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Final Analysis
Statistical Analysis Plan (SAP)

Mylan

Protocol Title:	A Multi Center, Randomized, Double-Masked, Active-Controlled, Comparative Clinical Study to Evaluate the Efficacy and Safety of MYL-1701P and Eylea® in Subjects with Diabetic Macular Edema
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[redacted]

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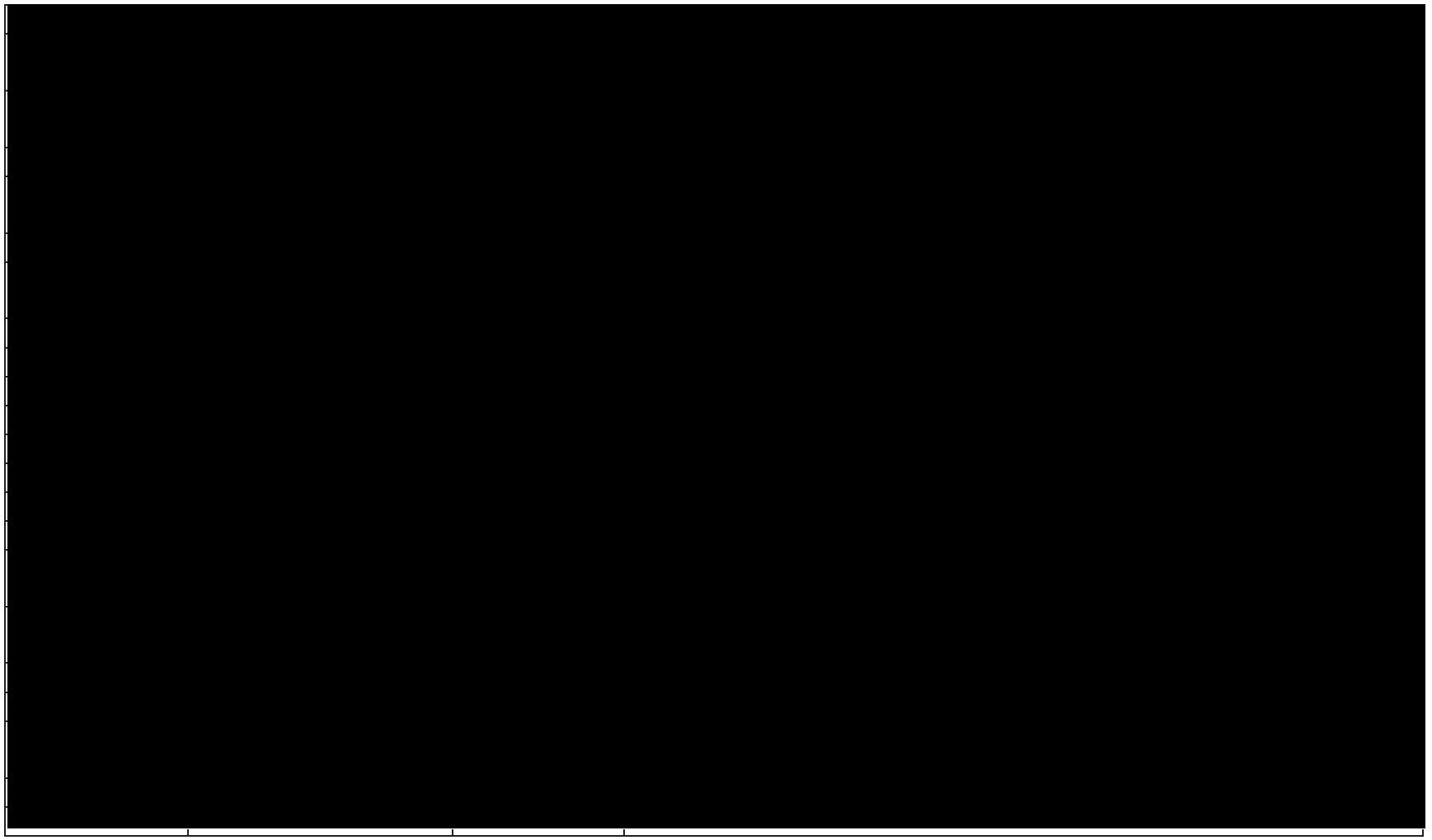
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Statistical Analysis Plan (SAP)

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TABLE OF CONTENTS

SIGNATURE PAGE 2
REVISION HISTORY 3
TABLE OF CONTENTS 5
LIST OF ABBREVIATIONS 8
1 INTRODUCTION 11
2 STUDY OBJECTIVES 12
2.1 Primary objective 12
2.2 Secondary objectives 12
3 STUDY DESIGN 13
3.1 General study design 13
3.2 Study Eye 14
3.3 Randomization and masking 15
3.4 Reporting Strategy 15
3.5 Study treatments and assessments 16
4 STUDY ENDPOINTS 22
4.1 Primary efficacy endpoint 22
4.2 Secondary efficacy endpoints 22
4.3 Safety endpoints 22
4.4 Immunogenicity endpoints 22
4.5 Pharmacokinetics endpoint 23
5 SAMPLE SIZE AND POWER 24
6 ANALYSIS SETS 25
6.1 Intention-to-treat (ITT) analysis set 25
6.2 Safety analysis set (Safety) 25
6.3 Full analysis set (FAS) 25
6.4 Per-protocol (PP) analysis set 25
6.5 PK subset analysis set 26
7 Statistical Considerations and analysis 27
7.1 Derived variables 27
7.2 Handling of missing data and outliers 27
7.2.1 Missing data analysis methods for sensitivity analyses 27
7.2.2 Handling of missing or incomplete dates 28
7.2.2.1 Imputation rules for missing or partial AE start date 28
7.2.2.2 Imputation rules for missing or partial medication start/stop dates 28
7.3 Data cut-off rules for 24-week analysis 29
7.4 Handling of Week 52 assessments 29
8 STATISTICAL METHODS 30

