will assign a SID. Each SID will be unique and serve as the primary subject identifier throughout all phases of the study. The SID must appear on all CRF pages, source documents, laboratory data, ECG and diary data. Subjects qualifying to enter the study drug treatment phase, will be assigned an additional "randomization number" by the IXRS at randomization.

For those patients added to the study as per section 7.1, randomization will be according to the original randomization schedule, i.e the next one available will be enrolled, and NOT replace the old patients' treatment.

5.7 Breaking the Mask

Regardless of the assigned treatment arm, all subjects in the study are provided with active treatment, MYL-1701P or Eylea.

The masked treatment code must not be broken, except in emergency situations for which the identification of the study treatment of a subject is required by the Investigator in case of a medical emergency and when the knowledge of the study treatment allocation is required for appropriate management of the medical event. Investigator should access the 'Emergency Codebreak' module in the IXRS system for breaking the mask. The details of the procedure for "Emergency Codebreak via Web" are provided in the IXRS User Manual. In such situations, the randomization information will be held by designated individual(s), and the date and reason for breaking the mask must be recorded. The investigator should follow the study's randomization procedures and should ensure that the code is broken only in accordance with the protocol. As the study is masked, the investigator should promptly document and explain to the sponsor any premature unmasking (e.g., accidental unmasking,

unmasking due to a serious adverse event) of the investigational product(s). Unmasking of treatment code for final data analysis will be done after database lock. Unmasking process will be performed in accordance to both Sponsor's and CRO's unmasking SOPs, as detailed in the statistical analysis plan.

In the event that the mask is broken for a subject by the Investigator, this subject is to be withdrawn from the study.

5.8 Concomitant Medications

All concomitant medications taken during the study (from signing informed consent to post-study follow-up) must be recorded with indication, daily dose, frequency, and start and stop dates of administration in the CRF. All subjects will be questioned about concomitant medication at each clinic visit and at follow up.

Medications taken within 90 days prior to screening and prior to dosing with study medication will be documented as a prior medication. Any other important medications relevant to the treatment condition or the study treatment (e.g., prior treatment for DME) taken before the 90 days are also recommended to be recorded.

Medications taken after dosing with study medication will be documented as concomitant medications.

Prohibited Medications

Subjects will abstain from all prohibited medications as described in Table 2. Use of prohibited medication after randomization and during the study will be deemed a protocol deviation and such subjects will be assessed by Mylan or designee regarding potential need to early terminate study drug (e.g. for safety reasons - see Section 4.3.3).

Table 2: List of Prohibited Treatment

- Use of intraocular or periocular corticosteroids or other DME therapy in study eye
- Antiangiogenic drugs for study eye (e.g., pegaptanib, bevacizumab, ranibizumab, aflibercept)
- Systemic antiangiogenic drugs (e.g., bevacizumab, aflibercept)
- Drugs that optimize (retinal) microcirculation e.g., calcium dobesilate
- Pan-retinal or macular laser photocoagulation in the study eye for the treatment of DME
- Systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol
- Concurrent treatment with an investigational drug or device in the either eye
- Any other medication/treatment which can impact the visual acuity or safety while on concurrent treatment with aflibercept based on Investigator's discretion.

Permitted Medication

Any medication other than the identified prohibited medications that were considered necessary for the subject's best interest and not expected to interfere with the safety or efficacy of the study drug can be given at the discretion of the Investigator. Investigator is recommended to consult the Medical Monitor if he/she is unclear on the impact of a concomitant medication on the study endpoints.

5.8.1 Study Eye

Subjects will not be allowed to receive any medications (approved or investigational) for their DME in the study eye other than the study treatment (MYL-1701P or Eylea), as

specified in the protocol, until they had completed the end of study (week 52) or early termination visit assessments. The prohibited medications should neither be administered locally (e.g., IVT, topical, juxtascleral, or periorbital routes), nor systemically, with the intent of treating the study eye.

5.8.2 Fellow / Non-study Eye

If the fellow eye had DME involving or threatening the center of the macula, requiring treatment, standard of care therapy can be administered, if necessary. All fellow eye treatments must be recorded on the eCRF as a concomitant medication and/or procedure for the fellow eye. The fellow eye will not be considered an additional study eye. Subjects who receive treatment for the fellow eye will not be withdrawn from the study. Safety of the fellow eye should be monitored, and all AEs collected. Other conditions in the fellow eye could be treated with approved therapies.

Immunogenicity and safety of subjects who received intravitreal anti-VEGF therapy in the fellow eye will be analyzed separately and the analysis will be detailed in the statistical analysis plan.

5.8.3 Management of Diabetes

The subject will receive treatment for diabetes as per standard of care, per institutional practice and as prescribed by the treating physician.

6 STUDY CONDUCT

Subjects eligible for study recruitment will have the nature, purpose, and risks of the study explained to them by the investigator. They will be provided with a written copy of the informed consent form (ICF) for the study and given sufficient time to consider the study's implications before deciding to participate. A separate PK consent form will be provided to the subjects willing to participate in the PK subpopulation at the participating sites. Subjects agreeing to participate in the study will sign the ICF and be given a duplicate copy before undergoing any screening or pre-screening (if required) procedures. For every subject screened, a unique SID will be issued at the time of consent by contacting the IXRS system.

Once a subject enrolls in this study, the site will make every effort to retain the subject for the planned duration of the study. Clinical study site staff are responsible for developing and implementing support and retention plans. Elements of this plan may include the following.

- Thorough explanation of the complete clinical study visits schedule and procedural requirements during the informed consent process and re-emphasis at each clinic visit
- A simple explanation of the key data and key time points that are critical for the study's successful analysis, and the importance of all the treatment groups to the overall success of the study
- Discussion at screening, and subsequent regular review of possible barriers to clinic visit attendance and full study participation and compliance
- Collection of contact information at screening (address, phone numbers, email), which is regularly reviewed at subsequent clinic visits
- Use of appropriate and timely study visit reminders
- Immediate and multifaceted follow-up on missed clinic visits, including the possible use of trained staff to complete in-person contact with subjects at their homes

In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject so that they can appropriately be withdrawn from the study. All contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the CRF. Regardless of site plans to support and retain subjects within the study, subjects may voluntarily withdraw from the study for any reason and at any time.

For a subject that completes the study and all procedures, it is anticipated that the duration of study would be up to 13 months (56 weeks).

6.1 Screening Procedures

Each prospective subject must agree to participate in screening procedures by signing the most recent ICF before any screening procedure is initiated. Each subject will be assigned a SID via IXRS. The Principal Investigator or Sub-Investigator will review the inclusion and exclusion criteria to confirm eligibility of each subject prior to enrolment.

6.1.1 Screening Visit [Day -28 to Day -1]

Subjects will commence screening procedures within 28 days prior to randomization, to confirm that they meet the selection criteria for the study. If the time between screening procedures and potential randomization exceeds 28 days as a result of unexpected delays, then the subject's status will need to be discussed with Mylan or designee to consider potential for re-screening (if re screening is agreed, the subject will need to be re-consented

and assigned a new SID via IXRS). Re-screening for other reasons may be possible following discussion with the CRO Medical Monitor. If re-screening occurs this will be clearly documented within the site file.

