Mylan

AFIL-IJZ-3002 CLINICAL STUDY PROTOCOL

Protocol Title	A Multi Center, Extension Study to Evaluate the Safety and Efficacy of MYL-1701P in Subjects with Diabetic Macular Edema Completed MYL-1701P-3001 Study.
Product	MYL-1701P (M710)
Protocol Number	AFIL-IJZ-3002
Study Type	Extension study of MYL-1701P-3001 for safety and efficacy
Version	Version 01
Protocol Date	19 Aug 2020
Legal/Filing Sponsor	Mylan [redacted]

Confidentiality:
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SIGNATURE PAGE

Protocol Description	A Multi Center, Extension Study to Evaluate the Safety and Efficacy of MYL-1701P in Subjects with Diabetic Macular Edema Completed MYL-1701P-3001 Study.
Product Code	MYL-1701P
Protocol Version	Version 01
Protocol Version Date	19 Aug 2020

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

[redacted]

Date: 20 Aug 2020

Date: 20 Aug 2020

Date: 20 Aug 2020

Date: 20 Aug 2020

Date: _____

PRINCIPAL INVESTIGATOR ACCEPTANCE FORM

SIGNATURE OF INVESTIGATOR

I, the undersigned, as Investigator for this study, have read this protocol numbered AFIL-IJZ-3002 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, 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 (Site Address and Contact Number):

CLINICAL STUDY CONTACT LIST

Sponsor:	Mylan [redacted]
Contract Research Organization:	[redacted]
Clinical Trial Supplies Facility:	
CRO Medical Monitor:	
CRO Project Manager:	
CRO Statistical Representative	
Sponsor GCRD Representative:	

Sponsor Statistical Representative:	[redacted]
Sponsor GCO Representative:	
Sponsor Bioanalytical Representative:	
Sponsor Safety Reporting Hotline:	

PROTOCOL SYNOPSIS

Protocol Title	A Multi Center, Extension Study to Evaluate the Safety and Efficacy of MYL-1701P in Subjects with Diabetic Macular Edema Completed MYL-1701P-3001 Study.
Protocol Number	AFIL-IJZ-3002
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 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). Mylan [redacted] are developing MYL-1701P, a proposed biosimilar to Eylea. Parent study (MYL-1701P-3001) was designed to demonstrate the clinical similarity of MYL-1701P and Eylea with regard to efficacy, safety, pharmacokinetics, and immunogenicity in the treatment of subjects with Diabetic Macular Edema (DME). This extension study (AFIL-IJZ-3002) is designed to further evaluate the safety, efficacy and immunogenicity of MYL-1701P among a group of participants successfully completing the parent study MYL-1701P-3001. All subjects participating in the extension study will receive 3 doses of MYL-1701P, every 8 weeks. The total study duration will be 24 weeks.
Primary Objective	The primary objective is to evaluate the safety and tolerability of MYL-1701P in subjects with DME who completed study MYL-1701P-3001.
Primary Endpoint	Incidence of treatment emergent adverse events (TEAEs)
Secondary Objectives	The secondary objective is to compare the group that switched from Eylea to MYL-1701P in the extension study with the group that continued MYL-1701P from the parent study regarding the following: ✓ Efficacy of MYL-1701P as measured by change from baseline (Day 1 of parent study) in BCVA at Week 20 ✓ Efficacy of MYL-1701P as measured by change from baseline (Day 1 of parent study) in CRT at Weeks 8, 16 and 20 ✓ Efficacy of MYL-1701P as measured by change from baseline (Day 1 of parent study) in BCVA at Weeks 8 and 16 ✓ Safety, tolerability, and Immunogenicity of MYL-1701P ✓ Impact of immunogenicity on efficacy and safety
Secondary Endpoints	• **Efficacy** ✓ Mean change from baseline (Day 1 of parent study) in BCVA as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at Week 20

	✓ Mean change from baseline (Day 1 of parent study) in CRT as determined by spectral-domain-optical coherence tomography (SD-OCT) at Weeks 8, 16 and 20 ✓ Mean change from baseline (Day 1 of parent study) in BCVA as assessed by ETDRS letters at Weeks 8 and 16 ✓ Proportion of subjects who gained ≥5 letters, ≥10 letters and ≥15 letters from baseline in BCVA, assessed by change from baseline (Day 1 of parent study) in ETDRS letters at Weeks 8, 16 and 20 ✓ Mean change in BCVA from Day 1 of extension study at Week 20 ✓ Mean change in CRT from Day 1 of extension study at Week 20 Note: For all the efficacy endpoints, Day 1 of parent study will be considered as baseline unless otherwise specified. • **Safety** ✓ Safety and tolerability will be assessed over time, based on the following evaluations: ▪ Vital signs ▪ Targeted physical examination ▪ Complete ophthalmological examination (OE) ▪ Safety labs (serum chemistry, hematology, and urinalysis) ▪ Twelve-lead electrocardiograms (ECGs) • **Immunogenicity** ✓ Anti-drug antibodies to aflibercept: occurrence, titer, and neutralizing capacity
Study Design, Methodology, and Treatments	This will be a multi center, extension clinical study of the parent study MYL-1701P-3001. Up to one hundred (100) subjects will be enrolled in the study who meet all the following criteria: participated and completed Week 52 visit of the parent study MYL-1701P-3001 from India, provide informed consent, and meet all the eligibility criteria for the extension study. The first dose of the extension study will be administered on Day 1 which will be scheduled 8 weeks (± 7 days) from the last dose (Week 48 ± 7 days) of administration of the randomized study medication of the parent study. If the dosing at Week 48 visit of the parent study was missed due to unforeseen reasons, the first dose in the extension study can be scheduled as soon as possible after the Week 52 visit (parent study). Eligible subjects who provide written informed consent to participate in the extension study will be screened during the end of study visit of the parent study. The extension study will have a screening visit/visit 1 (Week 52-end of study visit of the parent study), enrollment visit/visit 2