8.1 General statistical conventions 30
8.2 Subject disposition 30
8.3 Exclusions from analysis sets and protocol deviations 31
8.4 Demographics and baseline characteristics 31
8.4.1 Demographics 31
8.4.2 Baseline and disease characteristics 31
8.4.3 Medical, surgical and ophthalmic history 32
8.4.4 Prior and concomitant medications 32
8.5 Extent of exposure 32
8.5.1 Treatment duration 32
8.5.2 Treatment compliance 33
8.5.3 Missed or delayed doses 33
8.6 Efficacy analyses 33
8.6.1 Analysis methods 34
8.6.1.1 Analysis of mixed model for repeated measures (MMRM) 34
8.6.1.2 Multiplicity 34
8.6.1.3 Treatment by center interaction analysis (multi-center study) 34
8.6.2 Analysis of primary efficacy endpoint 34
8.6.2.1 Analysis to meet FDA requirements 35
8.6.2.2 Analysis to meet EMA requirements 35
8.6.3 Sensitivity analysis for primary efficacy endpoint 35
8.6.4 Subgroup analyses for primary efficacy endpoint 36
8.6.5 Analysis of secondary efficacy endpoints 37
8.6.5.1 Key secondary efficacy endpoint 37
8.6.5.2 Other secondary efficacy endpoints 37
[redacted]
8.6.7 Analyses to assess the impact of COVID-19 on the study 38
8.7 Safety analyses 39
8.7.1 Adverse events 40
8.7.1.1 Incidence of TEAEs 41
8.7.1.2 Severity of TEAEs 42
8.7.1.3 Relationship of treatment-emergent adverse events to the study drug 42
8.7.1.4 Serious adverse events 42
8.7.1.5 Adverse events leading to study drug withdrawal 42
8.7.1.6 Injection procedure related ocular TEAE 42
8.7.1.7 Any MACE (APTC events) 42
8.7.2 Clinical laboratory evaluations 43
8.7.3 Vital signs 43
8.7.4 Electrocardiograms 44
8.7.5 Physical examinations 44
8.7.6 Other ophthalmological examinations 44
8.7.7 Fundus photography/Fluorescein angiography 45
[redacted]

8.8 Other analyses 45
8.8.1 Immunogenicity 45
8.8.2 Treatment of fellow eye 45
8.8.3 Pharmacokinetics 45
8.9 Interim analysis 45
9 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL 46
10 REFERENCES 47
11 APPENDICES 48

LIST OF ABBREVIATIONS

The following abbreviations will be used within this SAP.

Abbreviation or special term	Explanation
ADA	Antidrug Antibodies
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
APTC	Anti-platelet trialists' collaboration
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
BCVA	Best corrected visual acuity
BDR	Blinded data review
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
cm	Centimetre
Cmax	Maximum plasma concentration
CRF	Case report form
CRO	Contract research organization
CRT	Central retinal thickness
CSR	Clinical study report
DBL	Database lock
DME	Diabetic macular edema
DRSS	Diabetic retinopathy severity score
ECG	Electrocardiogram
eCRF	Electronic case report form
ETDRS	Early treatment diabetic retinopathy study
FAS	Full analysis set
FDA	Food and drug administration
GCP	Good clinical practice

HR	Heart rate
ICF	Informed consent form
ICH	International conference on harmonisation
IOP	Intraocular pressure
ITT	Intention-to-treat
IXRS	Interactive response system
kg	Kilogram
LOCF	Lost observation carried forward
MACE	Major adverse cardiovascular event
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
MMRM	Mixed model for repeated measurements
PK	Pharmacokinetic
PP	Per protocol
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
QTc	QT corrected
QTcF	QT corrected (Fridericia's correction)
RoW	Rest of the world
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
SD-OCT	Spectral domain – optical coherence tomography
SI	Standard international
SID	Subject identification number
SOC	System organ class
SOP	Standard operating procedure

SSP	Study specific procedure
TE	Treatment-emergent
TEAE	Treatment emergent adverse event
TFLs	Tables, figures and listings
US	United States
VEGF	Vascular Endothelial Growth Factor
WHODDE	World health organization drug dictionary enhanced

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol MYL-1701P-3001, Version 3.0, titled with "A Multi Center, Randomized, Double-Masked, Active Controlled, Comparative Clinical Study to Evaluate the Efficacy and Safety of MYL-170P and Eylea® in Subjects with Diabetic Macular Edema" dated 09 June 2020 for final analysis. The table of contents and templates for the Tables, Figures and Listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonization (ICH) E3 and E9 guidelines [1, 2].

All data analyses and generation of TFLs will be performed using Statistical Analysis System (SAS®) version 9.3 or higher.

2 STUDY OBJECTIVES

2.1 Primary objective

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

2.2 Secondary objectives

The key secondary objective is:

- To compare the efficacy of MYL-1701P and Eylea® as measured by change in central retinal thickness (CRT) at Week 8 with CRT measured as central subfield thickness read by DARC.

The other secondary objectives are:

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

3 STUDY DESIGN

3.1 General study design

This study is a multi-center, randomized, double-masked, active-controlled, comparative clinical study between MYL-1701P and US-licensed Eylea® in subjects with Diabetic Macular Edema (DME) treated up to 52 weeks, with maximum total study duration of 13 months/56 weeks, consisting of 3 periods:

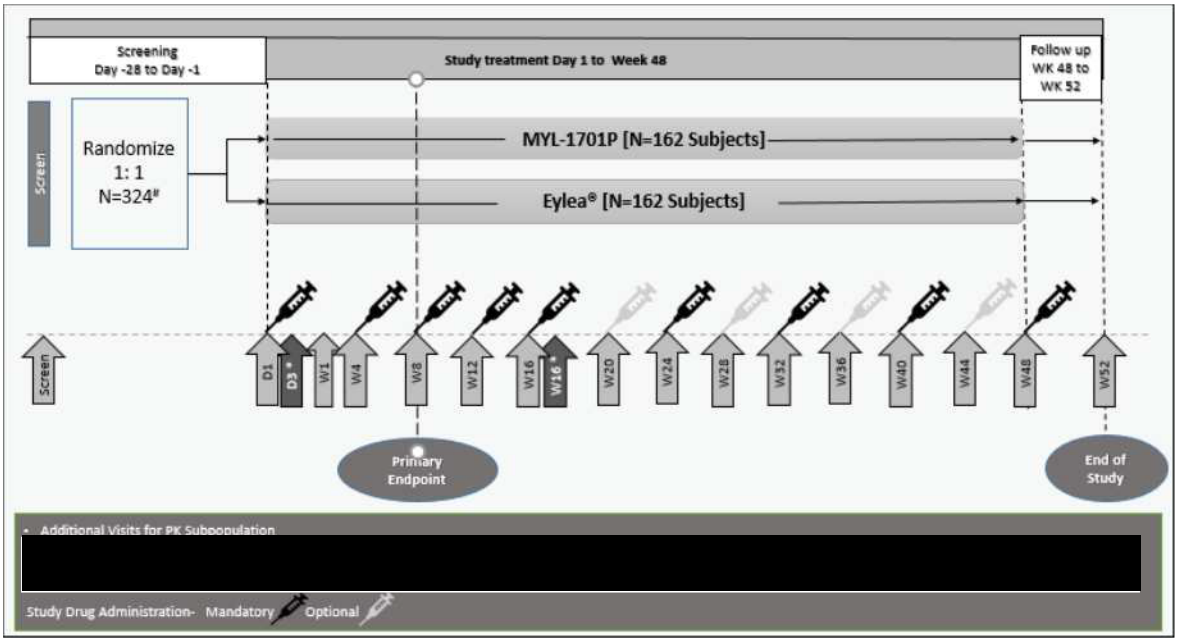
- Screening period (4 weeks, Day −28 to Day −1)
- Double-masked treatment period (48 weeks, Visits 1 to 15, Day 1 to Week 48)
- Follow-up period (4 weeks, Visit 16, Week 48 to 52)

