Clinical Development and Regulatory Affairs

Biostatistics and Data Management

REGENERON

Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN

Title:	A PHASE 3, DOUBLE-MASKED, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF INTRAVITREAL AFLIBERCEPT INJECTION IN PATIENTS WITH MODERATELY SEVERE TO SEVERE NONPROLIFERATIVE DIABETIC RETINOPATHY
Protocol:	VGFTe-OD-1411
Investigational product:	Intravitreal Aflibercept Injection
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Date:	**09 July 2018**
Version:	**3.0**

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALT	Alanine Aminotransferase
ASNV	Anterior segment neovascularization
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutically Chemical
AUC	Area Under the Curve
BCVA	Best Corrected Visual Acuity
BUN	Blood Urea Nitrogen
CI-DME	Central-Involved DME
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
DME	Diabetic Macular Edema
DRSS	Diabetic Retinopathy Severity Score
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAS	Full Analysis Set
FP	Fundus Photography
IAI	Intravitreal Aflibercept Injection
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IOP	Intraocular Pressure
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
IVT	Intravitreal
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
(MedDRA) HLT	High Level Term
(MedDRA) LLT	Low Level Term
(MedDRA) PT	Preferred Term
(MedDRA) SOC	System Organ Class

NPDR	Nonproliferative Diabetic Retinopathy
OCT	Optical Coherence Tomography
PPS	Per Protocol Set
PDR	Proliferative Diabetic Retinopathy
PRP	Panretinal Photocoagulation
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAF	Safety Analysis set
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
TEAE	Treatment-emergent Adverse Event
UPCR	Urine protein creatinine ratio
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WHO	World Health Organization

DOCUMENT VERSION HISTORY

Version	Date	Version History
1.0	21DEC2015	Initial Version
2.0	17FEB2016	Purpose: Update to incorporate the following revisions in response to feedback from the Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA): 1. Revise the significance levels for testing of the secondary efficacy endpoints in Table 1 of Section 5.1, per FDA feedback 2. Add multiple imputation SAS code in Appendix 10.7 per FDA feedback 3. Add a hemoglobin A1c assessment at week 24, and fundus photography at week 8 in Appendix 10.1, per PMDA feedback
3.0	09JUL2018	Purpose: Change the timepoint for evaluation of the secondary endpoints from week 100 to week 52. Changes may be found in Section 1, Figure 1 of Section 2.1, Section 4.5.2, Section 4.5.3, Section 5.1, Section 5.5, Section 5.5.2, Section 5.5.3 and Appendix 10.2

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of the study. The statistical evaluation will be done according to the specifications given in the protocol and, if applicable, the corresponding amendments.

The SAP is intended to be a comprehensive and detailed description of the strategy and statistical technique to be used for the analysis of Week 24 (Visit 7), Week 52 (Visit 11), and Week 100 (Visit 18) data from the VGFTe-OD-1411 study. The statistical analysis of the Week 24 and Week 52 (the primary timepoints) data will be performed as soon as the Week 24 and Week 52 data of all patients are available, even though the study will be ongoing.

This SAP covers the following three analyses:

- Analysis of the data through Week 24 as primary analysis for combined 2Q8 and 2Q16 groups (only data from the combined treatment group and the sham group will be summarized)
- Analysis of the data up to Week 52 as primary and secondary analysis for 2Q8 and 2Q16 groups separately
- Analysis of all endpoints in an exploratory manner at Week 100 for all 3 groups

1.1. Background/Rationale

Diabetes mellitus and its complications are a worldwide health epidemic that is expected to increase. In 2013, the World Health Organization (WHO) estimated that 347 million people had diabetes and this number has been projected to increase to 366 million by 2030 and potentially more if rates of obesity continue to increase. Despite early intervention programs and better methods of glycemic control, morbidity and mortality as a consequence of diabetes, including diabetic retinopathy, are expected to rise. Diabetic retinopathy is microvascular damage to the blood vessels in the retina, and it can progress to vision-threatening stages including proliferative diabetic retinopathy (PDR), where new vessels that are susceptible to hemorrhage grow initially from the retina and/or optic disc and extend beyond the internal limiting membrane, and diabetic macular edema (DME), where fluid accumulates disrupting the macular architecture and function. Although there are treatments for DME (eg, anti-vascular endothelial growth factor [VEGF] agents), there is a significant unmet medical need for the treatment of diabetic retinopathy. More advanced retinopathy (proliferative) is often treated with panretinal photocoagulation (PRP). Although PRP may stop the progression of a proliferative disease, it is inherently destructive to the retina and, therefore, likely to cause visual symptoms such as visual field defects, reduced contrast sensitivity, and impaired night and color vision, and can also lead to exacerbation of macular edema. There is currently no treatment for nonproliferative diabetic retinopathy (NPDR), and patients are observed until disease progresses sufficiently to warrant PRP.

Intravitreal (IVT) anti-VEGF therapy is currently the standard of care treatment for DME, and it has proven to be generally safe and effective in patients with DME. In the phase 3 VISTA and VIVID studies of EYLEA® (aflibercept, known in the scientific literature and in clinical studies as VEGF Trap-Eye or intravitreal aflibercept injection [IAI]), patients treated with either

aflibercept 2 mg every 4 weeks (2Q4) or aflibercept 2 mg every 8 weeks (2Q8) (following 5 initial monthly doses) regimens gained 11.5 and 10.7 letters, respectively, in best corrected visual acuity (BCVA) at week 52.

Despite advances in treatment for DME, there are currently no approved treatments for NPDR in patients without DME, leaving patients at risk for the development of PDR and/or DME. Based on the evidence from the VISTA and VIVID studies in patients with DME showing that EYLEA (in addition to treating macular edema) also improves the underlying diabetic retinopathy, we propose to investigate EYLEA in patients with moderately severe to severe NPDR who do not have DME by assessing the proportion of patients who improve by at least 2 steps on the DRSS (Diabetic Retinopathy Severity Score).