	(Day 1), visit 3 (Week 8 ± 7 days) and visit 4/end of treatment visit (Week 16 ± 7 days) and visit 5/end of study visit (Week 20 ± 7 days). The Day 1/enrollment visit should be scheduled such that, it is 8 weeks ± 7 days from actual date of the dosing at Week 48 visit of the parent study. All enrolled subjects will receive three doses of the investigational product MYL-1701P at 8-weekly intervals during visit 2 (Day 1), visit 3 (Week 8 ± 7 days) and visit 4 (Week 16 ± 7 days) in an open-label manner. All subjects will return to the clinic every 8 weeks for dosing, safety, and efficacy evaluations. Note: The nomenclature used in this document for denoting the visits for the extension study as visit 1 (screening), visit 2 (enrollment), visit 3 (Week 8), visit 4 (Week 16) and visit 5 (Week 20) corresponds to the time points of Week 52, Week 56, Week 64, Week 72 and Week 76 respectively from the Day 1/baseline of the parent study (MYL-1701P-3001). Safety assessments including targeted physical examination, vital signs, 12-lead ECG, monitoring of AEs, complete ophthalmological examination, IOP measurement will be performed during the study. Clinical examinations will be conducted for subjects with signs and symptoms suggestive of COVID-19 (such as fever, cough, difficulty in breathing). Subjects with history of travel/contact with any COVID-19 positive subject/isolation/ quarantine will be evaluated at each visit as per standard practices followed at site by the Investigator's discretion. Subjects having signs and symptoms of COVID-19 or history of travel/contact with any COVID-19 positive subject/isolation/quarantine will be managed as per investigator's discretion as per site's standard clinical practice. Patients who are currently in quarantine or having active COVID-19 infection must refrain from visiting the site for the study and should be managed by their treating physician. The investigator should also make a determination based on the risk benefit evaluation of whether an upcoming patient visit is essential, through weighing the risk of infection exposure to COVID-19 against the risk of not continuing treatment. This determination will vary by region and over time based on the local prevalence of infection. Any delayed and missed visits due to COVID-19 should be documented as protocol deviations with reference to COVID-19 in the deviation description. Subjects will undergo assessment of visual acuity (BCVA based on ETDRS letters) and central retinal thickness (CRT by SD-OCT) at all study visits. Immunogenicity will be assessed for all subjects participating in the study, through assessment of blood samples for anti-drug antibody and neutralizing antibody at prespecified time points.
Investigational Product	MYL-1701P (a proposed biosimilar to Eylea) injection for intravitreal injection.

Inclusion/ Exclusion Criteria	**Inclusion criteria** Subjects must meet all of the following inclusion criteria to be eligible to participate in the study: 1. Subject participated in the parent study MYL-1701P-3001 and completed Week 52 visit (visit 16) of that study. 2. Subject requires continued treatment with intravitreal anti-VEGF therapy for the study eye (same as study eye of parent study) as per the principal investigator's clinical judgment. 3. Subject is able to understand and voluntarily provide written informed consent to participate in the study. 4. If female of childbearing potential, the subject must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at enrollment visit, and should not be nursing or planning a pregnancy. 5. 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 from screening and continuing at least 90 days following the last treatment dose. c. Of non-childbearing potential (i.e., postmenopausal for at least 1 year). 6. 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 #5b) or abstain from sexual relations during the study period and up to 90 days following the last treatment dose. 7. 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. 2. Subjects will be excluded if any of the following conditions are met in the study eye: a. Subjects with active ocular inflammation. b. Subjects with uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication); subjects with controlled

<table>
<tr><td></td><td>glaucoma may participate in the study.
c. Surgery for glaucoma in the past or likely to be needed in the future.
3. Subjects with active or suspected ocular or periocular infection including but not limited to infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye.
4. Subjects who plan to participate in another clinical study while enrolled in this study.
5. Subjects receiving treatment for a serious systemic infection.
6. Subjects with uncontrolled hypertension defined as systolic blood pressure > 160 mm Hg or diastolic blood pressure > 95 mm Hg.
7. Subjects with a history of cerebrovascular accident or myocardial infarction within 6 months of enrollment visit.
8. Subjects with renal failure requiring dialysis or renal transplant.
9. 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.</td></tr>
<tr><td>Planned Number of Subjects</td><td>There is no formal sample size estimation. The extension study is open for all subjects from India who completed the parent study MYL-1701P-3001. It is expected that up to 100 subjects will be considered for participation in the extension study.

For mean change from baseline (Day 1 of parent study) in BCVA at Week 20, the point estimate for the difference between the group of subjects that switched from Eylea in parent study and those continued on MYL-1701P should be within the range of [redacted] letters, which is a recommended similarity margin for a 1-year endpoint. The following table gives the power with which this can be achieved for expected numbers of subjects per group, assuming a treatment regimen difference of 0 and a standard deviation of 10.5 letters:

<table><tr><td></td><td>Number of subjects per group</td></tr><tr><td></td><td>[redacted]</td></tr><tr><td>Power</td><td></td></tr></table></td></tr>
<tr><td>Statistical Methods</td><td>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. The analyses will be performed on the safety population.

For mean change from baseline (Day 1 of parent study) in BCVA at Week 20, the analysis will be based on a mixed model repeated measures analysis with terms for group (switch from Eylea to MYL-1701P or continue on MYL-1701P), visit and group by visit interaction, together with baseline BCVA as a covariate. This model will provide an estimate,</td></tr>
</table>

	standard error, and 90% two-sided confidence interval for the group difference at Week 20. The analysis will be performed on the Full Analysis Set (FAS).
Reporting Strategy	All appropriate data from the study will be reported in a final report. [redacted]

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LIST OF COMMONLY USED ABBREVIATIONS