A total of 324 eligible adult subjects with type 1 or 2 diabetes mellitus with central DME involvement and BCVA between 73 and 38 letters based on Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/40 – 20/200 Snellen equivalent) in the study eye with CRT ≥ 300 µm, as determined by spectral domain – optical coherence tomography (SD-OCT), in the study eye will be randomized 1:1 to intravitreal treatment with MYL-1701P or Eylea®.

[redacted]

The Study Flow Chart is presented in Figure 1.

Figure 1: Study Flow Chart



3.2 Study Eye

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

3.3 Randomization and masking

At each study center, subjects who are eligible to enter the double-masked treatment period will be randomized to one of the two treatment arms (MYL-1701P or Eylea®), in a 1:1 ratio through an Interactive response system (IXRS). Randomization will be stratified based on BCVA at baseline (ETDRS Letter Scores 73-55 vs 54-38) and geographical region (US, EU, Japan and Rest of the World [RoW]). For those subjects added to the study as per section 7.1 of protocol version 3.0, randomization will be according to the original randomization schedule, i.e. the next available randomization number will be assigned. The subjects are additional subjects and do not replace any subjects.

Assignment of Subject Identification number (SID), randomization number and study medication, as well as site drug inventory control will be managed by an automated IXRS.

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

The masked treatment code must not be broken except in emergency situations for which the identification of the study treatment of a subject is required by the Investigator in case of a medical emergency and when the knowledge of the study treatment allocation is required for appropriate management of the medical event. In such situations, the randomization information will be held by designated individual(s), and the date and reason for breaking the mask must be recorded. The date the mask was broken is also to be documented in the electronic case report form (eCRF).

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

3.4 Reporting Strategy

Two statistical analyses will be performed: a 24-week analysis and a 52-week analysis.

If not otherwise specified, all tables, figures and listings will be prepared for both analyses.

At the time of writing 24-week CSR, a pre-identified team from Mylan, Momenta and [redacted] will be unmasked and the rest of the study team will continue to be masked (see Masked/Unmasked Management Plan). The investigator and subjects will remain masked to their treatment for as long as they are participating in the study.

The 24-week analysis will be performed as soon as all data until Visit 9 (Week 24) have been locked. Only data until Visit 9 (Week 24) will be included in the 24-week analysis. All deviations/violations and exclusions of subjects from analysis sets will be identified and finalized at a Blinded Data Review (BDR) meeting prior to study unmasking for the 24-week analysis. The 24-week analysis will be performed by an independent [redacted] Biostatistics and Programming team.

The PK, ADA and Nab data may not be available at the time of unmasking for the Week 24 analysis. However, the information associated with EDC such as collection date, visit, and accession ID will remain unaltered and treatment will remain masked during the laboratory bioanalytical assay. These data will be available later and will be analyzed as described in section 8.8.1 and 8.8.3.

The 24-week CSR will contain the primary efficacy analysis.

The 24-week CSR will also contain other efficacy, safety, immunogenicity and pharmacokinetic data through week 24.

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

3.5 Study treatments and assessments

The maximum study duration from screening to end of the follow-up period is up to 13 months (or 56 weeks).

All subjects eligible for study participation will enter the double-masked treatment Period (Visit 1). At study week 8, the primary endpoint will be assessed and subjects will continue to receive the assigned treatment until Week 48. An end of study visit will be conducted at Week 52.

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

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

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

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

Pharmacokinetics (free aflibercept concentrations) will be evaluated for subjects participating in

pharmacokinetic subset. At least 32 subjects in each study arm will be included in the pharmacokinetic (PK) subset.

A detailed description of procedures and assessments to be conducted during this study is summarized in the Scheduled of Study Assessments in **Table 1** below.

ble 1: Schedule of study assessments

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

Assessment	Period	Screening	Treatment period															
	Visit	Screening Visit	V1/ BL	V2[q]	V3	V4	V5	V6	V7	V7A[p]	V8	V9	V10	V11	V12	V13	V14	V15	V16
	Day or week:	D -28 to D -1	D1	D3 (±0 d)	W1 (±2d)	W4 (±3d)	W8 (±3d)	W12 (±7d)	W16 (±7 d)	W16 +2d (±0 d)	W20 (±7d)	W24 (±7d)	W28 (±7d)	W32 (±7d)	W36 (±7d)	W40 (±7d)	W44 (±7d)	W48 (±7d)	W52 (±7d) EOS/ ET
12- Lead Electrocardiogram[i]		x	x		x							x							x
Complete Ophthalmologic Examination[j]		x	x	x[r]	x	x	x	x	x	x		x	x	x	X	x	x	x	x	x
Best Corrected Visual Acuity (Bilateral)		x	x			x	x	x	x	x		x	x	x	X	x	x	x	x	x
Spectral Domain – Optical Coherence Tomography / Central Retinal Thickness (Bilateral)		x	x			x	x	x	x	x		x	x	x	X	x	x	x	x	x
Fluorescein Angiography/ Fundus Photography (Bilateral)[k]		x																		x

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

Abbreviations: aPTT = activated partial thromboplastin time; BL = baseline visit; EOS = end of study; ET = Early Termination; INR = International Normalized Ratio
PT = Prothrombin Time.

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

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

4 STUDY ENDPOINTS

4.1 Primary efficacy endpoint

The primary efficacy endpoint of this study is the mean change from baseline in BCVA as assessed by ETDRS letters at week 8.