At the Screening Visit, the following procedures will be completed:

- Written informed consent
- Medical, surgical, ophthalmic and smoking history, demographics
- Check study inclusion/exclusion criteria
- Measure height and weight
- Serum pregnancy test (if female of child-bearing potential)
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Prothrombin time, activated partial thromboplastin time and INR
- Record vital signs – sitting blood pressure, pulse rate and temperature
- Targeted physical examination
- Record 12-lead ECG
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of Intraocular pressure (IOP)
- SD-OCT/CRT (*used for eligibility assessment by central reading*)
- Fluorescein Angiography (FA)/Fundus Photography (FP)
- Review AEs and concomitant medications

6.2 Treatment phase

6.2.1 Baseline Visit/Visit 1 (Day 1)

The following Procedures will be completed:

- Measure weight
- Urine pregnancy test (if female of child-bearing potential)
- Record vital signs – sitting blood pressure, pulse rate and temperature
- Targeted physical examination
- BCVA (*confirm eligibility*)
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of Intraocular pressure (IOP)
- SD-OCT/CRT (*used for eligibility assessment, based on Investigator assessment performed at site*)
- Check study inclusion/exclusion criteria
- Randomization
- Blood Sampling for Immunogenicity prior to dosing
- Sampling for assessment of drug tolerance or PK prior to dosing
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Record 12-lead ECG
- Study Drug Administration
- Measurement of IOP and assessment of vision by hand movements or counting fingers post-injection
- Review AEs and concomitant medications
- Issue study diary

6.2.2 Visit 2 (Day 3)

<u>This visit will be conducted at clinic only for the subjects in sentinel cohort and subjects in the pharmacokinetic subgroup; for all other subjects, it will be a telephonic visit.</u>

For Subjects in Sentinel Cohort, following procedures will be performed:

- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- Review study diary
- Review AEs and concomitant medications

For Subjects in PK Subgroup, following procedures will be performed:

- Review study diary
- Review AEs and concomitant medications
- Blood sampling for PK

For the other subjects, telephonic follow up will be done to

- Review study diary
- Review AEs and concomitant medications

6.2.3 Visit 3 (Week 1 ± 2 days)

The following Procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature
- Targeted physical examination
- Record 12-lead ECG
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- Blood Sampling for Immunogenicity
- Sampling for assessment of drug tolerance or PK
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Review study diary
- Review AEs and concomitant medications

6.2.4 Visit 4 (Week 4 ± 3 days)

The following Procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- SD-OCT/CRT
- Blood Sampling for Immunogenicity prior to dosing
- Sampling for assessment of drug tolerance or PK prior to dosing
- Urine pregnancy test (if female of child-bearing potential)
- Study Drug Administration
- Measurement of IOP and assessment of vision by hand movements or counting fingers post-injection
- Review study diary
- Review AEs and concomitant medications

6.2.5 Visit 5 (Week 8 ± 3 days)

The following Procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- SD-OCT/CRT
- Blood Sampling for Immunogenicity prior to dosing
- Sampling for assessment of drug tolerance or PK prior to dosing
- Urine pregnancy test (if female of child-bearing potential)
- Study Drug Administration
- Measurement of IOP and assessment of vision by hand movements or counting fingers post-injection
- Review study diary
- Review AEs and concomitant medications

6.2.6 Visit 6 (Week 12 ± 7 days)

The following Procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- SD-OCT/CRT
- Clinical laboratory tests (serum chemistry, hematology and urinalysis)
- Prothrombin time, activated partial thromboplastin time and INR (For patients in Czech Republic only)
- Urine pregnancy test (if female of child-bearing potential)
- Study Drug Administration
- Measurement of IOP and assessment of vision by hand movements or counting fingers post-injection
- Review study diary
- Review AEs and concomitant medications

6.2.7 Visit 7 (Week 16 ± 7 days)

Visit 7

The following Procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- SD-OCT/CRT
- Blood Sampling for Immunogenicity prior to dosing
- Sampling for assessment of drug tolerance or PK prior to dosing
- Urine pregnancy test (if female of child-bearing potential)
- Study Drug Administration

- Measurement of IOP and assessment of vision by hand movements or counting fingers post-injection
- Review study diary
- Review AEs and concomitant medications

Visit 7A (Only for PK subpopulation)

Additionally, a Visit 7A (2 days after the Visit 7) will be performed for subjects included in the PK subpopulation:

- Blood sampling for PK
- Review study diary
- Review AEs and concomitant medications

6.2.8 Visit 8 (Week 20 ± 7 days)/ Visit 10 (Week 28 ± 7 days)/ Visit 12 (Week 36 ± 7 days)/Visit 14 (Week 44 ± 7 days)

The following Procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- SD-OCT/CRT
- Urine pregnancy test (if female of child-bearing potential)
- Prothrombin time, activated partial thromboplastin time and INR (Only at Visit 12 [Week 36 ± 7 days]) [For patients in Czech Republic only]
- Optional Study Drug Administration (based on Investigator discretion as described in Section 5.1.2
- Measurement of IOP and assessment of vision by hand movements or counting fingers post-injection (if study drug is administered)
- Review study diary
- Review AEs and concomitant medications

6.2.9 Visit 9 (Week 24 ± 7 days)

The following Procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature
- Targeted physical examination
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- SD-OCT/CRT
- Blood Sampling for Immunogenicity prior to dosing
- Sampling for assessment of drug tolerance or PK prior to dosing
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Prothrombin time, activated partial thromboplastin time and INR (For patients in Czech Republic only)
- Record 12-lead ECG
- Urine pregnancy test (if female of child-bearing potential)
- Study Drug Administration

- Measurement of IOP and assessment of vision by hand movements or counting fingers post-injection
- Review study diary
- Review AEs and concomitant medications

6.2.10 Visit 11 (Week 32 ± 7 days)

The following Procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- SD-OCT/CRT
- Blood Sampling for Immunogenicity prior to dosing
- Sampling for assessment of drug tolerance or PK prior to dosing
- Urine pregnancy test (if female of child-bearing potential)
- Study Drug Administration
- Measurement of IOP and assessment of vision by hand movements or counting fingers post-injection
- Review study diary
- Review AEs and concomitant medications

6.2.11 Visit 13 (Week 40 ± 7 days)

The following Procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- SD-OCT/CRT
- Blood Sampling for Immunogenicity prior to dosing
- Sampling for assessment of drug tolerance or PK prior to dosing
- Urine pregnancy test (if female of child-bearing potential)
- Study Drug Administration
- Measurement of IOP and assessment of vision by hand movements or counting fingers post-injection
- Review study diary
- Review AEs and concomitant medications

6.2.12 Visit 15 (Week 48 ± 7 days)

The following Procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- SD-OCT/CRT
- Prothrombin time, activated partial thromboplastin time and INR (For patients in Czech Republic only)Urine pregnancy test (if female of child-bearing potential)
- Study Drug Administration

- Measurement of IOP and assessment of vision by hand movements or counting fingers post-injection
- Review study diary
- Review AEs and concomitant medications

6.2.13 Visit 16 (Week 52 ± 7 days) [End of Study Visit]

The following Procedures will be completed:

- Measure weight
- Record vital signs – sitting blood pressure, pulse rate and temperature
- Serum pregnancy test (if female of child-bearing potential)
- Targeted physical examination
- Record 12-lead ECG
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- SD-OCT/CRT
- Blood Sampling for Immunogenicity
- Sampling for assessment of drug tolerance or PK
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Fluorescein Angiography/Fundus Photography
- Review AEs and concomitant medications
- Collect the study diary

6.2.14 Early Termination (ET) visit

Subjects may request termination of study drug or withdrawal from the study at any time, or be required to withdraw or terminate study drug by the investigator or sponsor for reasons as per Section 4.3.3. If study drug is terminated or the subject withdraws or is withdrawn, the reason for termination/withdrawal should be established and recorded. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document the outcome of subject contact attempt, if possible. The investigator will contact Mylan or designee in the event that a subject fails to complete the study or violates the protocol.