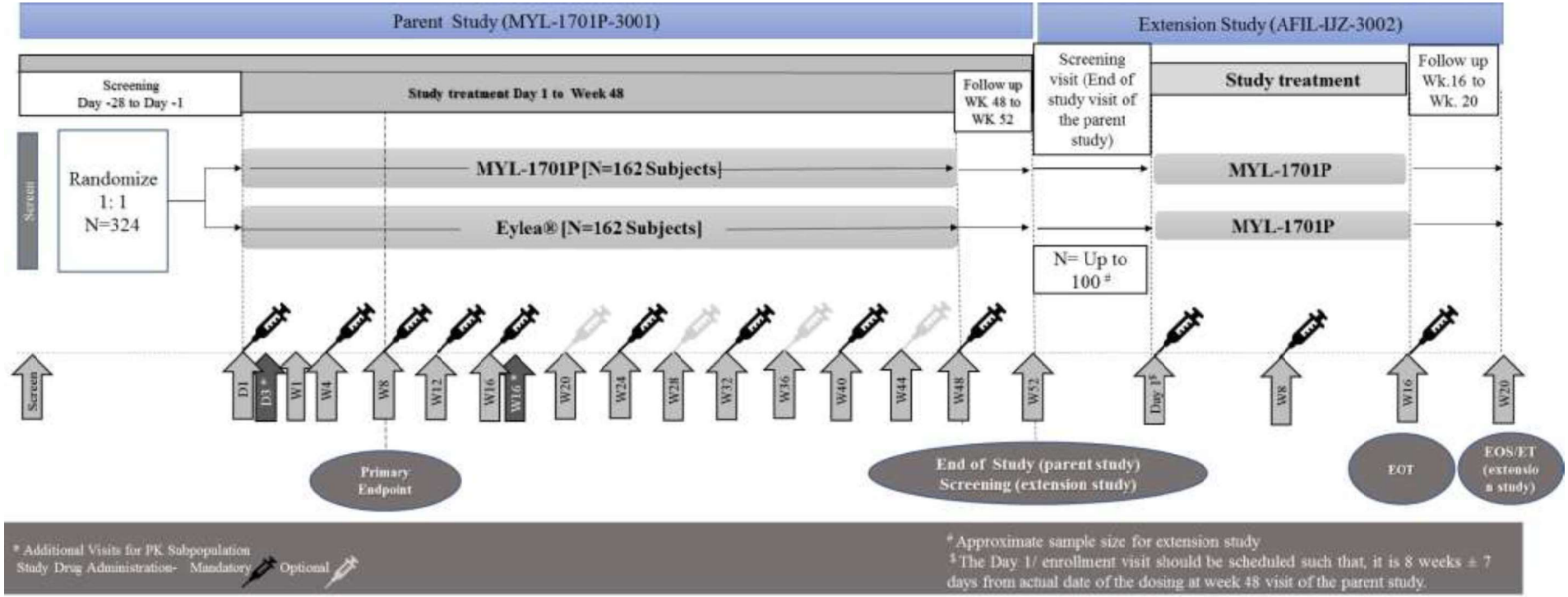
%	Percentage
µL	Microliter
ADA	Anti-Drugs Antibodies
ADR	Adverse Drug Reactions
AE	Adverse Event
ALT	Alanine Transaminase
AMD	Age-Related Macular Degeneration
AST	Aspartate Transaminase
BCVA	Best Corrected Visual Acuity
BP	Blood Pressure
CI	Confidence Interval
COVID-19	Corona Virus Disease-2019
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Central Retinal Thickness
CSR	Clinical Study Report
DBL	Database Lock
DME	Diabetic Macular Edema
ECG	Electrocardiogram
ECs	Ethics Committees
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA1c	Hemoglobin A1C
hCG	Human Chorionic Gonadotropin
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council For Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IOP	Intraocular Pressure
IRB	Institutional Review Board
IVT	Intravitreal
kg	Kilogram
MedDRA	Medical Dictionary For Regulatory Activities
mg	Milligram
mL	Milliliter
mmHg	Millimeter of Mercury
MMRM	Mixed Model Repeated Measures
N	Number
Nab	Neutralizing Anti-Drug Antibodies

NCI-CTCAE	National Cancer Institute- Common Terminology Criteria For Adverse Events
NIAID/FAAN	National Institute of Allergy and Infectious Disease / The Food Allergy and Anaphylaxis Network
OE	Complete Ophthalmological Examination
PEF	Peak Expiratory Flow
pH	potential of hydrogen
PI	Prescribing Information
PK	Pharmacokinetic
PP	Per Protocol
PSRM	Product Safety and Risk Management
PV	Pharmacovigilance
QC	Quality Control
QTc	QT Corrected
QTcF	QT Corrected (Fredericia's Correction)
RBC	Red Blood Cells
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain – Optical Coherence Tomography
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSARs	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
US	United States
USA	United States of America
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WoCBP	Women of Childbearing Potential

1 STUDY DIAGRAM AND STUDY SCHEDULE OF ACTIVITIES

The study diagram provides an overview of the protocol visits. 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	**Visit 1 (Screening Visit[a])**	**Visit 2 (Enrollment visit)**	**Visit 3**	**Visit 4**	**Visit 5**
	Week (window period):	**Week 52/ EOS visit of the parent study**	**Day 1 of extension study[b]**	**Week 8 (± 7 days)**	**Week 16 (± 7 days) EOT**	**Week 20 (± 7 days) EOS/ET**
Reference to Day1/BL of Parent Study		**Week 52**	**Week 56**	**Week 64**	**Week 72**	**Week 76**
Informed consent[c]		x				
Demography[d]		x				
Medical, surgical and ophthalmic history[e]		x				
Inclusion/exclusion criteria		x	x			
Height/weight		x	x[f]			x[f]
Pregnancy test[g]		x	x	x	x	x
Clinical safety laboratory test[h]		x				x
Targeted physical examination including examination for signs and symptoms of COVID-19 [i]		x	x	x	x	x
Vital signs[j]		x	x	x	x	x
12- Lead electrocardiogram		x				x
Complete ophthalmologic examination[k]		x	x	x	x	x
Best corrected visual acuity (Bilateral)		x	x	x	x	x
SD-OCT (Bilateral) for central retinal thickness (CRT)		x	x	x	x	x
Study drug administration			x	x	x	
Immunogenicity sampling[l]		x[m]		x		x
Adverse events[n]		x	x	x	x	x
Record concomitant medication		x	x	x	x	x
Study diary issue/review[o]			x	x	x	x