4.2 Secondary efficacy endpoints

The key secondary efficacy endpoint of this study is:

- The mean change from baseline in CRT as determined by SD-OCT at Week 8 with CRT measured as central subfield thickness read by DARC

The other secondary efficacy endpoints of this study are:

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

4.3 Safety endpoints

The safety and tolerability endpoints will be assessed over time, based on the following evaluations:

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

4.4 Immunogenicity endpoints

The immunogenicity endpoints of this study are:

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

4.5 Pharmacokinetics endpoint

The pharmacokinetics endpoint of this study is:

- Concentration of aflibercept (free drug)

5 SAMPLE SIZE AND POWER

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

[redacted]

Randomization will be stratified by BCVA at baseline (ETDRS Letter Scores 73-55 vs 54-38) and geographical region (US, Europe, Japan and RoW).

More details regarding the sample size determination (assumptions, reference studies etc.) can be found under the Protocol section 7.1.

6 ANALYSIS SETS

All deviations/violations and exclusions of subjects from analysis sets will be identified and finalized at BDR meeting prior to the study unmasking for the 24-week analysis.

6.1 Intention-to-treat (ITT) analysis set

The ITT analysis set will consist of all subjects who were randomized.

Subjects will be included in the analysis according to the treatment to which they were randomized.

The ITT analysis set will be the primary analysis set for efficacy analyses.

6.2 Safety analysis set (Safety)

The safety analysis set will consist of all subjects who received at least one dose of study drug.

Subjects will be included in the analysis according to the actual treatment received. The safety analysis set will be the primary analysis set for safety analyses.

6.3 Full analysis set (FAS)

The FAS will consist of all randomized subjects who receive any study drug, who have a baseline BCVA, and who also have at least one post dosing BCVA assessment up to Week 8.

Subjects will be included in the analysis according to the treatment to which they were randomized. The FAS will provide supportive data for the primary efficacy analysis.

6.4 Per-protocol (PP) analysis set

The PP analysis set will consist of all FAS subjects who have no major protocol deviations (i.e. no violation which may affect the primary efficacy outcome). Major protocol deviations will include one or more of the following categories:

- Did not receive treatment to which they were randomized
- Inclusion/exclusion criteria violations which can impact the primary efficacy analysis
- Intake of forbidden concomitant medication which can impact the primary efficacy analysis
- Treatment deviation (missed 1 or more injections prior to Week 8)

In addition, further deviations may be considered major if they impact the primary efficacy analysis. Potential protocol deviations will be collected during the study within [redacted] system. The list of subjects excluded from the PP analysis set and the precise reasons for exclusion will be finalized at the BDR meeting to be held prior to database lock for Week 24. Details on the BDR will be provided in a BDR Plan and the outcome of the meeting will be recorded in a BDR Report.

The PP analysis set will provide supportive data for the efficacy analyses.

6.5 PK subset analysis set

The PK subset analysis set will consist of all subjects who have signed the ICF for participation in PK subpopulation and have at least one measured concentration of study treatment.

7 STATISTICAL CONSIDERATIONS AND ANALYSIS

7.1 Derived variables

The below table provides the list of derived variables for demographic and baseline characteristics, various duration derivations, drug compliance, baseline derivations and other important derivations applicable for this study.

Variables	Formula
Demographic and baseline characteristics	
Body mass index (BMI) (kg/m^2)	weight (kg)/[height (m)]^2 (rounded to 1 decimal place)
Derivation of duration	
Study day at any visit	Date of interest – date of first dose of study drug. One day is added if this difference is ≥ 0
Extent of exposure (days)	Date of last randomized study medication intake – date of first randomized study medication intake + 28 days
Drug compliance	
Compliance	100x[(number of planned doses taken)/(number of planned doses)] (only the 9 planned doses should be considered; in case of premature termination only those up to last visit reported)
Baseline derivations	
Baseline	The baseline value is defined as the last observation prior to or on the date of the first dose of study drug.
Change from baseline	Post baseline value – baseline value
Relative change from baseline	[(Post baseline value – baseline value)/baseline value]*100

7.2 Handling of missing data and outliers

Missing data will not be imputed in the primary analysis of the primary efficacy endpoint. No imputation will be employed for the descriptive summaries and listings.

Missing post-baseline values will be imputed using the last observation carried forward (LOCF) before calculating the proportions of subjects who gained or lost letters (secondary efficacy endpoints).

7.2.1 Missing data analysis methods for sensitivity analyses

The following sensitivity analyses of the primary endpoint will be performed to determine the effect

on the inference allowing data to be missing not at random.

Last Observation Carried Forward (LOCF):

In this approach, missing values will be imputed with a LOCF approach. Missing post-baseline data will be imputed using the last non-missing observation (except baseline, unscheduled visits prior to week 8 will be considered) prior to calculating change from baseline.

Tipping point analysis for delta method using multiple imputation:

Details are provided in section 8.6.3.

7.2.2 Handling of missing or incomplete dates

7.2.2.1 Imputation rules for missing or partial AE start date

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with Treatment-emergent (TE) period to determine whether the AE is pre-treatment AE, Treatment-emergent adverse event (TEAE) or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date.
- Otherwise, impute the AE start Month as January and the Day as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pre-treatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing and the AE end date is before the first dose date then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.

7.2.2.2 Imputation rules for missing or partial medication start/stop dates

Missing or partial medication start date:

- If only Day is missing, use the first day of the month.
- If Day and Month are both missing, use the first day of the year.
- If Day, Month and Year are all missing, use a date before the first dose date.

Missing or partial medication stop date:

- If only Day is missing, use the last day of the month.
- If Day and Month are both missing, use the last day of the year.
- If Day, Month and year are all missing, assign 'continuing' status to stop date

7.3 Data cut-off rules for 24-week analysis

Data cut off will be performed at raw data level prior to creating SDTM datasets.

All data will be included for screening failed subjects, not dosed subjects and subjects who terminated the study prior to Week 24.

Week 24 visit date will be used as data cut-off date for subjects who are on study at or beyond Week 24.

Data assessment/collection/event date will be compared with data cut-off date for each individual subject, data after cut-off date will be excluded for the analysis.

For AEs or concomitant medications, if their start dates are on or prior to data cut-off date, but end dates are after data cut-off date, end dates will be set to missing, ongoing flags will be set to 'Yes', AE outcomes will be set to 'Not Recovered/Not Resolved'.