This phase 3 study will assess the efficacy and safety of IVT aflibercept in patients with moderately severe to severe NPDR.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of the study is to assess the efficacy of IVT aflibercept compared to sham treatment in the improvement of moderately severe to severe NPDR.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To characterize the safety of IVT aflibercept in patients with moderately severe to severe NPDR
- To determine if IVT aflibercept will prevent the worsening of diabetic retinopathy and reduce the incidence of DME
- To determine the anatomic effects of IVT aflibercept in patients with moderately severe to severe NPDR

1.2.3. Modifications from the Statistical Section in the Final Protocol

Not applicable

1.2.4. Modifications from the Approved Statistical Analysis Plan

Not applicable

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a phase 3, double-masked, randomized study of the efficacy and safety of IVT aflibercept for the improvement of moderately severe to severe NPDR.

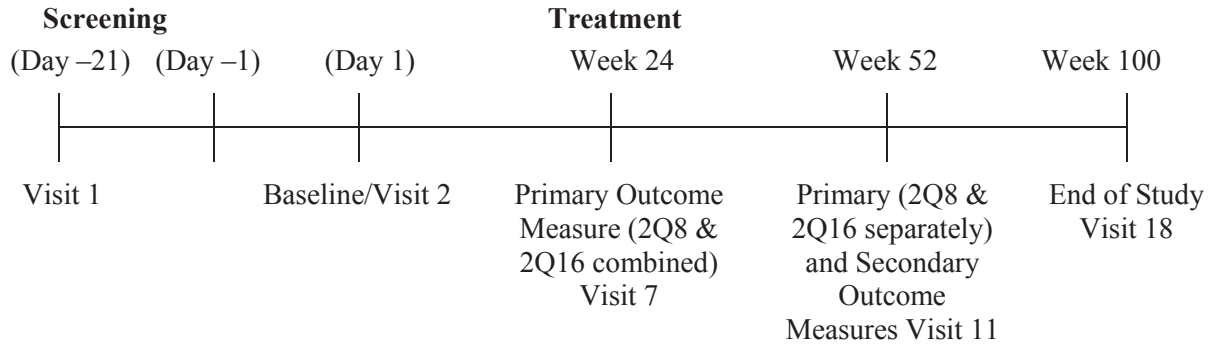
After providing informed consent, patients will be assessed for study eligibility at the screening visit, up to 3 weeks before day 1/baseline. At the day 1/baseline visit, patients will undergo safety assessments prior to receiving the first dose of study drug.

Eligible patients will be enrolled into 1 of 3 treatment groups in a 1:1:1 randomization scheme, and will be stratified based on their DRSS score (level 47 vs. level 53). Only 1 eye will be selected as the study eye. The 3 treatment groups will have the following dosing regimens from day 1 to week 48: 1) 2Q8 aflibercept IVT after 5 initial monthly doses; 2) 2Q16 aflibercept IVT after 3 initial monthly doses and one 8-week interval; and 3) sham treatment. In year 2 (beginning at week 56), the 2Q8 group will be treated with a flexible treatment regimen.

The primary outcome measure of the study is the proportion of patients who have improved by ≥2 steps from baseline on the DRSS in the combined 2Q8 and 2Q16 groups at week 24, and in each group individually at week 52. Patients will be evaluated for efficacy (BCVA using the 4-meter ETDRS (Early Treatment Diabetic Retinopathy Study) protocol, spectral domain optical coherence tomography [SD-OCT], and fluorescein angiography [FA]/fundus photography [FP]) and for ocular and systemic safety (including ophthalmic exams, visual field testing, and laboratory assessments) through week 100 (Figure 1).

Patients who develop PDR, anterior segment neovascularization (ASNV), or DME will qualify for rescue treatment. If treatment is given, subsequent patient data will be censored for the primary analysis.

Figure 1: Study Flow Diagram



Approximately 360 patients will be randomized in a 1:1:1 ratio to receive either aflibercept 2Q8, aflibercept 2Q16, or sham according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified according to the patient's DRSS level (level 47 vs. level 53 at the screening visit).

The study event table is presented in Appendix 10.1.

2.2. Sample Size and Power Considerations

Anticipating approximately 41% of patients with a ≥2-step improvement from baseline in DRSS score at week 52 in either the 2Q8 or 2Q16 groups versus 17% in the sham group, 102 patients per group are required to detect a difference with a power of 90% for rejecting the null hypothesis at a 2-sided 1.67% (5%/3) significance level. A sample size of 102 patients per group will provide at least 90% power to detect a difference between combined aflibercept group vs. sham group at week 24, if a 38% response rate is assumed in the combined aflibercept group. The assumption of the proportions for the aflibercept group and sham group is based on VIVID and VISTA data at a given time point. To account for about a 15% dropout rate, 120 patients per group will be enrolled.

The sample size calculation was computed using the Chi square test (continuity corrected) from the commercial software nQuery nTerm 7.0.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following analysis populations will be used for all statistical analysis:

3.1. Full Analysis Set

The full analysis set (FAS) includes all randomized patients who received any study treatment. Analysis of the FAS will be performed according to the treatment assigned at baseline (as randomized). The efficacy analysis on the FAS is considered to be the primary one (statistical evaluation of superiority). The FAS will be used to evaluate all efficacy endpoints for Week 24, Week 52 and Week 100 data.

3.2. Safety Analysis Set

Safety analysis set (SAF) includes all randomized patients who receive at least 1 study treatment (aflibercept or sham). Patients will be summarized according to the treatment actually received (as treated). The 'as-treated' assignment will only differ from the "as randomized" if the patient is systematically receiving treatment from an alternative treatment group. However, isolated incorrect treatments will not constitute a change in the "as treated" assignment. Patients whose "as treated" assignment differs from their "as randomized" assignment will be listed.

Treatment administration/ compliance, all clinical safety, and tolerability assessments will be analyzed using the SAF for Week 24, Week 52 and Week 100 data. The safety analysis will be performed on the observed safety data.