Abbreviations: EOS = End of Study; ET = Early Termination; SD-OCT: Spectral Domain – Optical Coherence Tomography; EOT = End of Treatment; COVID-19 = Corona Virus Disease-2019

a. Screening visit for the extension study may occur on the same day as the end of study (visit 16/Week 52) visit of the parent study. If assessments are performed on different days then vital signs must be repeated and all the other assessments of EOS (visit 16/Week 52) visit of parent study can be used. If required additional visit can be performed between end of study visit of the parent study and enrollment visit of extension study based on Investigator's discretion.
b. The Day 1/ enrollment visit should be scheduled such that, it is 8 weeks ± 7 days from actual date of the dosing at Week 48 visit of the parent study. If the dosing at Week 48 visit of the parent study was missed due to unforeseen reasons, the first dose in the extension study can be scheduled as soon as possible after the Week 52 visit (parent study).
c. Written informed consent will be obtained prior to the initiation of any study related procedures.
d. Demographic information including gender, if female, is the subject of childbearing potential, year of birth, age, smoking status, ethnicity, race and screening number (of parent study), randomization number (of parent study) etc. will be recorded during the screening visit.
e. Medical, surgical, ophthalmic and smoking history, and current medical conditions and medications.
f. Weight only at the identified visits.
g. Female subjects of childbearing potential will have a serum pregnancy test at screening visit and at the EOS visit (study week 20) and urine pregnancy test at other identified visits.
h. Clinical safety laboratory tests include serum chemistry, hematology, and urinalysis.
i. A targeted physical examination will be performed. If indicated, based on report of adverse events or results of safety laboratory test, directed physical exam will be performed at additional visits. Clinical examinations will be conducted for subjects with signs and symptoms suggestive of COVID-19 (such as fever, cough, difficulty in breathing). Subjects with history of travel/contact with any COVID-19 positive subject/isolation/ quarantine will be evaluated at each visit as per standard practices followed at site by the Investigator's discretion. Subjects having signs and symptoms of COVID-19 or history of travel/contact with any COVID-19 positive subject/isolation/quarantine will be managed as per investigator's discretion as per site's standard clinical practice.
j. Vital signs include blood pressure (BP), pulse rate and temperature. BP will be measured after the subject is sitting for 5 mins
k. 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 (between +20 and +60 minutes post-dose) after study drug administration
l. Immunogenicity (ADA/NAb) blood sample will be taken prior to study drug administration whenever applicable. Immunogenicity assessment results from the end of study (visit 16/Week 52) visit of the parent study can be utilized for the screening visit of the extension study.
m. This sample collection was the same immunogenicity sample already planned at the end of the parent study (Week 52). This is not an additional sample collection for the present extension study.
n. Ocular AEs for the study eye, the fellow eye and non-ocular AEs will be collected and analyzed separately.
o. Study diary will be issued at enrollment visit, reviewed during subsequent visits, and returned during the visit 5/EOS or ET visit. Study diary will be used by subjects to record the AEs and concomitant medications in between the study visits.

Note: 1) An unscheduled visit may be necessary and can occur at any time if the Investigator believes it is essential for any reason.

2) Patients who are currently in quarantine or having active COVID-19 infection must refrain from visiting the site for the study and should be managed by their treating physician. The investigator should also make a determination based on the risk benefit evaluation of whether an upcoming patient visit is essential, through weighing the risk of infection exposure to COVID-19 against the risk of not continuing treatment. This determination will vary by region and over time based on the local prevalence of infection. Any delayed and missed visits due to COVID-19 should be documented as protocol deviations with reference to COVID-19 in the deviation description.

2 INTRODUCTION

2.1 Indication

Mylan [redacted] in collaboration with [redacted] 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 the US and visual impairment due to myopic choroidal neovascularization in the EU.

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 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.

Complete information of the investigational medicinal product is available in the reference safety document, which for this study is the MYL-1701P Investigator's Brochure.

2.2.1 Rationale for Study

Parent study (MYL-1701P-3001) was designed to demonstrate the clinical similarity of MYL-1701P and Eylea with regard to efficacy, safety, pharmacokinetics, and immunogenicity in the treatment of subjects with DME.

This extension study (AFIL-IJZ-3002) is being designed and conducted by Mylan to further evaluate the safety, efficacy and immunogenicity of MYL-1701P among a group of participants successfully completing the parent study MYL-1701P-3001. All subjects participating in the extension study will receive 3 doses of MYL-1701P, every 8 weeks. The total study duration will be 24 weeks.

2.2.1.1 Rationale for Study Population- Diabetic Macular Edema

AFIL-IJZ-3002 is an extension study of MYL-1701P-3001, subjects completing Week 52 visit of MYL-1701P-3001 study, providing written informed consent, and meeting the eligibility criteria will be enrolled in the study.

2.2.1.2 Rationale for Subject Selection and Study Endpoints

The inclusion criteria detailed in the protocol largely reflect the population described in MYL-1701P-3001 study with some optimizations for the extension study. Subjects who

require continued treatment with intravitreal anti-VEGF therapy for the study as per the principal investigator's clinical judgment will be enrolled in the AFIL-IJZ-3002 study.

The extension study is designed to evaluate the safety and tolerability of MYL-1701P in subjects with DME who completed the parent study MYL-1701P-3001 among the subjects who continued on MYL-1701P and those who transitioned from Eylea to MYL-1701P. The primary endpoint of incidence of TEAEs is designed to evaluate the primary objective of the study.

Efficacy will also be evaluated as secondary objectives. Change from baseline BCVA is a clinically relevant endpoint and is adequately sensitive to detect any clinically meaningful differences between study groups. Central retinal thickness is being evaluated as a secondary endpoint. CRT assesses the pharmacodynamic aspects of aflibercept and is supportive in detecting differences between study groups.

As MYL-1701P is a proposed biosimilar, immunogenicity will also be evaluated in this study.

2.3 Study Design

This will be a multi center, extension clinical study of the parent study MYL-1701P-3001 study.

Up to one hundred (100) subjects will be enrolled in the study who meet all the following criteria: participated and completed Week 52 visit of the parent study MYL-1701P-3001 from India, provide informed consent, and meet all the eligibility criteria for the extension study.