7.4 Handling of Week 52 assessments

Early Termination visits and End of Study (Week 52) visits are both captured in the Visit 16 folder in the database. For the Week 52 analysis, the Visit 16 assessments done at Week 52 ± 7 days will be summarized separately and displayed in outputs.

8 STATISTICAL METHODS

8.1 General statistical conventions

All statistical procedures will be completed using SAS version 9.3 or higher. SDTM v1.4, SDTM IG v3.2, ADaM v2.1, ADaM IG v1.1 will be used.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. Two-sided 95% CI will be provided when relevant.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, SD, Q1, median, Q3, minimum and maximum. Minimum and maximum will be presented with same number of decimal places as reported/collected, one additional decimal place for mean and quartiles, and two additional decimal places for SD.

For categorical variables, summaries will include counts of subjects and percentages based on number of subjects in the corresponding treatment group or overall. Percentages will be rounded to one decimal place.

For summary purposes, baseline will be defined as the last available pre-dose value; all summaries will be presented by treatment group, unless otherwise specified.

The number of missing values will be presented as a separate category with no percentage, but only if 1 or more subjects are missing data for the summary. Otherwise, all categories will be presented (even if no subjects are counted in the category). Counts of zero in any category will be presented without percentage.

All subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within subject listings only. All listings will be sorted by investigational site, subject number and visit. The treatment group (MYL-1701P, Eylea®) as well as subject's gender and age will be stated on each listing. Unless otherwise stated, data listings will be based on all subjects consented, i.e. all subjects who provided written informed consent prior to performing any specific study-related procedures.

8.2 Subject disposition

Subject disposition information will be summarized by treatment group and overall. The number of subjects screened, the number of screen failures and the number of subjects with each reason for screen failure will be presented (overall). All screened subjects will be included.

The number and percentage of subjects who are randomized, who took a dose of study drug, who were randomized and not treated, who complete the study and who withdraw early from the study will be presented for the ITT analysis set.

The primary reason for early withdrawal will also be tabulated.

The number of subjects randomized will be used as the denominator for the percentage calculation.

8.3 Exclusions from analysis sets and protocol deviations

The number of subjects excluded from FAS, Safety and PP analyses sets and reasons for exclusion will be summarized by treatment group and overall.

All major protocol deviations identified will be summarized by treatment group and overall. In addition, the following information will be displayed:

- Total number of protocol deviations
- Number of subjects reporting at least one protocol deviation
- Number of key/important protocol deviations
- Number of subjects reporting at least one key/important protocol deviation
- Number of non-key/unimportant protocol deviations
- Number of subjects reporting at least one non-key/unimportant protocol deviation
- Number of major protocol deviations
- Number of subjects reporting at least one major protocol deviation.

A listing will include the inclusion/exclusion criteria violated at Screening and at Baseline Visits as well as other protocol deviations identified based on data recorded on the eCRF and/or protocol deviation Logs from [redacted] Medical. If applicable, site deviations will be listed separately.

8.4 Demographics and baseline characteristics

All analyses described in section 8.4.1 and 8.4.2 will be based on ITT analysis set, FAS, and PP analysis set. If two analysis sets are identical, the analyses will be performed only once. Analyses described in section 8.4.3 and 8.4.4 will be based on ITT analysis set only.

8.4.1 Demographics

Age (in years) will be summarized descriptively. Age category (< 55, ≥ 55 - < 65, ≥ 65 - < 75, ≥ 75), gender, geographical region/country (US, Europe, Japan, RoW), race and ethnicity will be summarized. The corresponding tables will be prepared for the 24-week analysis only.

8.4.2 Baseline and disease characteristics

The categorical baseline characteristics such as smoking status (never, former, current), BMI category (≤30, >30 - ≤35, > 35), HbA1c category (< 8, ≥ 8), BCVA score category (< 45, ≥ 45 - < 55, ≥ 55 - < 65, ≥ 65), and diabetic retinopathy severity score (DRSS) category/level (10, 20, 35, 43, 47, 53, 61, 65, 71, 75, 85, 90) for study eye and fellow eye will be summarized using frequency counts. Continuous baseline variables such as height (in cm), weight (in kg) and BMI (in kg/m^2),

HbA1c at baseline, BCVA score (study eye and fellow eye), intraocular pressure (IOP, study eye and fellow eye) and central retinal thickness (study eye and fellow eye) will be summarised by descriptive statistics in the same way as continuous demographic variables. The corresponding tables will be prepared for the 24-week analysis only.

8.4.3 Medical, surgical and ophthalmic history

Summaries of non-ocular and ocular medical history will be presented by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities® (MedDRA) Version 20.1 or higher by treatment group and overall. The corresponding tables will be prepared for the 24-week analysis only. For ocular medical history, the conditions or events will be separately displayed for study eye and for fellow eye. In case an event or condition has been reported for both, study and fellow eyes, it will be counted for both.

8.4.4 Prior and concomitant medications

Medications used in this study will be coded using the latest available version (i.e. March 2016 or later) of the World Health Organization Drug Dictionary Enhanced (WHODDE).

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

Concomitant medications: are defined as those medications with a start date on or after the first dose of study drug.

Prior and concomitant medications will be summarized descriptively using frequency tables by Anatomical Therapeutic Chemical (ATC) class level 3 and preferred name (generic drug name) by treatment group. Subjects with multiple medications in the same ATC class or preferred name will be counted only once for that respective ATC class or preferred name.

Details for imputing missing or partial start and/or stop dates of medication are described in section 7.2.2.

Analyses regarding treatment of fellow eye by anti-VEGF treatments are described in section 8.8.1.

8.5 Extent of exposure

8.5.1 Treatment duration

Duration of study drug (in days) will be calculated as: last dose date – first dose date + 28 days, regardless of study drug interruption (28 days are added to account for the minimum 4-week dosing interval).

Study drug exposure will be summarized by treatment group on the safety analysis set using descriptive statistics.

8.5.2 Treatment compliance

Study drug compliance will be summarized by treatment group on the safety analysis set using descriptive statistics. The proportion completing all the planned study drug doses, at least one and all the optional doses by treatment group will be determined. In addition, number and percentage of subjects receiving both the planned and optional doses (1, 2, 3, …, 13) and missed doses (1, 2, > 2) will be provided.

Treatment compliance will be calculated for each subject as a percentage of actual to expected doses taken: (number of planned doses taken) / (number of planned doses) × 100. For this calculation, the 9 planned doses and visits with a planned dose should be considered only, any optional doses will not be included in this calculation. In case of premature discontinuation of study the number of expected doses will be adjusted to the period under observation.