If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Unless consent is withdrawn, subjects who prematurely terminate study drug will be asked to return to the clinic for an ET visit and will have this scheduled as soon as possible after their last dose of study drug.

The following Procedures will be completed:

- Measure weight
- Record vital signs – sitting blood pressure, pulse rate and temperature
- Serum pregnancy test (if female of child-bearing potential)
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Targeted physical examination
- Record 12-lead ECG
- BCVA

- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of IOP
- SD-OCT/CRT
- Blood Sampling for Immunogenicity
- Sampling for assessment of drug tolerance or PK
- Fluorescein Angiography/Fundus Photography
- Review AEs and concomitant medications
- Collect the study diary

6.3 Treatment Procedures

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator or designated representative will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the investigator or designated representative will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The monitor or designee from the CRO study team will be informed of these incidents in a timely fashion.

Activities specific to this protocol are expanded upon further below.

6.3.1 Efficacy Assessments

The refractionist and visual acuity examiner, the examiner for the primary outcome measurement, for each subject will be masked to the treatment assignment and study eye.

The subject and ophthalmologist (evaluating Physician) will be masked to whether the subject is receiving MYL-1701P or Eylea.

6.3.1.1 Ophthalmologic Examination

A study ophthalmologist (evaluating Physician) will perform a dilated eye examination of each eye of the subject to establish that the ocular inclusion criteria are met and that none of the ocular exclusionary conditions are present.

Only one eye will be classified as study eye. Study eye will be decided based on BCVA, CRT and other eligibility assessments at the discretion of the masked investigator. If both eyes are eligible, the study eye will be selected by the principal investigator (masked). Once the study eye has been determined, it should remain the study eye throughout. If the fellow eye develops DME or if the condition of DME in the fellow eye worsens during the study, the fellow eye must not be considered as the study eye.

The complete OE will include:

Prior to Study Drug Administration

Intraocular pressure:

Intraocular pressure of the study eye will be measured using standard devices (e.g., Goldmann applanation tonometry or Tono-pen™). The same method of IOP measurement will be used in each subject throughout the study.

Indirect Ophthalmoscopy:

Subjects' posterior pole and peripheral retina will be examined by indirect ophthalmoscopy.

Slit Lamp Biomicroscopy:

Subjects' anterior eye structure and ocular adnexa will be examined using a slit lamp.

After Study drug administration:

Finger Counting

Vision will be assessed post-injection by hand movements or counting fingers.

Intraocular pressure:

Intraocular pressure of the study eye will be measured using standard devices (e.g., Goldmann applanation tonometry or Tono-pen™). The same method of IOP measurement will be used in each subject throughout the study. Intraocular pressure is measured at approximately 30 minutes post-dose.

For Czech Republic, additionally, patient will be monitored by the masked or unmasked ophthalmologist for clinical signs and symptoms suggestive of adverse events for at least 60 minutes after the study drug administration.

6.3.1.2 BCVA

Visual acuity of the study eye and fellow eye will be evaluated using the ETDRS protocol at 4 meters (further detailed in a separate visual acuity testing protocol).

Refraction and testing of visual acuity to fulfill study eligibility criteria must be performed before the subject's eyes are dilated and before fundus photography and SD-OCT if these procedures are to be carried out on the same day. Refraction must precede visual acuity testing. A certified Visual Acuity Examiner must perform the standardized, ETDRS visual acuity testing. The visual acuity examiner will be masked to the treatment assignment. All efforts should be made for the visual acuity examiner to have no knowledge of the study eye and have no ready access to the subject's previous BCVA recorded.
It is recommended that same Visual Acuity Examiner performs VA throughout the study, specifically at baseline and Visit 5 (Week 8).

A detailed protocol for conducting the VA testing and refraction will be provided as part of study procedure manual.

6.3.1.3 SD-OCT/CRT

Central retinal thickness and other retinal characteristics will be evaluated at scheduled visits using SD-OCT. The CRT will be measured as central subfield thickness.

An OCT of the study eye and fellow eye will be performed by a certified OCT Technician according to the standardized procedures described in separate manual prepared for this study. OCT images for the study eye will be transmitted to an independent image reading center. All OCT images will be archived electronically at the study sites as part of the source documentation. OCT technicians will be certified to maintain quality and consistency. OCT technicians will be masked to the study drug assignment.

At screening, for subject eligibility assessment, CRT will be assessed by central reading of SD-OCT images.

At randomization, for assessment of continued eligibility of the subject, CRT reading by the Investigator performed at the site will be used.

Similarly, for assessment of requirement of additional 4-weekly doses as described in Section 5.1.2, the CRT reading by the Investigator performed at the site will be used.

However, for efficacy analysis the central CRT reading of SD-OCT at all visits will be considered.

Because the eye must be dilated for OCT, it must be performed after testing visual acuity if these procedures are carried out on the same day.

6.3.1.4 Fluorescein Angiography/ Fundus Photography

The anatomical state of the retinal vasculature of the study eye and fellow eye will be evaluated by FA/FP at the screening visit and end of study visit at Week 52. The FA/FP from the screening visit (visit 1) will be captured and transmitted to the central reading center for both eyes and reviewed before randomization for eligibility assessment.

FA/FP images from the end of study visit will be read by the investigator at the site, but the images must be transmitted to the central reading center for archival.

All FA/FP images will be archived electronically at the study sites as a part of source documentation.

Photography must be performed after testing visual acuity if these procedures are to be carried out on the same day. Fluorescein Angiography/Fundus Photography will be done after other investigations including blood and urine samples are collected to avoid any interference from fluorescein. A detailed protocol for image acquisition and transmission will be provided in the study procedure manual.

6.3.2 Safety Testing

6.3.2.1 Adverse Event Assessment

If subject reports any symptoms before drug administration, they will be evaluated by medical staff and necessary measurements will be performed. The Principal Investigator or Medical Sub-Investigator will be notified before dosing to determine the course of action.

Subjects will be routinely queried regarding the presence or absence of adverse events using open ended questions. The clinic will provide documentation of any adverse events in the subject's eCRF. The adverse event source documentation will minimally include the following information: date and time of assessment, the outcome of the response, and identification of the clinic staff member collecting the information.

Arterial thromboembolic events following intravitreal use of study drug will be classified according to Hicks et al, 2018 by an Independent Cardiovascular Adjudication Committee.

For any potential allergic reaction after administration of study drug, diagnosis and assessment of anaphylaxis will be done using NIAID/FAAN criteria of anaphylaxis; the management of anaphylaxis should follow the standard institutional practices (Appendix 11.1)

6.3.2.2 Laboratory Safety

The following clinical safety laboratory tests will be performed at times defined in the study schedules in Section 6.1 and Section 6.2.