The first dose of the extension study will be administered on Day 1 which will be scheduled 8 weeks (±7 days) from the last dose (Week 48 ± 7 days) of administration of the randomized study medication of the parent study. If the dosing at Week 48 visit of the parent study was missed due to unforeseen reasons, the first dose in the extension study can be scheduled as soon as possible after the Week 52 visit (parent study).

Eligible subjects who provide written informed consent to participate in the extension study will be screened during the end of study visit of the parent study.

The extension study will have a screening visit/visit 1 (Week 52-end of study of the parent study), enrollment visit/visit 2 (Day 1), visit 3 (Week 8 ± 7 days) and visit 4/end of treatment visit (Week 16 ± 7 days) and visit 5/end of study visit (Week 20 ± 7 days). The Day 1/ enrollment visit should be scheduled such that, it is 8 weeks ± 7 days from actual date of the dosing at Week 48 visit of the parent study.

All enrolled subjects will receive three doses of the investigational product MYL-1701P at 8-weekly intervals during visit 2 (Day 1), visit 3 (Week 8 ± 7 days) and visit 4 (Week 16 ± 7 days) in an open-label manner. All subjects will return to the clinic every 8 weeks for dosing, safety and efficacy evaluations.

Note: The nomenclature used in this document for denoting the visits for the extension study as visit 1 (screening), visit 2 (enrollment), visit 3 (Week 8), visit 4 (Week 16) and visit 5 (Week 20) corresponds to the time points of Week 52, Week 56, Week 64, Week 72 and Week 76 respectively from the Day 1/baseline of the parent study (MYL-1701P-3001).

Safety assessments including targeted physical examination, vital signs, 12-lead ECG, monitoring of AEs, complete ophthalmological examination, IOP measurement will be performed during the study.

Clinical examinations will be conducted for subjects with signs and symptoms suggestive of COVID-19 (such as fever, cough, difficulty in breathing). Subjects with history of travel/contact with any COVID-19 positive subject/isolation/ quarantine will be evaluated at each visit as per standard practices followed at site by the Investigator's discretion. Subjects having signs and symptoms of COVID-19 or history of travel/contact with any COVID-19 positive subject/isolation/quarantine will be managed as per investigator's discretion as per site's standard clinical practice.

Patients who are currently in quarantine or having active COVID-19 infection must refrain from visiting the site for the study and should be managed by their treating physician. The investigator should also make a determination based on the risk benefit evaluation of whether an upcoming patient visit is essential, through weighing the risk of infection exposure to COVID-19 against the risk of not continuing treatment. This determination will vary by region and over time based on the local prevalence of infection. Any delayed and missed visits due to COVID-19 should be documented as protocol deviations with reference to COVID-19 in the deviation description.

Efficacy assessments include assessment of visual acuity (BCVA based on ETDRS letters) and central retinal thickness (CRT by SD-OCT) at all study visits.

Immunogenicity will be assessed for all subjects participating in the study, through assessment of blood samples for anti-drug antibody and neutralizing antibody at prespecified time points.

2.4 Potential Risks

2.4.1 Safety Profile of Aflibercept

MYL-1701P is a proposed biosimilar of Eylea, which contains proposed aflibercept as the active substance. The adverse reactions available for the reference product, Eylea, could be reasonably assumed to be associated with MYL-1701P.

A complete overview of the undesirable effects of Eylea can be found in the Eylea SPC and Eylea USPI (Eylea SPC, 2020 and Eylea US Package Insert, 2019).

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.

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 the study medication is a therapeutic protein, there is a potential for immunogenicity. 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 intravitreal injection. Mild discomfort, ocular hyperemia, increased lacrimation, discharge or itching may occur which may last for a 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.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objective

The primary objective is to evaluate the safety and tolerability of MYL-1701P in subjects with DME who completed study MYL-1701P-3001.

3.1.2 Secondary Objectives

The secondary objective is to compare the group that switched from Eylea to MYL-1701P in the extension study with the group that continued MYL-1701P from the parent study regarding the following:

- ✓ Efficacy of MYL-1701P as measured by change from baseline (Day 1 of parent study) in BCVA at Week 20
- ✓ Efficacy of MYL-1701P as measured by change from baseline (Day 1 of parent study) in CRT at Weeks 8, 16 and 20
- ✓ Efficacy of MYL-1701P as measured by change from baseline (Day 1 of parent study) in BCVA at Weeks 8 and 16
- ✓ Safety, tolerability, and Immunogenicity of MYL-1701P
- ✓ Impact of immunogenicity on efficacy and safety

3.2 Endpoints

3.2.1 Primary Endpoint

- ✓ Incidence of treatment emergent adverse events (TEAEs)

3.2.2 Secondary Endpoints

3.2.2.1 Efficacy

- ✓ Mean change from baseline (Day 1 of parent study) in BCVA as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at Week 20
- ✓ Mean change from baseline (Day 1 of parent study) in CRT as determined by spectral-domain-optical coherence tomography (SD-OCT) at Weeks 8, 16 and 20
- ✓ Mean change from baseline (Day 1 of parent study) in BCVA as assessed by ETDRS letters at Weeks 8 and 16
- ✓ Proportion of subjects who gained ≥5 letters, ≥10 letters and ≥15 letters from baseline in BCVA, assessed by change from baseline (Day 1 of parent study) in ETDRS letters at Weeks 8, 16 and 20
- ✓ Mean change in BCVA from Day 1 of extension study at Week 20
- ✓ Mean change in CRT from Day 1 of extension study at Week 20

Note: For all the efficacy endpoints, Day 1 of parent study will be considered as baseline unless otherwise specified.

3.2.2.2 Safety

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

- Vital signs
- Targeted physical examination

- 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

4 STUDY POPULATION

4.1 Study Population

Up to one hundred (100) subjects will be enrolled in the study who meet all the following criteria:

- ✓ Participated in the parent study MYL-1701P-3001 from India,
- ✓ Completed Week 52 visit of the parent study,
- ✓ Provide informed consent for the extension study, and
- ✓ Meet all eligibility criteria for the extension study.

Extension clinical study duration from screening to end of study would be up to 6 months (24 weeks) approximately.