3.3. Subgroup Analysis Set

Subgroups are defined by key baseline factors recorded on the case report form (CRF) and listed as follows:

- Subgroups to be considered for both efficacy and safety analyses
  1. Sex
  2. Age: <40y; >=40-<65y; >=65y
  3. Race: White, Black or African American, Other
  4. Ethnicity: Hispanic or Latino (no/yes)
  5. HbA1C: ≤ 8%; > 8%

- Subgroups to be considered for efficacy analyses only
  1. Baseline DRSS score: 47 vs. 53
- Subgroups to be considered for safety analyses only
  1. Medical history of hypertension
  2. Medical history of cerebrovascular disease (e.g., CVA/stroke)
  3. Medical history of ischemic heart disease (e.g., myocardial infarction)
  4. Renal impairment
     - Normal: > 80 ml/min
     - Mild: > 50-80 ml/min
     - Moderate: > 30-50 ml/min
     - Severe: <= 30 ml/min or requiring dialysis

     CrCl is calculated according Cockcroft-Gault formula (renal impairment guideline of FDA, 1998):

$$CrCl \approx \frac{[140 - age(years)] * weight(kg)}{72 * serum\ creatinine(mg/dl)} * \begin{cases} 1.0, if\ \ male \\ 0.85, if\ \ female \end{cases}$$

     Subjects are considered requiring dialysis if their medical history includes one of preferred terms (PTs).

The detailed definition of the PTs for the safety subgroups above is presented in Appendix 10.3.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

Demographic and baseline assessments to be summarized will include:

- Age, gender, and race
- Age category: <40y; >=40-<65y; >=65y
- Weight, height, BMI (kg/m²)
- Smoking history
- HbA1C
- HbA1C category: <= 8%; >8%
- BMI <=30 kg/m², BMI >30- <=35 kg/m², BMI >35 kg/m²
- Vital Signs (Baseline heart rate, systolic blood pressure, diastolic blood pressure and temperature)
- Baseline Intraocular pressure (IOP)
- Medical History
- Duration of Diabetes (years): defined as time from diagnosis (based on medical history data (MedDRA HLT "diabetes mellitus") to randomization
- Diabetes Type (Type 1 and Type 2)
- Baseline DRSS
- Baseline ETDRS letter score
- Baseline central retinal thickness

4.2. Medical History

Medical history will be coded according to latest available version of Medical Dictionary for Regulatory Activities (MedDRA).

4.3. Pre-Treatment / Concomitant Medication

Medications taken during the study will be recorded and will be coded to ATC codes according to the World Health Organization Drug Dictionary (WHO Drug Dictionary) 2005Q3 enhanced version provided by Bayer Health Care.

Mediations will be summarized as follows:

- **Prior medication** is defined as medication that was started before and ended before a patient received first study treatment (active or sham treatment)
- **Concomitant medication** is defined as medications that are ongoing at, or begin after the start of study treatment

- **New medication** is defined as medications that began after the start of study treatment

The prior, concomitant and new medication will be summarized by ATC class (ATC level 1) and subclass (ATC level 2).

Variables for concomitant medication description and analysis will include Generic name, ATC level codes, Indication, Dose/Dose Unit, Frequency, Route, start/end date and study day, Duration, Ongoing.

4.4. Exposure, Compliance, Additional Treatment to Study Treatment

Exposure

For each patient, the following variables will be used to examine exposure to study treatment for the study eye (rescue treatment will not be taken into account here:

- Total number of active injections in aflibercept groups
- Total number of sham injections separately by treatment groups
- Duration of treatment calculated (Weeks) as: [(last study treatment date) - (first study treatment date) + 28]/7 (28 days are added because of the minimum 4-week dosing interval in the study)
- For patients who receive rescue treatment for PDR, ASNV, or CI-DME, the type, frequency and duration of treatment will be summarized

Compliance

Per patient, compliance with protocol-defined study medication during the time periods: 24 weeks, 52 weeks and 100 weeks will be calculated as follows:

Treatment Compliance =
(Number of received injections [sham or active] through week time period)/(Number of planned injections [sham or active] during period of participation in the study through time period) x 100%

For the calculation of compliance all injections (regardless if they were sham or active) will be used.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable (s)

The primary efficacy variable is the proportion of patients who have improved by ≥2 steps from baseline in the DRSS score at week 24 in the combined 2Q8 and 2Q16 groups and at week 52 for the separate groups.

4.5.2. Secondary Efficacy Variable(s)

The secondary outcome measures will be tested at week 52 and are as follows:

- Proportion of patients developing a vision-threatening complication due to diabetic retinopathy

  Vision-threatening complications are defined as composite outcome of PDR (inclusive of patients who have vitreous hemorrhage or tractional retinal detachment believed to be due to PDR) and ASNV

  Note: ASNV is defined as neovascularization of the iris (at least 2 cumulative clock hours), and/or definitive neovascularization of the iridocorneal angle
- Proportion of patients who develop central-involved DME (CI-DME)
- Time to development of a vision-threatening complication
- Time to development of CI-DME
- Proportion of patients who receive PRP, inclusive of patients undergoing vitrectomy with endolaser
- Area under the curve (AUC) for change in BCVA from baseline

4.5.3. Additional Efficacy Variable(s)

The additional outcome measures in the study are:

- Time to first improvement of ≥2 steps from baseline in the DRSS score through week 52 and week 100
- Proportion of patients with ≥2-step improvement from baseline in the DRSS score at week 100
- Proportion of patients with ≥2-step worsening from baseline in the DRSS score at week 52 and at week 100
- Proportion of patients with ≥3-step worsening from baseline in the DRSS score at week 52 and at week 100
- Proportion of patients with ≥3-step improvement from baseline in the DRSS score at week 52 and at week 100
- Proportion of patients who receive vitrectomy through week 52 and through week 100
- Change in central retinal thickness from baseline at week 52 and at week 100
- Change in mean deviation on visual field testing from baseline at week 52 and at week 100
- Change in BCVA from baseline at week 24, week 52 and week 100
- Proportion of patients who have gained ≥5, ≥10, or ≥15 letters from baseline at week 52 and at week 100
- Proportion of patients who have lost ≥5, ≥10, or ≥15 letters from baseline at week 24, week 52 and week 100

- The proportion of patients who are equal to or better than 20/20 or equal to or better than 20/40 at week 52 and at week 100.
- Proportion of patients developing either a vision-threatening complication or CI-DME through week 100
- Time to development of either a vision-threatening complication or CI-DME through week 100

Secondary Endpoints to be tested as Exploratory

- Proportion of patients developing a vision-threatening complication through week 100
- Proportion of patients who develop CI-DME through week 100
- Time to development of a vision-threatening complication through week 100
- Time to development of CI-DME through week 100
- Proportion of patients who receive PRP through week 100, inclusive of patients undergoing vitrectomy with endolaser
- Area under the curve (AUC) for change in BCVA from baseline through week 24 and 100

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug.