The number of subjects with a compliance <75% and ≥75% will be presented based on the safety analysis set.

8.5.3 Missed or delayed doses

The number of subjects with missed or delayed doses and the primary reason for the miss or delay will be summarized by visit and treatment group.

The reasons will be categorized as COVID-19 related or not COVID-19 related, with the following subcategories for COVID-19 related reasons: hospital restricted access/limited staff availability, patient's fear/lack of transportation, local country level restrictions, patient infected with COVID-19, patient in quarantine or investigator judgment due to COVID-19 situation for patient's safety.

8.6 Efficacy analyses

This section addresses separately the analyses to be conducted on the primary, key secondary and secondary efficacy variables. All efficacy analyses will be performed on the ITT analysis set and the PP analysis set. The primary analysis will also be performed on the FAS.

All the defined efficacy analyses will be performed based on the study eye. The information collected from fellow eye will only be displayed in the summary tables.

All definitions relative to efficacy endpoints are detailed in section 4.

8.6.1 Analysis methods

8.6.1.1 Analysis of mixed model for repeated measures (MMRM)

The primary analysis of the primary endpoint will be based on an MMRM analysis on mean change from baseline in BCVA as assessed by ETDRS letters at week 8. This analysis will be based on data collected up to Week 8.

This model will include treatment, visit/time (in weeks), treatment-by-visit interaction, and region as fixed effects and baseline BCVA as a covariate. The within subject variance-covariance matrix will be assumed to be unstructured (which does not presume a particular correlation structure for repeated measurement within subjects over time), estimation will use restricted maximum likelihood, and the denominator degrees of freedom will use the Kenward-Roger estimate.

The MMRM model results will be presented with an estimate (Least Square [LS] means), standard error, and 90% as well as 95% two-sided CIs for the treatment difference (with Eylea® group being the reference category) at week 8.

The SAS code used to implement this test will be similar to that shown below:

```
PROC MIXED DATA=dataset COVTEST NOCLPRINT METHOD=REML;
    CLASS ID Trt week region;
    MODEL BCVA=base Trt week region Trt*week / SOLUTION CL DDFM=KenwardRoger;
    REPEATED week /SUBJECT = ID TYPE = UN R RCORR;
    LSMEANS Trt*week / CL;
    ESTIMATE 'MYLversus Eylea at Week 8' Trt 1 -1 Trt*week 0 1 0 -1/ CL ALPHA = 0.05;
    ESTIMATE 'MYLversus Eylea at Week 8' Trt 1 -1 Trt*week 0 1 0 -1/ CL ALPHA = 0.1;
RUN;
```

In case of non-convergence of the above model using an unstructured covariance matrix, a Toeplitz variance structure will be used. The final covariance structure used will be documented in the CSR.

8.6.1.2 Multiplicity

Not applicable as there is only one primary endpoint.

8.6.1.3 Treatment by center interaction analysis (multi-center study)

Region (Europe, US, Japan and RoW) will be included in the model as a fixed effect. Otherwise, there is no direct exploration of Treatment*center interaction effect.

8.6.2 Analysis of primary efficacy endpoint

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

MMRM will be used to analyze change from baseline in BCVA as mentioned in section 8.6.1.1.

The null hypotheses H_0 given below will be tested against the alternative hypotheses H_A:

H_0: $|\mu_M - \mu_E| \geq \Delta$ (i.e. H_0: $\mu_M - \mu_E \leq -\Delta$ or $\mu_M - \mu_E \geq \Delta$)

H_A: $|\mu_M - \mu_E| < \Delta$

where μ_M and μ_E denote the mean absolute change in BCVA from baseline to week 8 in MYL-1701P and Eylea® groups respectively.

The corresponding tables will be prepared for the 24-week analysis only.

8.6.2.1 Analysis to meet FDA requirements

Equivalence will be demonstrated if the 90% CI for the treatment difference of mean change from baseline to week 8 for BCVA is fully contained within the interval (-3, 3). The primary efficacy analysis will be performed on the ITT analysis set and will include data from all visits regardless of whether the subject is still receiving study medication.

8.6.2.2 Analysis to meet EMA requirements

Equivalence will be demonstrated if the 95% CI for the treatment difference of mean change from baseline to week 8 for BCVA is fully contained within the interval (-3, 3). The primary efficacy analysis will be performed on the ITT analysis set and will include data from all visits regardless of whether the subject is still receiving study medication.

8.6.3 Sensitivity analysis for primary efficacy endpoint

The following sensitivity analyses will be performed:

- Analysis of the primary endpoint based on the FAS.
- Analysis of the primary endpoint based on the PP analysis set.
- Analysis of the primary endpoint in which BCVA values after discontinuing study medication will be excluded.
- Analysis of the primary endpoint in which missing BCVA values at week 8 will be replaced by LOCF approach using the analysis of covariance (ANCOVA) model.
- Tipping point analysis for delta method using multiple imputation

[redacted]

[redacted]

8.6.4 Subgroup analyses for primary efficacy endpoint

Subgroup analyses will be performed for the primary efficacy endpoint to determine whether significant differences exist in primary endpoint results within subgroup categories.

For the following parameters (with applicable definitions in parentheses), subgroup analyses will be

performed:

- Baseline BCVA score for study eye (73-55, 54-38)
- Age in years (< 55, ≥ 55 - < 65, ≥ 65 - < 75, ≥ 75)
- Gender (male, female)
- Race (Black or African American, White, Other (= everyone not in Black or African American or White category))
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Geographic Region/Country (US, Europe, Japan, RoW)
- Baseline HbA1c (< 8, ≥ 8)
- Any anti-VEGF therapy in fellow eye prior to visit 5 (week 8).
- ADA status (positive, negative)

In addition, the results of all but the last two subgroup analyses will be shown in a forest plot.

The subgroup analyses will be based on ITT analysis set and PP analysis set. The corresponding tables will be prepared for the 24-week analysis only. Tables for all subgroups will be produced using method defined in section 8.6.1.1 except for ADA subgroup.

Mean change from baseline will be displayed per ADA subgroup and treatment group with assignment to ADA positive or negative defined for each timepoint using information up to each visit.