4.2 Inclusion and Exclusion Criteria

4.2.1 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. Subject participated in the parent study MYL-1701P-3001 and completed Week 52 visit (visit 16) of that study.
2. Subject requires continued treatment with intravitreal anti-VEGF therapy for the study eye (same as study eye of parent study) as per the principal investigator's clinical judgment.
3. Subject is able to understand and voluntarily provide written informed consent to participate in the study.
4. If female of childbearing potential, the subject must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at enrollment visit, and should not be nursing or planning a pregnancy.
5. 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 from screening and continuing at least 90 days following the last treatment dose.
    c. Of non-childbearing potential (i.e., postmenopausal for at least 1 year).
6. 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 #5b) or abstain from sexual relations during the study period and up to 90 days following the last treatment dose.
7. Subject is willing to comply with the study duration, study visits, and study related procedures.

4.2.2 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.
2. Subjects will be excluded if any of the following conditions are met in the study eye:
    a. Subjects with active ocular inflammation.
    b. Subjects with uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication); subjects with controlled glaucoma may participate in the study.
    c. Surgery for glaucoma in the past or likely to be needed in the future.
3. Subjects with active or suspected ocular or periocular infection including but not limited to infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye.
4. Subjects who plan to participate in another clinical study while enrolled in this study.
5. Subjects receiving treatment for a serious systemic infection.
6. Subjects with uncontrolled hypertension defined as systolic blood pressure > 160 mm Hg or diastolic blood pressure > 95 mm Hg.
7. Subjects with a history of cerebrovascular accident or myocardial infarction during parent study within 6 months of enrollment visit.
8. Subjects with renal failure requiring dialysis or renal transplant.
9. 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.

4.2.3 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).

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

- The subject withdraws his or her 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 includes 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 non-response that requires treatment with a prohibited medication or procedure, which in the opinion of the investigator warrants treatment withdrawal.

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.

4.3 Contraception

4.3.1 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.

4.3.2 Females - Childbearing Potential

Female subjects of childbearing 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 from screening and continuing at least 90 days following the last treatment dose, 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).

4.4 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 enrollment 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

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]

MYL-1701P (a proposed biosimilar to Eylea) will be provided in a single vial kit with unique kit number, once the subject is eligible the kit may be selected in sequence by authorized site personnel and dispensed to the subject.

5.1.1 Administration of Study Drugs

All enrolled subjects are planned to receive MYL-1701P as an intravitreal injection at a dose of 2 mg at 8-weekly interval during visit 2 (Day 1), visit 3 (Week 8 ± 7 days) and visit 4 (Week 16 ± 7 days) in an open-label manner. The Day 1/enrollment visit should be scheduled such that, it is 8 weeks ± 7 days from actual date of the dosing at Week 48 visit of the parent study.

Note: If the dosing at Week 48 visit of the parent study was missed due to unforeseen reasons, the first dose in the extension study can be scheduled as soon as possible after the Week 52 visit (parent study).

5.1.2 Delayed and Missed Visits and/or Dose

Every attempt should be made to complete the visits and/or dosing within 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 ocular conditions are suitable for dosing prior to every dosing.

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

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

5.1.3 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 intraocular pressure is more than 30 mm Hg (Eylea EU SPC, 2020).

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.

Each vial should only be used for the treatment of a single eye (Study 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 to the study sites packaged and labeled at Clinical Trial Supplies Facility per local legal/regulatory requirements.

Clinical Supplies will provide prepackaged supplies for each subject.

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
- 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 labeled 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

As this is an open-label study, masking will not be applicable in this study.

5.6 Randomization

Not applicable as it is single-arm study.

5.7 Concomitant Medications

All concomitant medications taken during this extension study 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.

Medications taken from end of study visit of study MYL-1701P-3001 to enrollment visit in the current study will be documented as a prior medication.

Medications taken after the first dose of study medication in the current study will be documented as concomitant medications.

Prohibited Medications

Subjects will abstain from all prohibited medications as described in Table 2. Use of prohibited medication from screening or Week 52 visit of parent study, whichever is earlier to end of 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 4.2.3).

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
- Panretinal 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 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 concomitant medication on the study endpoints.

5.7.1 Study Eye

Study eye for this extension study must be same as the study eye for the parent study. 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), as specified in the protocol, until they had completed the end of study (Week 20) 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.

5.7.2 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.

5.7.3 Management of Diabetes

The subjects 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 participation 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. 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.

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 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 the extension study would be up to 6 months (24 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. The principal investigator or sub-investigator will review the inclusion and exclusion criteria to confirm eligibility of each subject prior to enrollment. A unique subject number will be allocated to the subjects participating in the extension study.

6.1.1 Visit 1/Screening Visit [Week 52 (EOS Visit of the Parent Study)]

Screening visit for the extension study may occur on the same day as the end of study (visit 16/Week 52) visit of the parent study. The EOS assessments of the parent study completed at Week 52 can be considered for extension study screening visit.

At the screening visit, the following procedures will be completed:

- Written informed consent
- Medical, surgical, ophthalmic and smoking history, demographics and current medical conditions and medications
- Check study inclusion/exclusion criteria
- Measure height and weight
- Serum pregnancy test (if female of childbearing potential)
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Blood sampling for Immunogenicity (This sample collection was the same immunogenicity sample already planned at the end of the parent study (Week 52). No additional sample collection for the present extension study)
- Record vital signs – sitting blood pressure, pulse rate and temperature
- Targeted physical examination
- Clinical examination will be conducted for subject with signs and symptoms suggestive of COVID-19 (such as fever, cough, difficulty in breathing). Subjects with history of travel/contact with any COVID-19 positive subject/isolation/ quarantine will be evaluated
- Record 12-lead ECG
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy and measurement of Intraocular pressure (IOP)
- SD-OCT/CRT
- Review AEs and concomitant medications

Note:

1) Screening visit for the extension study may occur on the same day as the end of study (visit 16/Week 52) visit of the parent study. If assessments are performed on different days then vital signs must be repeated and all the other assessments of EOS (visit 16/Week 52) visit of parent study can be used. If required additional visit can be performed between end of study visit of the parent study and enrollment visit of extension study based on Investigator's discretion.