Adverse events will be collected at each visit from the time of informed consent signature until the end of the study. If the patient withdraws from the study during the screening, AEs will be collected up until the patient withdraws. If the patient withdraws at any point after receiving the first dose of study medication, AEs will be collected up until 30 days after the last dose of study drug or the termination visit, whichever is later.

Adverse events will be summarized as:

- **Pre-treatment AE:** Include adverse events that occur after the patient has signed the informed consent, but prior to Visit 2 (Day 1, date of the patient's first dose of study drug).
- **Treatment-Emergent Adverse Event (TEAE):** TEAE is defined as AE that is observed or reported after first and not later than 30 days after last administration of study medication (active or sham injection) or aflibercept injection in the fellow eye. Only worsening, pre-existing AEs and new AEs reported during treatment period (period after first treatment) will be collected in the study.

The following study periods will be used for TEAE and AE summaries:

- **Day 1 to Week 24**

- **Day 1 to Week 52**
- **Day 1 to Week 100, End of Study**

The data cut-off rules for Week 24 and Week 52 AE reporting are described in Appendix 10.6.

Other variables for AE description and analysis will include AE Verbatim Term, AE start date and end date/ongoing and corresponding study day, AE Duration, relationship of AE to study drug, relationship of AE to study procedure, seriousness, intensity, action due to AE, treatment of AE and outcome.

4.6.2. Surgeries

All the surgeries after informed consent are collected on the CRF and are coded by MedDRA.

The following variables will be tabulated by MedDRA preferred term:

- Pre-treatment surgery is defined as surgery performed before the start of study treatment (active or sham)
- Treatment emergent surgery is defined as surgery performed on or after the start of study treatment (active or sham)
  - Ocular treatment emergent surgery for study eye and fellow eye
  - Non-ocular treatment emergent surgery

4.6.3. Laboratory Safety Variables

Clinical laboratory variables will include the following:

- Blood chemistry panel: Sodium, Potassium, Chloride, Carbon dioxide, Calcium, Glucose, Albumin, Total Protein, serum, Creatine, Blood urea nitrogen (BUN), Aspartate, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase, Lactate dehydrogenase (LDH), Total bilirubin, Total cholesterol, Uric acid, Creatine phosphokinase
- Hematology panel: Hemoglobin, Hematocrit, Red blood cells (RBC), White blood cells (WBC), Red Cell Indices, Platelet count, Differential count: Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils
- Urinalysis: Color, Clarity, pH, Specific gravity, Ketones, Protein, Urine protein creatinine ratio (UPCR), Glucose, Blood, Blood, Bilirubin, Leukocyte esterase, Nitrite, WBC, RBC, Hyaline and other casts, Bacteria, Epithelial cells, Crystals, Yeast, Creatinine
- Hemoglobin A1c, Vitamin D

4.6.4. Vital Signs

Variables of analysis for vital signs include temperature, heart rate and blood pressure measures.

4.6.5. 12-Lead Electrocardiography (ECG)

12-Lead ECG parameters include

ECG variables will include heart rate, PR interval, RR interval, QRS duration, QT interval, overall interpretation of ECG (normal/abnormal) and clinically relevant abnormalities (no/yes). QTc with Bazett and Fridericia correction will be calculated.

4.6.6. Ocular Safety Measures

Variables of analysis for ocular safety measures include during Week 24, Week 52 and Week 100:

- Proportion of patient with increased intraocular ocular pressure (IOP)
  - ≥ 10 mmHg increase in IOP measurement from baseline to any pre-dose measurement
  - > 21 mmHg for any pre-dose measurement
  - ≥ 25 mmHg for any pre-dose measurement
  - ≥ 35 mmHg at any time

Post dose IOP measurement should be the last IOP recorded.

5. STATISTICAL METHODS

All efficacy and safety variables will be summarized descriptively with appropriate statistics: categorical variables by frequency (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by visit and as change from Baseline, if applicable.

5.1. Statistical Hypothesis

This study will examine the following hypotheses for the primary efficacy variable regarding the proportion of patients with a ≥2-step improvement from baseline in DRSS score in the study eye at week 24 in the combined 2Q8 and 2Q16 groups, and at week 52 for the 2Q8 and 2Q16 groups individually. Statistical testing of week 24 and week 52 will be conducted to demonstrate the superiority of the aflibercept groups (combined, 2Q8 and 2Q16) to the sham group, respectively.

For each test, let p_t (and p_c) be the true proportion of patients with a ≥2-step improvement from baseline in DRSS score at week 24 for the combined 2Q8 and 2Q16 groups, and at week 52 for the 2Q8 and 2Q16 groups individually (and the sham group, p_c).

The following hypotheses will be tested:

$$H_0: p_t = p_c \text{ versus } H_1: p_t \neq p_c$$

To control the family-wise type I error rate of 5%, primary efficacy endpoints for the combined group (week 24) and endpoints for the 2Q8 and 2Q16 groups (week 52) will be tested separately at the significance level of $\alpha = 1.67\%$ (5%/3). Secondary efficacy endpoints at week 52 will be tested for 2Q8 and 2Q16 groups by the hierarchical testing procedure at a significance level based on values in Table 1 for different scenarios with the predefined testing order.