8.6.5 Analysis of secondary efficacy endpoints

8.6.5.1 Key secondary efficacy endpoint

The key secondary efficacy variable is the mean change from baseline in CRT as determined by SD-OCT at week 8. The corresponding tables will be prepared for the 24-week analysis only.The analysis of the key secondary efficacy variable will be performed in a similar manner as the analysis of the primary efficacy endpoint (section 8.6.2) using central CRT reading of all the SD-OCT images across visits including subgroup analyses and forest plot for subgroups. In addition, a line graph with time (in weeks) presented on the x-axis and mean change from baseline in CRT presented on the y-axis will be provided with as well as without LOCF imputation method for the ITT analysis set.

8.6.5.2 Other secondary efficacy endpoints

The other secondary efficacy variables are:

- The mean change in BCVA over time.
- The mean change in CRT over time.
- Proportion of subjects who gained ≥15 letters from baseline in BCVA, assessed in change

from baseline in ETDRS letters over time.
- Number of administrations of study drug required.

The mean change in BCVA over time will be analyzed in a similar manner as the primary efficacy endpoint (section 8.6.2), but the analysis will be based on data collected up to the data cut for the respective CSR (Week 24 or Week 52). In addition, a line graph with time (in weeks) presented on the x-axis and mean change from baseline in BCVA presented on the y-axis will be provided with as well as without LOCF imputation method for the ITT analysis set.

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

Along with above unadjusted, an adjusted (for covariates) analysis will be performed: a logistic regression with "gained ≥15 letters from baseline in BCVA" binary variable (Yes/No) as dependent factor and treatment as fixed independent factor and baseline BCVA as covariate. Odds ratio and 95% CI will be presented.

The same summary will also be presented for subjects who gained ≥5 and ≥10 letters as well as subjects who lost ≥5, ≥10 and ≥15 letters. In addition, bar charts per treatment group will be produced for gaining of ≥5 and ≥10 letters at Week 24 (LOCF) and loss of ≥5, ≥10 and ≥15 letters at Week 24 (LOCF).

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

All analyses will be performed on the ITT analysis set and the PP analysis set (except bar charts and where otherwise stated).

[redacted]

8.6.7 Analyses to assess the impact of COVID-19 on the study

For the primary efficacy endpoint, the following additional sensitivity and supplementary analyses will be done to assess the impact of COVID-19-related disruptions on the study:

- [redacted]

The analyses, with exception of the tipping point analysis, will be also done for the key secondary efficacy endpoint.

The number of subjects with missed or delayed BCVA examinations and the reason for the miss or delay will be summarized by visit and treatment group.

The reasons will be categorized as COVID-19 related or not COVID-19 related, with the following subcategories for COVID-19 related reasons: hospital restricted access/limited staff availability, patient's fear/lack of transportation, local country level restrictions, patient infected with COVID-19 or patient in quarantine.

A listing will include subjects affected by COVID-19 related disruptions based on data recorded on the protocol deviation log from [redacted] CTMS.

8.7 Safety analyses

All definitions relative to safety endpoints are detailed in section 4.3.

All the safety analyses will be conducted on the Safety Analysis Set (treated subjects).

All safety data will be summarized by treatment group.

The safety analyses of changes from baseline to a specific time point in safety variables (e.g., laboratory parameters, vital signs, and ECG) will only include subjects from the safety analysis set who have data available for both the baseline and the time point under consideration unless otherwise specified.

No inferential statistical analysis of safety endpoints will be performed.

8.7.1 Adverse events

All AEs (both ocular and non-ocular) will be coded using MedDRA Version 20.1 or higher.

In summaries by SOC and PT, adverse events will be sorted within each SOC and PT by decreasing frequency (MYL-1701P group) according to the alphabetical order.

All AEs will be listed, but only treatment-emergent AEs (TEAEs) will be summarized. An AE will be considered a TEAE if it occurs or worsens on or after receipt of the first dose of study drug. Details for imputing missing or partial start dates of adverse events are described in section 7.2.2.

A TEAE will be analyzed as a related TEAE, if the relationship to the investigational drug was assessed by the investigator as definitely, probably or possibly.

The occurrence of AEs and SAEs will be summarized in terms of incidence, as well as in terms of total number of AEs.

All AE tables will be created for all AEs, ocular AEs study eye, ocular AEs fellow eye and non-ocular AEs.

A list of major adverse cardiovascular events (MACE) will be provided by Mylan and included in the analyses.

An AE overall summary table will be presented with the following information:

- All AEs
- All TEAEs
- Related TEAE
- Serious AEs (SAEs)
- Related SAEs
- TEAEs leading to death
- Injection procedure related TEAEs
- TEAEs leading to study drug withdrawal
- TEAEs by maximum severity
- TEAEs by maximum relationship to investigational drug
- Any MACE (APTC events)

- Ocular TEAEs
  - Study eye
  - Fellow eye
- Related ocular TEAEs
  - Study eye
  - Fellow eye
- Ocular SAEs
  - Study eye
  - Fellow eye
- Related ocular SAEs
  - Study eye
  - Fellow eye
- Injection procedure related ocular TEAEs
  - Study eye
  - Fellow eye
- Ocular TEAEs by maximum severity
  - Study eye
  - Fellow eye
- Non-ocular TEAEs
- Related non-ocular TEAEs
- Non-ocular SAEs
- Related non-ocular SAEs
- Injection procedure related non-ocular TEAEs
- Non-ocular TEAEs by maximum severity

This AE overview table will be created for the safety analysis set.

The overall number of subjects with TEAE as well as the number of subjects with study eye ocular TEAE will separately be presented for the subgroups of ADA positive and ADA negative subjects.

All TEAEs, all TEAES by maximum severity, all TEAEs by maximum relationship, all SAEs, all TEAEs leading to IP discontinuation, Ocular injection procedure related TEAE, any MACE (APTC events) and non-serious AEs will be summarized by SOC, PT and treatment group using frequency counts and percentages (i.e., number and percentage of subjects with an event).

8.7.1.1 Incidence of TEAEs

A summary of TEAEs will be presented by SOC and PT by treatment group. If a subject reports the same PT multiple times, then that subject will only be counted once for that PT. As with the PT, if a

subject reports multiple AEs within the same SOC, then the subject will only be counted once for that SOC.

This summary will be created for the safety analysis set as well as for the subgroups of ADA positive and ADA negative subjects.

8.7.1.2 Severity of TEAEs

A summary of TEAEs by SOC, PT, and severity will be presented by treatment group. Severity will be graded by the investigator as "Mild", "Moderate", "Severe", "Life-Threatening" or "Death". If a subject reports multiple occurrences of the same PT or SOC, only the most severe will be presented.