2) Additionally, screening number, randomization number, BCVA value of baseline visit and CRT value of baseline visit of parent study will be entered by the site team into source document and EDC of the screening visit of the extension study.

6.2 Treatment Period

6.2.1 Visit 2/Enrollment Visit (Day 1 of Extension Study)

The following procedures will be completed:

- Measure weight
- Urine pregnancy test (if female of childbearing potential)
- Record vital signs – sitting blood pressure, pulse rate and temperature

- Targeted physical examination
- Clinical examination will be conducted for subject with signs and symptoms suggestive of COVID-19 (such as fever, cough, difficulty in breathing). Subjects with history of travel/contact with any COVID-19 positive subject/isolation/ quarantine will be evaluated.
- BCVA
- Complete OE- Slit Lamp examination, Indirect Ophthalmoscopy, and measurement of Intraocular pressure (pre-dose IOP)
- SD-OCT/CRT
- Check study inclusion/exclusion criteria
- Study drug administration
- Measurement of post-dose 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 3 (Week 8 (±7 days))

The following procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature
- Targeted physical examination
- Clinical examination will be conducted for subject with signs and symptoms suggestive of COVID-19 (such as fever, cough, difficulty in breathing). Subjects with history of travel/contact with any COVID-19 positive subject/isolation/ quarantine will be evaluated.
- Urine pregnancy test (if female of childbearing potential)
- Complete OE- Slit lamp examination, Indirect Ophthalmoscopy, and measurement of pre-dose IOP
- Blood sampling for immunogenicity prior to dosing
- BCVA
- SD-OCT/CRT
- Study drug administration
- Measurement of post-dose IOP and assessment of vision by hand movements or counting fingers post-injection
- Review study diary
- Review AEs and concomitant medications

6.2.3 Visit 4 (Week 16 (±7 days)) [End of Treatment]

The following procedures will be completed:

- Record vital signs – sitting blood pressure, pulse rate and temperature

- Targeted physical examination
- Clinical examination will be conducted for subject with signs and symptoms suggestive of COVID-19 (such as fever, cough, difficulty in breathing). Subjects with history of travel/contact with any COVID-19 positive subject/isolation/ quarantine will be evaluated.
- Urine pregnancy test (if female of childbearing potential)
- Complete OE- Slit lamp examination, Indirect Ophthalmoscopy, and measurement of pre-dose IOP
- BCVA
- SD-OCT/CRT
- Study drug administration
- Measurement of post-dose IOP and assessment of vision by hand movements or counting fingers post-injection
- Review study diary
- Review AEs and concomitant medications

6.2.4 Visit 5 (Week 20 ± 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 childbearing potential)
- Targeted physical examination
- Clinical examination will be conducted for subject with signs and symptoms suggestive of COVID-19 (such as fever, cough, difficulty in breathing). Subjects with history of travel/contact with any COVID-19 positive subject/isolation/ quarantine will be evaluated.
- Record 12-lead ECG
- BCVA
- Complete OE- Slit lamp examination, Indirect Ophthalmoscopy, and measurement of IOP
- SD-OCT/CRT
- Blood sampling for immunogenicity
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Review AEs and concomitant medications
- Collect the study diary

6.2.5 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 4.2.3. 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 childbearing potential)
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Targeted physical examination
- Clinical examination will be conducted for subject with signs and symptoms suggestive of COVID-19 (such as fever, cough, difficulty in breathing). Subjects with history of travel/contact with any COVID-19 positive subject/isolation/ quarantine will be evaluated.
- Record 12-lead ECG
- BCVA
- Complete OE- Slit lamp examination, Indirect Ophthalmoscopy, and measurement of IOP
- SD-OCT/CRT
- Blood sampling for immunogenicity
- Review AEs and concomitant medications
- Collect the study diary

Note: Clinical examinations will be conducted for subjects with signs and symptoms suggestive of COVID-19 (such as fever, cough, difficulty in breathing). Subjects with history of travel/contact with any COVID-19 positive subject/isolation/ quarantine will be evaluated at each visit as per standard practices followed at site by the Investigator's discretion. Subjects having signs and symptoms of COVID-19 or history of travel/contact with any COVID-19 positive subject/isolation/quarantine will be managed as per investigator's discretion as per site's standard clinical practice.

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

6.3.1.1 Ophthalmologic Examination

A study ophthalmologist (evaluating physician) will perform a dilated eye examination of each eye of the subject.

The same study eye of the parent study MYL-1701P-3001 must be selected as study eye for the extension study. The study eye will remain same throughout the study.

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 (between + 20 and + 60 minutes post-dose).

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 must be performed before the subject's eyes are dilated and before 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. All efforts should be made for the visual acuity examiner to have no ready access to the subject's study eye and previous BCVA recorded.

It is recommended that same visual acuity examiner performs VA throughout the study.

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.

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.

6.3.2 Safety Assessment

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.

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

[a] HbA1c testing will be done at Screening and EOS/ET
[b] Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
[c] At visits, as per study schedule

Hematology and chemistry will be analyzed by local 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 local laboratory. Overall, local laboratory will be utilized to perform laboratory investigations for this extension study.

Laboratory safety assessment results from the end of study (visit 16/Week 52) of the parent study can be utilized for screening visit of the extension study.

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 Twelve-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. The position of subject for 12-lead ECG recording will be as per the site standard practice.

To ensure safety of the subjects, a medically qualified individual at the site will assess ECG recordings. 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.

Clinical examinations will be conducted for subjects with signs and symptoms suggestive of COVID-19 (such as fever, cough, difficulty in breathing). Subjects with history of travel/contact with any COVID-19 positive subject/isolation/ quarantine will be evaluated at each visit as per standard practices followed at site by the Investigator’s discretion. Subjects having signs and symptoms of COVID-19 or history of travel/contact with any COVID-19 positive subject/isolation/quarantine will be managed as per investigator’s discretion as per site’s standard clinical practice.

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 significance and seriousness will be based on the investigator's medical judgment.