Table 1: Significance Levels for Testing Secondary Efficacy Endpoints

Scenario	1	2	3	4	5	6	7
Combined Group at Week 24 Positive?	X	X	X		X		
2Q8 Group at Week 52 Positive?	X	X		X		X	
2Q16 Group at Week 52 Positive?	X		X	X			X
Significance level for secondary endpoints	0.05	0.033	0.033	0.033		0.0167	0.0167
Significance level for Testing for 2Q8 Group at week 52	0.025	0.033		0.0167		0.0167	
Significance level for Testing for 2Q16 at week 52	0.025		0.033	0.0167			0.0167

5.2. Demographics, Baseline Characteristics, Medical History, and Prior/ Concomitant Medication

Demographic data and baseline characteristics variables described in Section 4.1 will be summarized using descriptive statistics for SAF and FAS.

Medical history is evaluated for SAF by a frequency table, showing number of patients with medical history findings by primary system organ class (SOC), high level term (HLT) by MedDRA terms.

Prior/concomitant medication will be summarized by WHO-DD 2005Q3 enhanced version ATC codes (ATC 3-digit class and ATC 5-digit subclass) for medication taken during the study. Separate frequency tables will be displayed for patients with prior medications, new medications and concomitant medications by the time periods described in Section 4.3.

Concomitant medications will be summarized by the following periods:

- Day 1 up to Week 24
- Day 1 up to Week 52
- Day 1 up to End of study

5.3. Subject Disposition

The following categories for patient disposition will be summarized descriptively:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the informed consent form (ICF)
- The total number and percentage of randomized patients: received a randomization number
- The number and percentage of patients in each analysis set
- The total number and percentage of patients who discontinued the study at Week 24, Week 52 and Week 100 with the reasons for discontinuation

The following listings will be provided to assess the patient disposition:

- A listing of patients treated but not randomized and patients randomized but not treated if any
- A listing of patients who developed a vision threatening complication or central-involved DME through week 52 and through week 100
- A listing of patients who received rescue treatment in the study eye
- A listing of patients who were withdrawn from the study, along with reasons for discontinuation
- Listing of major protocol deviations: violation of inclusion/exclusion criteria; post-enrollment deviations which will impact assessment of efficacy endpoints

5.4. Extent of Study Treatment Exposure and Compliance

The variables for dose exposure and compliance described in Section 4.4 will be summarized for study eye in SAF and FAS population, using descriptive statistics by the following time periods:

- Day 1 to Week 24 (excluding treatment at Week 24)
- Day 1 to Week 52
- Day 1 to Week 100

5.5. Analyses of Efficacy Variables

Efficacy analyses of all efficacy variables defined in Section 4.5 will be conducted using the FAS population.

The primary endpoint analysis for the study will be conducted at 2 time points (week 24 for the combined 2Q8 and 2Q16 groups and week 52 for the 2Q8 and 2Q16 groups individually). Each of the primary efficacy analyses will be tested at the 1.67% (5%/3) significance level to control for multiplicity.

The secondary endpoints described in Section 4.5.2 for 2Q8 and 2Q16 groups will be tested separately in a hierarchical manner at week 52 as described in Section 5.1.

5.5.1. Analysis of Primary Efficacy Variable(s)

5.5.1.1. Primary Analysis for Primary Efficacy Variable

The primary analysis is a statistical evaluation of superiority of 3 comparisons (combined aflibercept vs. sham at week 24, aflibercept 2Q8 vs. sham at week 52, and aflibercept 2Q16 vs. sham at week 52) in respect to the primary efficacy variable (see Section 4.5.1). The statistical analysis will be performed using the Cochran-Mantel-Haenszel (CMH) method, stratified by baseline DRSS level (level 47 vs. level 53). Missing or non-gradable post-baseline values will be imputed using the last observation carry forward (LOCF) procedure. For any patient who receives rescue treatment, measurements after rescue is given will be imputed using the last observation prior to rescue treatment. Baseline will be carried forward if all post-baseline observations are missing or non-gradable.

Patients will be considered as non-responders if baseline observations are missing or non-gradable.

Aflibercept treatment will be considered to be superior to sham if the estimated aflibercept group (combined, aflibercept 2Q8, or aflibercept 2Q16) is greater than the sham group, and the p-value is less than or equal to or statistically significant at a 1.67% level.

5.5.1.2. Sensitivity Analyses for Primary Efficacy Variable

The following sensitivity analyses are used for the primary efficacy variable:

- Observed case (OC) analysis

  Measurements taken after the initiation of rescue treatment will be censored; only observed, gradable, and non-censored values will be used for analysis, (i.e. missing or non-gradable data will not be imputed).

- Patients who have received rescue treatment

  In these analyses the value at the given timepoint will be used regardless of whether the patient received rescue treatment or not. Two different analyses will be conducted:

  – Ancillary LOCF (aLOCF) – Data obtained after the initiation of rescue treatment will be included; missing or non-gradable data will be imputed by LOCF. Baseline will be carried forward if all post-baseline observations are missing or non-gradable. The data will be analyzed in the same way as described for the primary analysis in Section 5.5.1.1.

  – Ancillary observed case (aOC) - All observed values will be used for analysis, including measurements taken after the initiation of rescue treatment is given. Missing or non-gradable data will not be imputed. The data will be analyzed in the same way as described for the primary analysis in Section 5.5.1.1.

- Multiple imputation

The primary efficacy variable will also be analyzed by multiple imputation on FAS. Multiple imputation method will be conducted by the following three steps:

a. Imputation - Missing or non-gradable DRSS data will be imputed using MI procedure based on the observed case (OC) data. First, missing data will be imputed to achieve a monotone missing pattern using the MCMC (Markov Chain Monte Carlo) method with number of imputations = 100. Subsequently missing data will be imputed by a regression model with number of imputation = 1.

b. Analysis - The responder variable which is the improvement at least 2-step in DRSS can be determined from the complete DRSS data sets. The proportion of the responder will be analyzed using Cochran-Mantel-Haenszel test with stratification adjustment for baseline DRSS level (level 47 vs. level 53).

c. Pooling - Cochran-Mantel-Haenszel statistic from step b, under the null hypothesis, has an asymptotic chi-square distribution. It will be transformed to standard normal distribution by Wilson-Hilferty transformation. After normalization, the analysis results from multiple imputed data sets will be combined into one overall result based on Rubin's rules using MIANALYZE procedure.