Table 3: Laboratory Safety Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	HbA1c[c]	pH	Serum hCG[b]
Hematocrit	Urea and Creatinine	Glucose (qual)	Urine Pregnancy Test (Locally)
RBC count	Glucose (non-fasting)	Protein (qual)	
Platelet count	Calcium	Blood (qual)	
WBC count	Sodium	Ketones	
Neutrophils	Potassium	Nitrites	
Eosinophils	Chloride	Leukocyte esterase	
Monocytes	Total CO_2 (Bicarbonate)	Microscopy[a]	
Basophils	AST, ALT		
Lymphocytes	Total Bilirubin		
PT	Direct/Indirect bilirubin		
aPTT	Alkaline phosphatase		
INR	Uric acid		
	Albumin		
	Total protein		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. At visits, as per study schedule
c. HbA1c testing will be done at Screening, Baseline, Visit 6 (week 12), Visit 9 (week 24), EOS/ET

Hematology and chemistry will be analyzed by central laboratory. Urinalysis will be conducted by dipstick at site and if urine is positive for blood, protein, nitrites, or leukocyte esterase, will be analyzed via microscopy by a central laboratory.

Additionally, prothrombin time, activated partial thromboplastin time and INR will be done at screening. For Czech Republic patients, additional tests of prothrombin time, activated partial thromboplastin time and INR will be performed every three months (at Visit 6, 9, 12 and 15) during the treatment period.

Blood volumes to be collected and blood and urine sample handling instructions will be provided in the central vendor laboratory manual. The central laboratory will provide collection materials and directions for packaging and shipment of samples.

If any blood sample could not be analyzed due to issues in the sample collection, processing or shipment, the investigator may repeat the sampling to be analyzed in the central laboratory.

Any clinically significant findings in laboratory safety data should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.3.2.3 Vital Signs

Vital signs include BP, pulse rate and temperature. Blood pressure will be measured after the subject was sitting for 5 mins. Vital signs will be measured at times specified in Section 6.1 and Section 6.2.

Sitting blood pressure will be measured with the subject’s arm supported at the level of the heart and recorded to the nearest mmHg after 5 minutes of rest. Where possible, the same arm (preferably the dominant arm) will be used throughout the study.

The same size blood pressure cuff, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring blood pressure (BP) and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. Any clinically significant changes in blood pressure and pulse rate should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.3.2.4 12-lead ECG

In this study, 12-lead ECGs should be collected at times specified in the study schedule in Section 6.1 and Section 6.2.

To ensure safety of the subjects, a medically qualified individual at the site will assess ECG recordings and make any comparisons to baseline measurements. The ECG data (QT interval, heart rate [HR], QRS duration, PR and RR interval) will be recorded.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. Any clinically significant ECG abnormalities measured at screening should be assessed for their effects on subject eligibility of the study and recorded in medical history. Any clinically significant changes between the screening and subsequent ECGs should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.3.2.5 Targeted Physical Examination

A targeted physical examination will be performed at time points specified in the study schedule in Section 6.1 and Section 6.2. The targeted physical examination will include evaluation of the head, eyes, ears, nose and throat. If indicated, based on report of adverse events or result of safety laboratory test, directed physical exam of relevant organ systems will be performed at additional visits as necessary.

Any clinically significant finding at Screening Visit should be recorded under medical history and changes between Screening Visit and subsequent examinations should be recorded as an AE. Determination of clinical s ignificance and seriousness will be based on the investigator's medical judgment.

6.3.3 Pharmacokinetic Assessment

The PK sampling will be done only in subjects enrolled in the PK subpopulation. The PK subpopulation will include at least 32 subjects in each study arm. The PK assessment will be performed at time points specified in the study schedule in Table 1 and Section 6.2.

The blood samples will be analyzed for free aflibercept concentrations using a fully validated analytical method.

The exact time of study drug dosing and PK sample collection will be noted for subjects in PK subpopulation.

6.3.4 Immunogenicity Assessment

The multi-tiered sample analysis recommendations for immunogenicity testing will be employed for the immunogenicity assessment. (FDA 2016; Mire-Sluis AR et al., 2004; Shankar G et al., 2008)

All samples designated for immunogenicity evaluation will undergo a screening assay to detect the presence of antidrug antibodies (ADA) against aflibercept. Samples identified as positive in the screening assay will then be tested in a confirmatory assay. Confirmed positive samples will be further evaluated for antibody titer and the presence of neutralizing antibodies against aflibercept.

Additionally, free aflibercept concentration in all the ADA samples will be determined to evaluate drug tolerance status.

Antidrug antibody, neutralizing antibody, and drug concentration analysis will use fully validated analytical methods. Bioanalytical methodology and procedures will be documented in a sample analysis protocol.

6.3.5 Blood Volume

Blood samples will be collected for immunogenicity, drug tolerance and safety laboratory investigations as detailed in Study Schedule (Table 1). Additionally, blood samples will be collected for PK analysis in the subjects who are part of the PK subpopulation as specified in Study Schedule (Table 1).

6.3.5.1 Immunogenicity Blood Sampling

Blood samples will be collected for immunogenicity analysis from all subjects at the time points presented in the Study Schedule (Table 1). Up to 4 blood samples (5 ml each) will be collected at each time point, except for baseline pre-dose time point, where 6 samples (5 ml each) will be collected. One sample will be used to determine the presence of ADA against aflibercept and 1 sample will be used to determine the presence of neutralizing antibodies against aflibercept. The other 2 samples collected will be stored in reserve for potential supplemental immunogenicity testing and/or characterization. The additional 2 samples, collected at baseline, will be applied for method optimization and validation. The blood samples will be collected by direct venipuncture, and the exact time of blood sampling will be recorded. Sample handling instructions are specified in the laboratory manual.

Blood samples will also be collected for drug concentration (drug tolerance) analysis from all subjects at the time points presented in the Study Schedule (Table 1). One blood sample of 4.5 mL will be taken in CTAD plasma tube (buffered citrate, theophylline, adenosine, and dipyridamole). The blood samples will be collected by direct venipuncture, and the exact time of blood sampling will be recorded. Sample processing and handling instructions are specified in the laboratory manual.

6.3.5.2 Pharmacokinetic Blood Sampling (CTAD Plasma)

One blood sample of 4.5 mL will be taken into a CTAD plasma tube (buffered citrate, theophylline, adenosine, and dipyridamole) at each time point, as outlined in Study Schedule (Table 1). Study Conduct Section (Section 6.1 and Section 6.2) provides detailed information on each procedure and assessment required for compliance with the protocol.

The blood samples will be taken by direct venipuncture, and the exact time of blood sampling will be recorded. Sample processing and handling instructions are specified in the laboratory manual.

6.3.5.3 Safety Blood Sampling

The blood samples will be collected at the time points as presented in Study Schedule (Table 1). The details of the sample handling and shipment will be provided in a separate laboratory manual.

6.3.5.4 Shipment of Samples

The shipment details and assay laboratory contact information will be provided to the investigator site prior to initiation of the study.

7 STATISTICAL ANALYSIS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

7.1 Sample Size Determination

[redacted] A total of 324 subjects will be randomized at 1:1 ratio to each arm after allowing for approximately 10% drop-outs.

[redacted]

[redacted] Randomization will be stratified by BCVA at baseline (ETDRS Letter Scores 73-55 vs 54-38) and geographical region (US, Europe, Japan and Rest of the world).

[redacted]

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7.2 Primary Endpoints

7.2.1 Definition of Primary Endpoints

The primary efficacy endpoint will be the mean change from baseline in BCVA as assessed by ETDRS letters at week 8.

7.2.2 Statistical Methodology for Primary Endpoints

The analysis of the primary endpoint will be based on a mixed model repeated measures analysis with terms for treatment, visit, treatment by visit interaction, and region, together with baseline BCVA as a covariate. The within subject variance-covariance matrix will be assumed to be unstructured, estimation will use restricted maximum likelihood, and the denominator degrees of freedom will use the Kenward-Roger estimate. This model will provide an estimate, standard error, and 90% as well as 95% two-sided CIs for the treatment difference at week 8.