6.3.3 Immunogenicity Assessment

The multi-tiered sample analysis recommendations for immunogenicity testing will be employed for the immunogenicity assessment (FDA 2019; EMA 2017; 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 anti-drug antibodies (ADA) against aflibercept.

Assessment of anti-drug antibody and neutralizing antibody will use fully validated analytical methods. Bioanalytical methodology and procedures will be documented in a sample analysis protocol.

6.3.4 Blood Volume

Blood samples will be collected for immunogenicity and safety laboratory investigations as detailed in study schedule (Table 1).

6.3.4.1 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). Four (4) blood samples (5 mL each) will be collected at each time point. 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.

6.3.4.2 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.

6.3.4.3 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

There is no formal sample size estimation. The extension study is open for all subjects from India who completed the parent study MYL-1701P-3001. It is expected that up to 100 subjects will be considered for participation in the extension study.

For mean change from baseline (Day 1 of parent study) in BCVA at Week 20, the point estimate for the difference between the group of subjects that switched from Eylea in parent study and those continued on MYL-1701P should be within the range of [redacted] letters, which is a recommended similarity margin for a 1-year endpoint. The following table gives the power with which this can be achieved for expected numbers of subjects per group, assuming a treatment regimen difference of 0 and a standard deviation of 10.5 letters:

Table 4: Power with Expected Number of Subjects Per Group

	Number of subjects per group
	[redacted]
Power	

7.2 Populations for Analyses

The safety population will consist of all subjects who received at least 1 dose of MYL-1701P in the extension study.

The Full Analysis Set (FAS) will consist of all subjects in the safety population who have at least one post-dosing BCVA assessment.

7.3 Statistical Analyses

7.3.1 Efficacy Analyses

The efficacy endpoints will include:

- Mean change from baseline (Day 1 in parent study) in BCVA as assessed by ETDRS letters at Week 20
- Mean change from baseline (Day 1 of parent study) in CRT as determined by spectral-domain-optical coherence tomography (SD-OCT) at Weeks 8, 16 and 20
- Mean change from baseline (Day 1 of parent study) in BCVA as assessed by ETDRS letters at Weeks 8 and 16
- Proportion of subjects who gained ≥5 letters, ≥10 letters and ≥15 letters from baseline in BCVA, assessed by change from baseline (Day 1 of parent study) in ETDRS letters at Weeks 8, 16 and 20
- Mean change in BCVA from Day 1 of extension study at Week 20
- Mean change in CRT from Day 1 of extension study at Week 20

Unless otherwise specified, Day 1 of parent study will be considered as the baseline value for all efficacy endpoints.

The analysis of the mean change from baseline in BCVA at Week 20 will be based on a mixed model repeated measures analysis with terms for group (switch from Eylea to MYL-1701P or continue on MYL-1701P), visit, and group by visit interaction, 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% two-sided CI for the group difference at Week 20.

The proportion of subjects who gained ≥ 5, 10, or 15 letters from baseline in BCVA at Weeks 8, 16, and 20 will be presented by group (switch from Eylea to MYL-1701P or continue on MYL-1701P). For each time point, the summary table will present the number of subjects in each group, the proportions by group, the difference in proportions, and the 95% CI for the difference. These estimates will be unadjusted for covariates.

The other efficacy endpoints will be analyzed in a similar manner as the mean change from baseline in BCVA at Week 20.

All analyses will be performed on the FAS.

7.3.2 Missing Data

Handling of missing data will be described in SAP.

7.3.3 Sub-Group Analyses

Subgroup analyses by baseline (Day 1 of parent study) BCVA, age, and gender for key efficacy endpoints will be performed. Details will be provided in the SAP.

7.3.4 Safety Analyses

Analysis of all safety data will be performed on the safety population.

7.3.4.1 Adverse Events

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.

7.3.4.2 Immunogenicity

Occurrence, titer, and neutralizing capacity of ADA will be summarized at each scheduled sampling time.

7.3.4.3 Prior and Concomitant Medications

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.

7.3.4.4 Vital Signs

Blood pressure and pulse rate will be listed and descriptively summarized (N, mean, standard deviation, minimum and maximum) by group (switch from Eylea to MYL-1701P or continue on MYL-1701P) and visit. Baseline (defined as the pre-dose value collected at Day 1 of extension study) and changes from baseline will be similarly summarized.

7.3.4.5 ECG Analyses

ECG data; QT, QTc (Fridericia's), heart rate (HR), QRS duration, PR and RR interval will be listed and descriptively summarized (N, mean, standard deviation, minimum and maximum) by group (switch from Eylea to MYL-1701P or continue on MYL-1701P) and visit.

7.3.4.6 Laboratory Data

Descriptive summaries of observed values and change from baseline (defined as the value collected at the screening visit in the extension study) will be presented for clinical laboratory evaluations (serum chemistry and hematology) by group. Assessments of laboratory variables according to clinical relevance will be tabulated by visit and group (switch from Eylea to MYL-1701P or continue on MYL-1701P) 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 group in shift tables.

The assessment of categorical urinalysis variables will be tabulated by visit for each urine parameter by group (switch from Eylea to MYL-1701P or continue on MYL-1701P) in frequency tables. Additionally, for each of the urine parameters, shifts in assessments from baseline (defined as the value collected at the screening visit in the extension study) to all post-baseline visits will be presented for each group in shift tables.

7.3.4.7 Other Analyses

For intraocular pressure, descriptive statistics at each visit and change from baseline (defined as the pre-dose value collected at Day 1 of extension study) at each visit will be provided. Other ophthalmological examinations will be summarized as shift tables.

7.3.5 Interim Analyses

Interim analysis is not planned for this study.

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.

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)

After completion of extension clinical study, CSR will be prepared. 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 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 in the extension 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 after enrollment visit through EOS visit of this extension study.

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.

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 end of study or 28 days after last dose of study treatment. Pre-existing diseases or conditions (reported at screening visit 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 study 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 5.0 or higher. 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 5: 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 6.

Table 6: 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 7):

Table 7: 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:

Mylan product Safety & Risk Management

PV MAIL HUB FOR IMMEDIATE SAFETY REPORTS:

[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 (WoCBP) 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., ECGs, 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