SAS procedure for multiple imputation is described in Appendix 10.7 .

5.5.2. Analysis of Secondary Efficacy Variables

If at least one of the aflibercept groups is shown to be superior to sham in the primary variable, additional comparisons will be made for this aflibercept group with respect to the secondary variables at week 52 with the specified significance level as described in Section 5.1.

A hierarchical testing procedure will be performed for each dose group to compare the secondary variables between the respective aflibercept group and sham in the following order:

- 2Q8 secondary endpoints at week 52
  - Proportion of patients developing a vision-threatening complication
  - Proportion of patients who develop CI-DME
  - Time to development of a vision-threatening complication
  - Time to development of CI-DME
  - Proportion of patients who receive PRP, inclusive of patients undergoing vitrectomy with endolaser
  - Area under the curve (AUC) for change in BCVA from baseline
- 2Q16 secondary endpoints at week 52
  - Proportion of patients developing a vision-threatening complication
  - Proportion of patients who develop CI-DME
  - Time to development of a vision-threatening complication
  - Time to development of CI-DME
  - Proportion of patients who receive PRP, inclusive of patients undergoing vitrectomy with endolaser
  - Area under the curve (AUC) for change in BCVA from baseline

The p-values at week 52 for the secondary endpoints will be reported for all comparisons between the aflibercept groups and the sham group; however, a superiority claim can be made for a given endpoint only if all preceding endpoint comparisons in the hierarchy are shown to be statistically significant at the significance level specified in Section 5.1. The hierarchical method ensures the overall type I error rate of 5% for this study, with multiplicity adjustment for primary and secondary endpoint analyses.

All endpoints will also be analyzed descriptively at week 100 in an exploratory manner.

The analysis of proportion variables will be done using the same methodology as for the analyses of the primary efficacy variable described in Section 5.5.1.

For continuous variables (ie, BCVA), an analysis of covariance (ANCOVA) model with baseline measurements of the continuous variable as covariates and treatment and baseline DRSS score (level 47 vs. level 53) stratification as fixed factors will be used for the endpoint. The pair-wise comparisons of each aflibercept group versus sham will be done in the ANCOVA model. In

addition, 2-sided 95% confidence intervals for the difference of each aflibercept group minus sham will be calculated.

Time to first vision-threatening complication will be analyzed using the Kaplan-Meier estimates. A log-rank test will be performed, comparing sham with the aflibercept groups, as well as 2-sided 95% confidence intervals for the time to first vision-threatening complication for the difference of each comparison group. Time to development of CI-DME will be analyzed similarly.

Similar to the analysis of the primary endpoint, missing or non-gradable post-baseline values will be imputed using the last observation carry forward (LOCF) procedure. Baseline will be carried forward if all post-baseline observations are missing. The following sensitivity analyses will be done for secondary efficacy endpoints: OC, aLOCF, and aOC as defined in Section 5.5.1.2.

5.5.3. Analysis of Additional Efficacy Variables

All additional efficacy variables (see Section 4.5.3) will be analyzed descriptively. The p-values in the analysis will be nominal and only for descriptive purpose. In addition, the primary and secondary variables will also be analyzed descriptively as additional variables at week 100. These descriptive analyses may include statistical tests on the proportion for the efficacy variables, in the same way as described for the primary and secondary efficacy variable analyses (see Section 5.5.1 and Section 5.5.2).

The analysis of categorical variables will be done using the same methodology used for the analysis of the primary efficacy variable described in Section 5.5.1. Analyses of continuous variables (eg, central retinal thickness, median deviation on visual field) will use a 2-way ANCOVA main effects models with treatment group and baseline DRSS (level 47 vs. level 53) stratification as fixed factors and respective baseline value for the efficacy measure in question as a covariate. The pairwise comparisons of each aflibercept treatment group versus sham will be done in these models by corresponding CONTRAST statements and a point-estimate. A 2-sided 95% confidence interval for the treatment difference of each aflibercept treatment group minus sham will be calculated. The analysis of time to event variables will be done using the same method as that described for the time to first vision-threatening complication in Section 5.5.2.

5.5.4. Subgroup Analyses

Subgroup analyses will be performed on the FAS population using descriptive statistics for primary and secondary efficacy variables with LOCF, OC, aLOCF, and aOC methods based on the subgroup variables defined in Section 4.5.

5.6. Analysis of Safety Data

The safety variables as described in Section 4.6 will be analyzed on SAF population through Week 24, Week 52 and Week 100 after final study database lock.

5.6.1. Adverse Events

AE summaries will be constructed displaying frequencies and proportions of patients reporting AEs within each SOC in decreasing order of total frequency according to the numbers of patients reporting the SOC and the AE within the SOC (not number of reports).

AEs will be classified as Pre-treatment AEs and TEAEs, and will further be summarized by the following categories:

- Ocular AEs in the study eye
- Ocular AEs in the fellow eye
- Non-ocular AEs

Serious Adverse Events (SAEs), drug-related AEs, drug-related SAEs, and TEAEs leading to discontinuation will be summarized in the same way as described for TEAE.

TEAEs in the study eye related to the injection procedure and those related to the study medication will be summarized separately.

An overall summary of the AE profile for aflibercept in this study will be provided. A listing will be constructed that includes the patient identification, the treatment group, category of AE (ocular study eye or fellow eye, non-ocular), AE, MedDRA term, seriousness, severity, causality, elapsed time to onset, duration, and outcome.

Adjudicated APTC events, intraocular inflammation, and hypertension will be tabulated and listed.

Subgroup analyses in TEAE reporting will be performed for the subgroups described in Section 3.3, for each of the following types of TEAE:

Summaries (by SOC and PT) of patients with:

- Ocular TEAEs study eye
- Non-ocular TEAEs
- Serious ocular TEAEs study eye
- Serious non-ocular TEAEs

5.6.2. Surgeries

An overall summary of number of patients undergoing surgery as described in Section 4.6.2 through the end of Week 24, Week 52 and Week 100 will be given by treatment group.