7.2.3 Primary Analysis for Primary Endpoints

Equivalence will be demonstrated if the CIs for the treatment difference of mean change from baseline to week 8 for BCVA are fully contained within the interval (-3, 3). The primary analysis will be performed on the Full Analysis Set (FAS) and will include data from all visits regardless of whether the subject is still receiving study medication.

7.2.4 Sensitivity Analyses for Primary Endpoints

A sensitivity analysis of the primary endpoint will be carried out in which BCVA values after discontinuing study medication will be excluded. Supportive analyses of the primary endpoint will also be produced based on the per protocol (PP) Population.

Additional sensitivity analyses may be performed to address the impact of missing data due to drop-outs. Details will be provided in the SAP.

7.2.5 Missing Data

Missing data will not be imputed in the primary analysis of the primary efficacy endpoint. Imputation techniques in sensitivity analyses will be described in the SAP.

In descriptive summaries and listings, no imputation will be employed.

7.2.6 Sub-Group Analyses

Subgroup analyses by baseline BCVA, age, gender, race, ethnic origin, and geographic region for key efficacy endpoints will be performed. Details will be provided in the SAP.

7.3 Secondary Endpoints

7.3.1 Efficacy

The key secondary efficacy endpoint is

- The mean change from baseline in CRT as determined by SD-OCT over time

Only the central CRT reading of all the SD-OCT images across visits will be used for efficacy analysis.

The other secondary efficacy endpoints will include:

- The mean change in BCVA over time
- Proportion of subjects who gained ≥15 letters from baseline in BCVA, assessed in change from baseline in ETDRS letters over time
- Number of administrations of study drug required

The proportion of subjects who gained ≥15 letters from baseline in BCVA at weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 will be presented by treatment. For each time point, the summary table will present the number of subjects in each treatment, the proportions by treatment, the difference in proportions, and the 95% CI for the difference. These estimates will be unadjusted for covariates.

The number of administrations of study drug required over the treatment period will be descriptively summarized.

The other secondary efficacy endpoints will be analyzed in a similar manner as the primary efficacy endpoint.

All analyses will be performed on the FAS and the PP Population.

7.3.2 Safety

Safety will be assessed over time, based on the following evaluations:

- Ocular (study and fellow eye) and non-ocular adverse events (AE)
- Vital signs
- Physical examinations performed
- Complete OE
- Safety labs (Serum chemistry, hematology and urinalysis)
- Twelve-lead ECGs

The analyses of safety data are described in Section 7.6.

7.3.3 Immunogenicity

Occurrence, titer, and neutralizing capacity of ADA will be summarized at each scheduled sampling time. Subgroup analysis of ADA positive and ADA negative groups on efficacy, safety and pharmacokinetic endpoints will be performed.

7.3.4 Pharmacokinetics

For all the subjects in the PK subpopulation, concentrations of aflibercept (free drug) will be summarized at each scheduled sampling time.

7.4 Analysis Set Definitions

The Safety Population will consist of all subjects who received at least 1 dose of study drug.

Full Analysis Set (FAS) will consist of all randomized subjects who receive any study drug, who have a baseline BCVA, and who also have at least one post dosing BCVA assessment.

Per Protocol (PP) Population will consist of those subjects in the FAS who have no major protocol deviations impacting efficacy as further detailed in the Statistical Analysis Plan. Assignment to the PP Population will be determined prior to unmasking the study.

7.5 Interim Analyses

Interim analysis is not planned for this study.

7.6 Other Safety Analyses

Analysis of all safety data will be performed on the Safety Population and will be presented by the treatment received.

Adverse events (both ocular and non-ocular AE) will be coded using latest version of Medical Dictionary for Regulatory Authorities (MedDRA). The occurrence of AEs and SAEs will be summarized in terms of incidence, as well as in terms of total number of AEs. Analysis of AEs in terms of incidence by severity and by relatedness will also be provided.

Prior and concomitant medications will be coded by the WHO Drug Dictionary Enhanced and will be summarized. Medical history will be listed by subject and coded using the latest version of MedDRA and will be summarized.

For intraocular pressure, descriptive statistics at each visit and change from baseline at each visit will be provided. Other ophthalmological examinations will be summarized as shift tables. Listings will also be provided for each type of safety data.

7.6.1 Vital Signs

Blood Pressure and pulse rate will be listed and descriptively summarized (N, mean, standard deviation, minimum and maximum) by treatment group and visit. Baseline (defined as the pre-dose value collected on Visit 1/Day 1) and changes from baseline will be similarly summarized.

7.6.2 ECG Analyses

ECG data; QT, QTc (Fridericia's), heart rate (HR), QRS duration, PR and RR interval will be listed.

Baseline and change from baseline for QT, QTcF, HR, QRS, RR and PR will be summarized using descriptive statistics (N, mean, standard deviation, minimum and maximum) by treatment and study week.

For QTcF a classification of absolute values and increases from baseline will be performed. The number of subjects with maximum absolute QTcF <450 msec, 450 msec ≤QTcF <480 msec, 480 msec ≤QTcF <500 msec and QTcF values ≥500 msec will be tabulated by treatment and visit. The number of subjects with maximum increase from baseline QTcF <30 msec, 30 msec ≤QTcF <60 msec and QTcF ≥60 msec will be tabulated by treatment and visit.

7.6.3 Laboratory Data

Descriptive summaries of observed values and change from baseline will be presented for clinical laboratory evaluations (Serum chemistry and hematology) by treatment group. Assessments of laboratory variables according to clinical relevance will be tabulated by visit and treatment group for each clinical laboratory parameter in frequency tables. Additionally, for each laboratory parameter, shifts in value from baseline to all post-baseline visits will be presented by treatment group in shift tables.

The assessment of categorical urinalysis variables will be tabulated by visit for each urine parameter by treatment group in frequency tables. Additionally, for each of the urine parameters, shifts in assessments from baseline to all post-baseline visits will be presented for each treatment group in shift tables.

8 ADMINISTRATIVE PROCEDURES

8.1 Source Documentation Forms

All clinical data will be recorded by the clinical staff on raw data sheets and/or recorded electronically using validated software. If computerized systems are used to create, modify, maintain, archive, retrieve or transmit source data, they must comply with the applicable regulatory regulations and/or guidance.

The nature and location of all source documents will be documented separately. Source data may be directly captured from devices, transferred from 3rd parties (e.g. laboratory data) or entered manually into eCRF/database.

8.2 Access to Data/Source Documentation

The Investigator or designated representative will permit full access to data and source documentation for the purpose of clinical monitoring, audits, IRB/IEC review and regulatory inspections.

8.3 Clinical Study Report and Case Report Forms (CRFs)

[redacted] The CSRs will be provided in accordance with the International Conference on Harmonization (ICH) E-3 guidelines including Annex I (Synopsis) documenting the clinical execution of the study. The reports will include a description of any protocol deviations. The reports will also include reasons for withdrawals and any necessary treatment. The reports will include changes in study conduct and contingency measures implemented during the restrictions related to the COVID-19 pandemic. A listing of all participants affected by the COVID-19 related study disruption will be included in the CSRs. Analyses and corresponding discussions that address the impact of implemented contingency measures on the safety and efficacy results will also be reported in the CSRs. The reports will also include tables presenting demographics (separate summary tables for enrolled and completed subjects), and adverse events recorded during the study. In addition, the clinical study reports will include a Quality Assurance statement, documenting that the reports have been reviewed for completeness, accuracy, and compliance with the protocol and applicable local and federal regulations. For final clinical reporting purposes only, adverse events deemed “definite”, “probable” or “possible” will be included in the treatment-related summaries/listings.