8.7.1.3 Relationship of treatment-emergent adverse events to the study drug

A summary of TEAEs by SOC, PT, and relationship to the study drug will be presented by treatment group. The relationships indicate the investigator's assessment of whether or not the event was caused by the study drug. The possible relationships are "Not Related", "Unlikely", "Possibly Related", "Probably Related" and "Definitely Related". If the investigator does not make a causality assessment, the event will be classified in the summary tables as if it were definitely related to the study drug.

If a subject reports multiple occurrences of the same PT or SOC, only the most strongly related occurrence will be presented.

8.7.1.4 Serious adverse events

A summary of SAEs and a summary of non-serious AEs will be presented by SOC and PT by treatment group. In addition, all SAEs will be listed by subject.

8.7.1.5 Adverse events leading to study drug withdrawal

A summary of all AEs leading to study drug withdrawal will be presented by SOC and PT by treatment group.

8.7.1.6 Injection procedure related ocular TEAE

A summary of all injection procedure related ocular TEAEs will be presented by SOC and PT by treatment group.

8.7.1.7 Any MACE (APTC events)

A summary of all MACE (APTC events) will be presented by MACE category and PT by treatment group.

8.7.2 Clinical laboratory evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be presented in SI units.

The clinical safety laboratory tests that will be performed at each scheduled visit are listed below:

Table 2: Laboratory safety tests

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

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

b. At visits, as per study schedule

c. HbA1c testing will be done at Screening, Baseline, Visit 6 (week 12), Visit 9 (week 24), EOS/ET

If a lab value is reported using a nonnumeric qualifier e.g., less than (<) a certain value, or greater than (>) a certain value, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

Descriptive summaries of observed values and change from baseline will be presented for clinical laboratory evaluations (Serum chemistry and hematology) by treatment group. Additionally, for each laboratory parameter, shifts in value (low, normal, high) from baseline to all post-baseline visits will be presented by treatment group in shift tables.

For each of the urine parameters, shifts in assessments from baseline to all post-baseline visits will be presented for each treatment group in shift tables.

8.7.3 Vital signs

Visit values and changes from baseline for vital sign measurements (pulse, temperature, systolic and diastolic blood pressure) will be summarized by treatment group at each scheduled visit using descriptive statistics.

8.7.4 Electrocardiograms

Visit values and changes from baseline of continuous ECG measurements (ECG Heart Rate (beats/min), QRS Duration (ms), PR Interval (ms), QT Interval (ms), QTcF (ms) and RR interval) will be summarized by treatment group at each scheduled visit using descriptive statistics.

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

The normality/abnormality of the ECG tracing, as determined by the investigator, will be summarized using frequency tables on number of subjects who have a normal/abnormal ECG tracing per visit. Summary will be presented by treatment group.

8.7.5 Physical examinations

Physical examination assessments will be listed only.

8.7.6 Other ophthalmological examinations

Other ophthalmological examination includes indirect ophthalmoscopy, intraocular pressure (IOP) and slit-lamp biomicroscopy.

All analyses will be performed for the study eye as well as for the fellow eye.

IOP will be measured from baseline through Week 52 (Visit 16), and at each visit twice (pre-dose, post-dose) whenever a dose was administered. Mean IOP and the change from baseline (Visit 1, pre-dose) will be summarized by treatment group at each scheduled visit (pre-dose as well as post-dose). In addition, the changes per visit between pre-dose and post-dose will be summarized by treatment group.

For each of the indirect ophthalmoscopy tests (vitreous, optic nerve, macula, retinal vessels, peripheral retina), shifts in results (normal, abnormal not clinically significant, abnormal clinically significant, not done) from baseline to all post-baseline visits will be presented for each treatment group in shift tables.

For slit-lamp biomicroscopy examination, shifts in each of the grading system assessment (N/A, 0, Tr, 1+, 2+, 3+, 4+), lens status (phakic, pseudophakic, aphakic, other) and response in each of the eye part (normal, abnormal, not examined) from baseline to all post-baseline visits will be presented for each treatment group in shift tables.

8.7.7 Fundus photography/Fluorescein angiography

For screening/baseline and Week 52 (Visit 16) assessment from site, the response related to the study eye as well as for the fellow eye for fundus photography and fluorescein angiography will be listed only.

The fundus photography and fluorescein angiography data coming from a central assessment (screening visit only) will be summarized by treatment group on safety analysis set.

[redacted]

8.8 Other analyses

8.8.1 Immunogenicity

Occurrence, titer, and neutralizing capacity of antidrug antibodies (ADA) will be summarized at each scheduled sampling time on Safety analysis set. Additionally, an overall summary for all subjects as well as subjects with no pre-study and/or on study aflibercept/any intravitreal anti-VEGF therapy in fellow eye will be produced for ADA and Nab incidence, including a distinction between treatment induced and treatment boosted ADA. Treatment induced ADA is defined as ADA developed any time after the initiation of dug administration in a subject without pre-existing ADA. Treatment boosted ADA is defined as any time after the initiation of drug administration the ADA titer is at least 4*the baseline titer in a subject who had a pre-existing ADA at baseline.

8.8.2 Treatment of fellow eye

The following analyses will be provided by treatment group on the safety analysis set:

- Number and percentage of subjects with at least one anti-VEGF injection in the fellow eye (overall and by ranibizumab or bevacizumab or aflibercept)

8.8.3 Pharmacokinetics

For all subjects in the PK subpopulation as well as for the subgroups of ADA positive and ADA negative subjects within the PK subpopulation, concentrations of aflibercept (free drug) will be summarized at each scheduled sampling time.

All concentrations below the lower limit of quantification (LLOQ) values will be analyzed as ‘0’. In the summary tables a row will be added showing the number of concentrations below LLOQ.

8.9 Interim analysis

No interim analysis is planned for this study.

9 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

Change to the analysis set for the primary analysis:

As described in section 7.2.2 of the protocol, the primary analysis was to be performed on the FAS. At the Biosimilar Biological Product Development Type 2 Meeting on 24 July 2020, FDA recommended that the primary analysis be performed on the intent-to-treat population including all randomized subjects. Therefore, the analysis set for the primary analysis has been changed to the ITT analysis set. The analysis based on the FAS will be used as supportive.

10 REFERENCES

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95-adopted December 1995).
2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).

11 APPENDICES

No appendices