5.6.3. Clinical Laboratory

Baseline clinical laboratory values and change from Baseline to each scheduled assessment visit in clinical laboratory variables described in Section 4.6.3 will be summarized using descriptive statistics.

Predefined lab abnormalities will be identified for selected clinical laboratory values according to the specified ranges (see Appendix 10.5). The frequency and percentage of subjects with at

least one predefined lab abnormalities during treatment period will be displayed by treatment group for each analytic. Shift tables will also be provided.

Lab values out of normal range will be flagged in lab value listings.

5.6.4. Vital Signs

Baseline vital signs and change from Baseline for vital sign variables described in Section 4.6.4 at each scheduled assessment visit will be summarized using descriptive statistics. These will include the number of patients, mean, median, standard deviation, minimum, and maximum.

5.6.5. Electrocardiogram

All ECG variables as described in Section 4.6.5 will be analyzed by appropriate descriptive methods and change from baseline or frequency tables and/or cross-tabulation of baseline vs. post-baseline status for categorical variables (overall interpretation of ECG normal/abnormal and clinical relevant abnormalities no/yes) by visit and treatment arms.

5.6.6. Ocular Safety Measures

Baseline IOP and change from Baseline in IOP to each scheduled assessment visit will be summarized with descriptive statistics for study eye and fellow eye. Assessment of significant values or increases will be made and summarized for the proportion of patients with increased IOP in the study eye or fellow eye with the categories defined in Section 4.6.6.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline

Unless otherwise specified, the Baseline assessment for all measurements will be the last available valid measurement taken prior to the administration of investigational product.

6.2. Unscheduled Assessments

Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator.

Unscheduled and extra assessments (e.g., laboratory data or vital signs associated with non-protocol clinic visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries with the exception of the tabulation of incidence rates (e.g. of lab abnormalities or predefined IOP increases) using all documented values post baseline.

If more than one value is available for a given visit, the visit value actually used for statistical summaries and analyses will be as follows:

- The last non-missing repeated measurement, if respective visit is before start of treatment
- First non-missing repeated measurement, if respective visit is after start of treatment

Early termination visit (ET): If a subject prematurely discontinues they are asked to come for an early termination visit. Visit based information of this visit will only be used in the tabulation and in the statistical analyses if the visit was performed 4 weeks (+/- 1 week) after the last scheduled visit. ET visits outside this window will not be used for analyses and handled in the same way as unscheduled assessments (see above) and the data will only be shown in the patient listings.

6.3. Subset of Week 24 and Week 52 Analysis Windows

All relevant Week 24 and Week 52 data will be kept in a separate database for the Week 24 and Week 52 analyses, respectively. In the Appendix 10.6, a detailed process to derive the Week 24 and Week 52 cut-off data from the global study is provided.

6.4. Handling of Patients who Discontinue

Patients who discontinue this study will not be replaced. The details for the handling of missing data due to patients who discontinue the study and study medication are described in Section 6.5.1.

6.5. Handling of Missing Data

6.5.1. General Rules

When appropriate, the following rules will be implemented so as not to exclude patients from statistical analyses due to missing or incomplete data:

- Efficacy Variables

For the primary, secondary and additional efficacy variables, missing observations will be imputed using LOCF. The details are described in the efficacy analysis section (see Section 5.5).

- AE variables

For some AEs it is important to determine whether the AE started before or after the first active aflibercept injection. If the AE start date is partially missing, it will be imputed by the latest possible date (considering other available data, e.g., stop date) to be conservative.

- Prior/concomitant medication

For the tabulation of prior and concomitant medication, partially missing start dates of the medication will be imputed by the earliest possible time point, partially missing stop dates will be imputed by the latest possible time point.

7. INTERIM ANALYSIS

No formal interim analysis is planned.

8. SOFTWARE

All analyses will be done using SAS Version 9.2 or higher.

9. REFERENCES

ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

10. APPENDIX

10.1. Schedule of Time and Events:

Schedule of Events (Year 1)

[redacted]

FA & FP
Visual field testing (study eye)[8]
Non-Ocular Assessments
Physical examination
Vital signs [11]
ECG
Adverse events [12]

[redacted]

11. Vital signs (body temper
12. Adverse events will be
withdraws from the study
13. All samples collected for
14. At visits at which FA is
be tested at visit 1 (scree
15. Sampling only for HbA1

[redacted]

Schedule of Events (Year 2)

childbearing potential[13]	
Anti-aflibercept antibody samples[14]	

1. Patients who are withdr
2. Patients will receive eitl
3. Gonioscopy in the study

be tested at visit 18 (weel
13. All women of childbeari
required before treatment
14. All ADA samples must b

[redacted]

10.2. Summary of Statistical Efficacy Analyses

Endpoint	Week 24	Week 52	Week 100	Major Analysis, population	Statistical Analysis	Subgroup Analysis	Sensitivity Analysis
Proportion of patients who have improved by ≥2 steps from baseline in the DRSS score at week 24 in the combined group, and at week 52 for the 2Q8 and 2Q16 groups individually	X	X	X*	LOCF, FAS	Superiority of VEGF aflibercept over Sham using CMH test adjusted by stratifying factor DRSS level	LOCF, OC, aLOCF, aOC in FAS	Multiple imputation, OC, aLOCF, aOC
Proportion of patients developing a vision-threatening complication through week 52		X	X*	LOCF, FAS	Superiority of aflibercept over Sham using CMH test adjusted by stratifying factor DRSS level	LOCF, OC, aLOCF, aOC in FAS	OC, aLOCF, aOC,
Proportion of patients who develop CI-DME through week 52		X	X*	LOCF, FAS	Superiority of aflibercept over Sham using CMH test adjusted by stratifying factor DRSS level	LOCF, OC, aLOCF, aOC in FAS	OC, aLOCF, aOC,
Time to development of a vision-threatening complication through week 52		X	X*	LOCF, FAS	Kaplan-Meier method and logrank test of aflibercept over Sham		OC, aLOCF, aOC,
Time to development of CI-DME through week 52		X	X*	LOCF, FAS	Kaplan-Meier method and logrank test of aflibercept over Sham		OC, aLOCF, aOC,
Proportion of patients who receive PRP through week 52, inclusive of patients undergoing vitrectomy with endolaser		X	X*	LOCF, FAS	Superiority of aflibercept over Sham using CMH test adjusted by stratifying factor DRSS level	LOCF, OC, aLOCF, aOC in FAS	OC, aLOCF, aOC,
AUC for change in BCVA from baseline at week 52	X*	X	X*	LOCF, FAS	Test for superiority of aflibercept over Laser using ANCOVA	LOCF, OC, aLOCF, aOC in FAS	OC, aLOCF, aOC,