Case report forms (CRFs) containing data transcribed from subject source documents (as appropriate) and copies of other source documents will be supplied by the clinical site. The Principal Investigator must sign each subject’s CRF after completion of data entry, signifying that the data entered in the CRF is complete and accurate. Electronic CRFs may be provided.

8.4 Adherence to Protocol

Except for an emergency in which proper care for the protection, safety and well-being of the study subjects requires medical treatment, the study will be conducted as described in the approved protocol (and amendments, if applicable), GCP, and applicable SOPs. In addition, the study will be conducted in accordance with the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted. Any deviation(s) from the protocol will be recorded and presented in the final report. Principal investigator should document protocol deviations for all disruptions due to COVID-19 pandemic by referring to COVID-19 in the deviation description.

8.5 Data Handling and Record Retention

All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the study subjects remains protected.

A CRF is required to be completed for each subject receiving study medication. The CRF is property of the sponsor and the Investigator must review all CRFs prior to submission to the sponsor.

All records pertaining to the receipt and return of study supplies (particularly study medication) and copies of final case report forms, worksheets, and other pertinent source documents must be retained in accordance with ICH-GCP and the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

The investigator must obtain in writing the sponsor's agreement to dispose of any records, even if the retention period has been reached.

8.6 Confidentiality

Information furnished to Clinical Investigators and IRBs/Ethics Committees will be maintained in confidence by the Clinical Investigator and IRB/Ethics Committee. By signing this protocol, the Investigator affirms to the Sponsor that he/she will maintain, in confidence, information furnished to the IRB/Ethics Committee relevant to this study under appropriate understanding of confidentiality with such IRB/Ethics Committee.

By signing the protocol, the Investigator agrees that within local regulatory restrictions and institutional and ethical considerations, the Sponsor may consult and/or copy source documents (e.g., laboratory/X-ray reports, ECG tracings, workbooks, medical records) in order to verify CRF data.

8.7 Ethics and Regulatory Authorities

Guidelines will be followed with regard to the treatment of human subjects in the study, in accordance with the requirements of the Declaration of Helsinki and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-E6) in addition to the regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

8.7.1 Institutional Review Board/Ethics Committee

The Investigator is responsible for obtaining initial and continuing review (at intervals not more than once per year) of the study by an IRB/Ethics Committee, or in accordance with applicable government regulations of the country where the study is being conducted as well as the country where the study will be submitted. This study will not enroll any subjects until the IRB/Ethics Committee provides written approval of the protocol and the informed consent to the investigator. In addition, a copy of the IRB/Ethics Committee approval documents must be provided to the sponsor prior to enrolling any subjects into the study.

8.7.2 Regulatory Authority

This clinical study protocol, title and a list of investigational sites, IEC(s)/IRB(s) approvals, as well as other relevant documentation will be submitted to the local Regulatory Authorities for review and approval prior to study start. Upon completion, the Regulatory Authorities will be notified the study has ended. The study will only be undertaken in compliance with the local regulatory requirements.

8.8 Informed Consent

A properly executed, written informed consent in compliance with current GCP guidelines and ICH guidelines shall be obtained from each volunteer prior to entering the study. A copy of the informed consent document to be used will be submitted by the investigator to an independent institutional review board (e.g., IRB or ethics committee) and the Sponsor and/or its agent for review and approval prior to the start of the study. The investigator shall provide a copy of the signed and dated informed consent to the subject, and a signed and dated copy shall be maintained in the volunteer's medical record.

8.9 Disclosure and Publication of Clinical Study Data

The disclosure and publication of clinical study data will be detailed in the clinical study agreement with the Investigators.

8.10 End of Study

The end of study is considered to be the date of last subject last visit or the date of early termination of the study whichever is the later.

9 ADVERSE EVENT REPORTING

9.1 Adverse events

All observed or subject-reported AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as outlined in this section.

Subjects will be provided a study diary to capture adverse events in between the visits. The Investigator/designee will review information recorded in the study diary during the visits. Study diary will be collected back from the Subject prior to study completion or early termination.

The Investigator must pursue and obtain information adequate both to determine the outcome of all AEs and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Mylan. The Investigator is required to assess causality and should obtain sufficient information to determine the causality of all AEs. All AEs will be followed until the event is resolved, deemed to be stable, or until the event is found to be due to another known cause (concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted with the sponsor concurring with that assessment.

9.2 Definitions

9.2.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with drug administration, whether or not related to the product.

The above definition covers also cases of

- Exacerbation of pre-existing diseases or conditions.
    - Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug or drug-food interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent; this should be reported regardless of sequelae.

An AE will be defined as a treatment-emergent adverse event (TEAE) if the first onset (or worsening, in the case of pre-existing disease) is after the first administration of MYL-1701P or Eylea after randomization through EOS/ET.

AEs should be categorized as those related to the Study eye, fellow eye and systemic AEs. AEs reported from subjects receiving Anti-VEGF treatment in fellow eye will be separately reported.

9.2.2 Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose of the investigation products should be considered adverse drug reactions (ADRs). The phrase “responses to an investigational product” means that a causal relationship between an investigational product and an AE is at least a reasonable possibility. All AEs judged by

either the reporting Investigator or the sponsor as having a reasonable causal relationship to an investigational product will be designated as ADRs.

All AEs, with the causal relationship to the study drug reported as “possible”, “probable” or “definite” will be considered ADRs. If the relationship to the study drug is not given, then the AE must be treated as if the relationship were “possible.”

9.2.3 Unexpected Adverse Event/Adverse Drug Reaction

An unexpected AE or ADR is defined as one whose nature or severity is not consistent with the applicable reference safety information designated for the study. For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

The reference safety document is the Investigator’s Brochure for MYL-1701P. For Eylea and any concomitant medication, the respective SmPC or US prescribing information will be the reference safety document.

9.2.4 Serious Adverse Events

A SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
  - NOTE: The term “**life-threatening**” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly.
  - NOTE: A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is considered an SAE. However, a newly diagnosed pregnancy in a subject that has received the study drug is not considered an SAE unless it is suspected that the study drug interacted with a contraceptive method and led to the pregnancy. The subject with newly diagnosed pregnancy will discontinue receiving study treatment and will be followed-up every 3 months until delivery or termination to gather information about the outcome of the pregnancy.
- Is an important medical event.
  - NOTE: Important Medical Event: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject and / or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
  - For this protocol, any cancer, including localized basal cell carcinoma, is considered an important medical event, to be reported as a SAE.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  - NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. Events NOT to be reported as SAEs are hospitalizations for the following:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen.
- Admission to a hospital or other institution for general care due to social or economic reasons (e.g., no access to local ambulatory medical care). Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Hospitalization also does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes

Any non-serious AE that is determined by the medical monitor/sponsor to be serious (per company policy or regulatory requirements) will be communicated to the Investigator for reclassification. To assist in the determination of case seriousness further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical study.

9.3 Management of Adverse Events

AEs or SAEs will be collected from the time the subject signs the informed consent form until the follow-up visit or 28 days after last dose of study treatment. Pre-existing diseases or conditions (reported at visit 1 in medical history) will not be considered as AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition. An SAE deemed to be related to the study drug by the Investigator in consultation with sponsor will be reported even after the Follow-up visit if reported by subjects.

9.3.1 Collection

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The Investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made by the Investigator during the visit will also be considered AEs.

The subject's diary should also be reviewed at each study visit for adverse events. When study diaries are issued, subjects will be appropriately educated by the study designee on what constitutes an adverse event and instructed to record adverse events in the study diary in a timely manner.

9.3.2 Evaluation

9.3.2.1 Severity Assessment of Adverse Events

The clinical severity of an AE will be graded using the NCI-CTCAE Criteria Version 4.03. A copy of these criteria will be provided to each study site. If an AE is not listed in the CTCAE, its clinical severity will be classified as follows:

Table 6: Clinical Severity of Adverse Events

The Investigator will use the terms defined below to describe the maximum intensity of the AE.	
Grade 1 – MILD	Does not interfere with subject's usual function
Grade 2 – MODERATE	Interferes to some extent with subject's usual function
Grade 3 – SEVERE	Interferes significantly with subject's usual function
Grade 4 - LIFE-THREATENING	Risk of death at time of event
Grade 5 – DEATH	Death related to AE

If an AE is graded 4 or 5 according to the above criteria, then the AE meets the criteria for an SAE and the Investigator should immediately notify the sponsor or designee as described in Section 9.3.2.8.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity based on the CTCAE grading or on the above table, whereas an SAE is an AE that meets any of the regulatory specified criteria required for designation as seriousness described in Section 9.2.4.

9.3.2.2 Action Taken

The possible actions taken for an AE are described in Table 7.

Table 7: Action Taken for an Adverse Event

Treatment interrupted	The treatment was temporarily interrupted
Treatment withdrawn	The treatment was permanently discontinued
Unknown	Not known, not observed, not recorded, or refused
No action taken	The AE did not require any intervention
Not applicable	AE occurred after study medication was permanently withdrawn or subject completed the treatment period

9.3.2.3 Outcome at the Time of Last Observation

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Sponsor or its designated representative.

- The outcome at the time of last observation will be classified as:
- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

All ongoing AEs without fatal outcome (i.e., did not cause death) will be recorded as not recovered/not resolved at the time of death.

*Only select fatal as an outcome when the AE results in death. If more than one AE is possibly related to the subject's death, the outcome of death should be indicated for the AE which is the most plausible cause of death in the opinion of the Investigator.

Note: although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

9.3.2.4 Causality Assessment of Adverse Events

For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality of each AE.

An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. The Investigator must make an assessment of the relationship of each AE (serious and non-serious) to the study treatment(s) and record this relationship in the CRF.

In addition, if the Investigator determines an AE or SAE is associated with the protocol specified study procedures, the Investigator must record this information about the causal relationship in the source documents and CRF, as appropriate, and report the assessment in accordance with the reporting requirements, as applicable, AE or SAE.

Factors that need to be considered when making a causality assessment include:

- Temporal relationship (e.g., time of onset)

- Clinical and pathological characteristics of the event(s)
- Pharmacological plausibility
- Exclusion of confounding factors (medical and medication history)
- Drug Interactions
- De-challenge/re-challenge
- Dose relationship

A suspected relationship (definite, probable, and possible) between the events and the study medication means, in general, that there are facts (evidence) or arguments to suggest a causal relationship. Receipt of additional or clarifying information may warrant reassessment of causality. The Investigator is responsible for assessing relationship of AEs to study treatment in accordance with the following definitions (Table 8):

Table 8: Definition of Suspected Relationship between the Events and Study Medication

DEFINITELY	Causal relationship is certain	For Example: the temporal relationship between drug exposure and the adverse event (AE) onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
PROBABLY	High degree of certainty for causal relationship	For Example: the temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to de-challenge (re-challenge is not required), and other causes have been eliminated or are unlikely.
POSSIBLY	Causal relationship is uncertain	For Example: the temporal relationship between drug exposure and the AE onset/course is reasonable or unknown, de-challenge information is either unknown or equivocal, and while other potential causes may or may not exist, a causal relationship to study drug does not appear probable.
UNLIKELY	Not reasonably related although a causal relationship cannot be ruled out	For Example: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible), or disease or other drugs provide plausible explanations.
UNRELATED/NOT RELATED	No possible relationship	The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is impossible.

If the relationship to the study treatment(s) is considered to be unlikely or not related/unrelated, an alternative suspected etiology should preferably be provided (e.g., concomitant medications, intercurrent condition) wherever applicable and available.

9.3.2.5 Documentation

All AEs occurring within the period of observation for the study must be documented in the CRF with the following information; where appropriate:

- AE name or term in standard medical terminology
- When the AE first occurred (start date and time); SAE start date is defined as the date the AE became serious
- When the AE stopped (stop date and time or date and time of last observation if ongoing, i.e., recovering or not recovered)

- Severity of the AE
- Seriousness criteria (hospitalization, death, etc.)
- Action taken with study medication as a result of AE
- Outcome
- Investigator's opinion regarding the AE relationship to the study treatments

9.3.2.6 Treatment of Adverse Events

AEs that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the reason should be documented in the CRF; this can include temporary interruption of study treatment. The decision about whether the subject may resume the study treatment will be made by the sponsor after consultation with the Investigator and/or medical monitor.

9.3.2.7 Follow-up

Any AE will be followed-up to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the appropriate CRF page.

New information and any important missing information from prior reports on a SAE must be provided promptly to the study sponsor. In addition, the Investigator may be requested by Mylan/designee to obtain specific additional follow-up information in an expedited fashion. The investigator should respond to targeted follow-up requests as soon as possible and no later than 48 hours from receipt of the request.

9.3.2.8 Notification

For SAEs, the active reporting period to Mylan, begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including the follow up visit. Should an Investigator be made aware of any SAE occurring any time after the active reporting period, the SAE must be promptly reported to Mylan only in case of reasonable causality (i.e. suspected ADR).

The SAE reporting form is to be completed for all serious adverse events, signed by the Investigator, and emailed or faxed with supporting documentation (e.g., CRFs, hospital records, laboratory reports). Subject identity details (such as but not limited to name or clinic/hospital number) must not be visible on SAE forms or any supporting documentation provided by the Investigator. These should be "blacked out" and replaced with the site and subject's study identification number on every page.

At that time of first notification, the Investigator/designee should provide the following information via the SAE report form:

- Protocol number
- Reporter (study site and Investigator)
- Subject's unique identification number
- Subject's age
- Investigational medicinal product
- Date of first dose of study treatment
- Date of last dose of study treatment, if applicable
- SAE term

- The seriousness criteria that were met
- Investigator's opinion of the relationship to the study treatment
- Severity
- Start and stop (if applicable) of the event (date and time)
- A brief description of the event, outcome to date, and any actions taken
- Concomitant medication at onset of the event
- Relevant past history information
- Relevant laboratory test findings

If the initial notification of an SAE is by telephone, within 24 hours of the initial telephone notification the Investigator must email the written SAE report form that describes the SAE to the Mylan Product Safety and Risk Management department.

The Investigator may be requested by Mylan to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Mylan.

Any missing or additional relevant information concerning the SAE should be provided on a follow-up SAE Report Form. Ensure that any additional information requested by the sponsor or designee about the event, as outlined above (e.g., hospital reports, autopsy report) is provided to the sponsor as soon as it is available.

Sponsor Contact Information for Immediately Reportable Events

All SAEs must be notified within 24 hours by email (preferred) or fax to:

[redacted]

In the event that an electronic acknowledgment is not received within 24 hours for a SAE report submitted by email, please forward the report via fax [redacted]

9.3.2.9 Regulatory Reporting

All AEs, including suspected serious unexpected AEs will be reported in accordance with applicable local regulations. The Investigator is required to comply with applicable regulations (including local law and guidance) regarding notification to her/his regulatory authorities, ethics committees (ECs) and institutions.

Suspected unexpected serious adverse reactions (SUSARs), SAEs and other cases required by the concerned competent authorities will be reported by the sponsor or the sponsor's representative to all concerned parties within the prescribed timeframe. The sponsor or representative will also submit periodic safety reports (for e.g., Development Safety Update Reports) as required by international regulations.

9.4 Special Situations

The Investigator should report any case of pregnancy within 24 hours via the pregnancy report form. Pregnancy exposures must be followed until a final outcome is determined (e.g., parturition, spontaneous or scheduled termination).

9.4.1 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the Investigator immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted throughout the study, as detailed in the schedule of assessments. A woman who is found to be pregnant at the Screening visit will be excluded from the study. A woman who becomes pregnant during the study will be immediately discontinued from study treatment. Early discontinuation visit assessments should be performed as soon as possible after learning of the pregnancy. This information should be captured in the pregnancy form and reported to Mylan Product Safety and Risk Management within 24 hours from the time of initial knowledge, even if beyond the closure of the clinical database.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or an SAE. A spontaneous abortion is always considered to be a SAE and will be reported to the sponsor within 24 hours of knowledge of the event.

Elective termination (i.e., without medical reasons) of an uncomplicated pregnancy is considered to be an elective procedure and not an AE, nevertheless, Mylan requests that the outcome (e.g., elective termination) be reported within 24 hours and sent as a follow-up on the Delivery and Infant Follow-up Form).

The Investigator is also responsible for following up the pregnancy at 3 monthly intervals until delivery or termination, informing the sponsor about its outcome.

9.4.2 Overdose, Medication Errors and Other Events

Overdose, per se of either study treatment or a concomitant medication will not be reported as an AE; unless it is an intentional overdose taken with possible suicidal/self-harming intent. Signs, symptoms, and clinical sequelae associated with intentional overdose are to be recorded on the AE CRF page. Dosing and other medication errors are to be recorded as protocol deviations.

9.4.3 Worsening of diabetic macular edema

Medical occurrences or symptoms of deterioration that are anticipated as part of the normal progression of DME of the study eye should be recorded as an AE only if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study.

When recording an unanticipated worsening of study eye DME on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated DME”). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. In cases of ocular inflammation, diagnoses terms like iritis, iridocyclitis, vitritis, endophthalmitis or uveitis should be used.

9.5 Abnormal Test Findings

Abnormal laboratory findings per se (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., ECG, X-rays, and vital signs) are not reported as AEs. However, abnormal findings that are deemed **clinically significant** or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (and recorded as an SAE if they

meet the criteria of being serious). Clinically significant abnormal laboratory or other abnormal findings that are detected after study drug administration or that are present at baseline and worsen following the administration of study drug are included as AEs (and SAEs, if serious). The Investigator should exercise his or her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Broad guidance for determining whether an abnormal objective test finding should be reported as an AE follows:

- The test result is associated with accompanying symptoms and/or
- The test result requires additional diagnostic testing or medical/surgical intervention and/or
- The test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, additional concomitant drug treatment, or other therapy; and/or
- The test result is considered to be an AE by the Investigator or sponsor.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE.

Any abnormal test result determined by retest to be an error does not require reporting as an AE.

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11 APPENDIX.

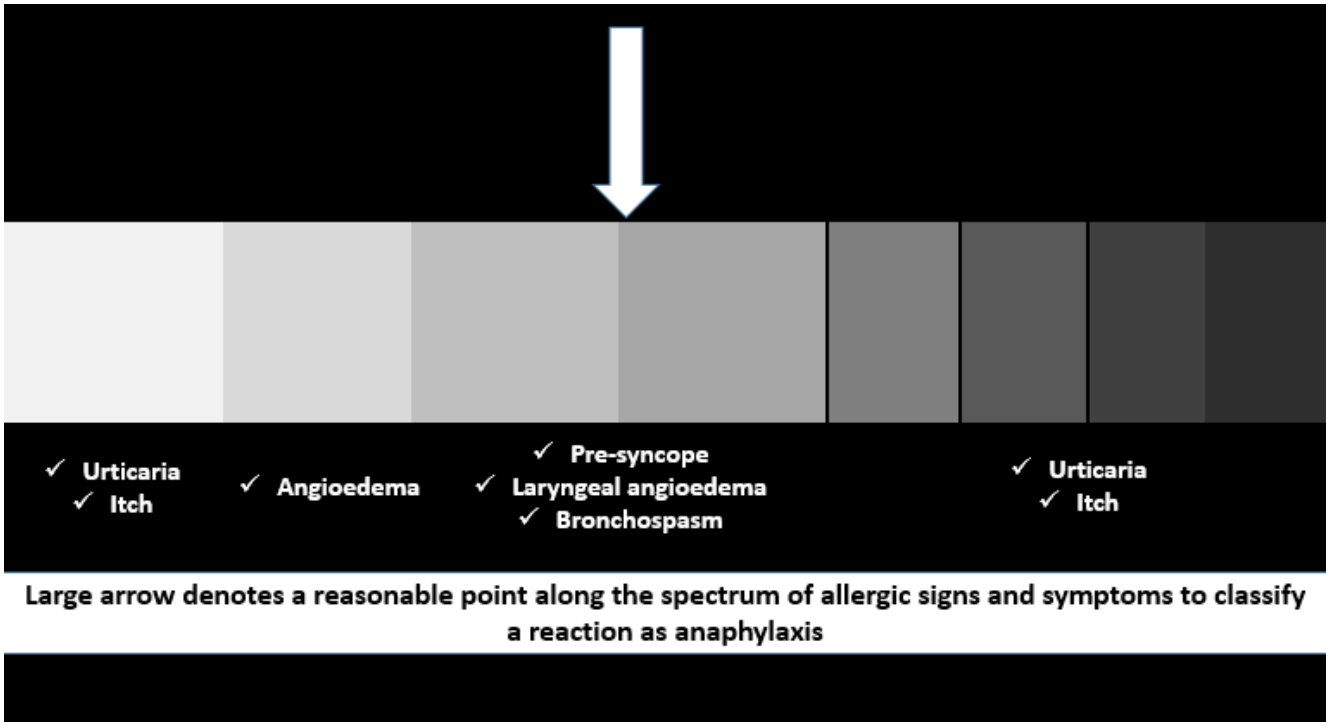
11.1 Appendix: NIAID / FAAN clinical criteria for diagnosis and assessment of Anaphylaxis (Sampson et al., 2006)

Anaphylaxis is highly likely when any ONE of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of skin, mucosal tissue or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) *AND AT LEAST ONE OF THE FOLLOWING*: a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two (or more) of the following that occurred rapidly (minutes to several hours) after exposure to a *likely allergen for that patient:* a. Involvement of the skin or mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) d. Persistent GI symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to a *known allergen for that patient (minutes to several hours):* a. Infants and Children: Low systolic BP (age specific), or greater than 30% decrease in systolic BP b. Adults: Systolic BP of less than 90 mmHg, or greater than 30% decrease from baseline

PEF- Peak expiratory flow; BP- blood pressure

The clinical spectrum of Allergic Manifestations



Large arrow denotes a reasonable point along the spectrum of allergic signs and symptoms to classify a reaction as anaphylaxis