Endpoint	Week 24	Week 52	Week 100	Major Analysis, population	Statistical Analysis	Subgroup Analysis	Sensitivity Analysis
Time to first improvement of ≥2 steps from baseline in the DRSS score through week 52 and week 100		X*	X*	LOCF, FAS	Kaplan-Meier method		OC, aLOCF, aOC,
Proportion of patients with ≥2-step improvement from baseline in the DRSS score at week 100			X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,
Proportion of patients with ≥2-step worsening from baseline in the DRSS score at week 52 and at week 100		X*	X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,
Proportion of patients with ≥3-step worsening from baseline in the DRSS score at week 52 and at week 100		X*	X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,
Proportion of patients with ≥3-step improvement from baseline in the DRSS score at week 52 and at week 100		X*	X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,
Proportion of patients who receive vitrectomy through week 52 and through week 100		X*	X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,
Change in central retinal thickness from baseline at week 52 and at week 100		X*	X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,
Change in mean deviation on visual field testing from baseline at week 52 and at week 100		X*	X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,
Change in BCVA from baseline at week 24, week 52 and week 100	X*	X*	X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,

Endpoint	Week 24	Week 52	Week 100	Major Analysis, population	Statistical Analysis	Subgroup Analysis	Sensitivity Analysis
Proportion of patients who have gained ≥5, ≥10, or ≥15 letters from baseline at week 52 and at week 100		X*	X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,
Proportion of patients who have lost ≥5, ≥10, or ≥15 letters from baseline at week 24, week 52 and at week 100	X*	X*	X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,
The proportion of patients who are equal to or better than 20/20 or equal to or better than 20/40 at week 52 and at week 100		X*	X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,
Proportion of patients developing a vision-threatening complication or CI-DME through week 100			X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,
Time to development of vision-threatening complication or CI-DME through week 100			X*	LOCF, FAS	Descriptive statistics		OC, aLOCF, aOC,

*As additional endpoints (exploratory)

10.3. Detailed Definition of Selected Subgroups

In the following the definitions for subgroups based on medical history are given. All PTs given are based on MedDRA version 16.0 and might be updated with the latest version used in the studies.

10.3.1. Hypertension

HT defined by selected PT of MSSO SMQ 20000147: 'Hypertension' (these selected PT form the PBMQ)

MSSO SMQ	MSS SMQ CODE	Preferred term
Hypertension	20000147	Accelerated hypertension
Hypertension	20000147	Blood pressure ambulatory increased
Hypertension	20000147	Blood pressure diastolic increased
Hypertension	20000147	Blood pressure inadequately controlled
Hypertension	20000147	Blood pressure increased
Hypertension	20000147	Blood pressure systolic increased
Hypertension	20000147	Diastolic hypertension
Hypertension	20000147	Endocrine hypertension
Hypertension	20000147	Essential hypertension
Hypertension	20000147	Hypertension
Hypertension	20000147	Hypertension neonatal
Hypertension	20000147	Hypertensive angiopathy
Hypertension	20000147	Hypertensive cardiomegaly
Hypertension	20000147	Hypertensive cardiomyopathy
Hypertension	20000147	Hypertensive crisis
Hypertension	20000147	Hypertensive emergency
Hypertension	20000147	Hypertensive encephalopathy
Hypertension	20000147	Hypertensive heart disease
Hypertension	20000147	Hypertensive nephropathy
Hypertension	20000147	Labile hypertension
Hypertension	20000147	Malignant hypertension
Hypertension	20000147	Malignant hypertensive heart disease
Hypertension	20000147	Malignant renal hypertension
Hypertension	20000147	Maternal hypertension affecting foetus
Hypertension	20000147	Mean arterial pressure increased
Hypertension	20000147	Neurogenic hypertension
Hypertension	20000147	Orthostatic hypertension
Hypertension	20000147	Prehypertension
Hypertension	20000147	Renal hypertension
Hypertension	20000147	Renovascular hypertension
Hypertension	20000147	Retinopathy hypertensive
Hypertension	20000147	Systolic hypertension

10.3.2. Medical history of Cerebrovascular accident (CVA) / Stroke

SMQ Code	Preferred term
20000060	Agnosia
20000060	Amaurosis fugax
20000060	Amyloid related imaging abnormalities
20000060	Angiogram cerebral abnormal
20000060	Aphasia
20000060	Balint's syndrome
20000060	Basal ganglia haemorrhage
20000060	Basal ganglia infarction
20000060	Basal ganglia stroke
20000060	Basilar artery occlusion
20000060	Basilar artery stenosis
20000060	Basilar artery thrombosis
20000060	Blood brain barrier defect
20000060	Brachiocephalic artery occlusion
20000060	Brain hypoxia
20000060	Brain injury
20000060	Brain stem haematoma
20000060	Brain stem haemorrhage
20000060	Brain stem infarction
20000060	Brain stem ischaemia
20000060	Brain stem microhaemorrhage
20000060	Brain stem stroke
20000060	Brain stem thrombosis
20000060	Capsular warning syndrome
20000060	Carotid aneurysm rupture
20000060	Carotid angioplasty
20000060	Carotid arterial embolus
20000060	Carotid arteriosclerosis
20000060	Carotid artery aneurysm
20000060	Carotid artery bypass
20000060	Carotid artery disease
20000060	Carotid artery dissection
20000060	Carotid artery insufficiency
20000060	Carotid artery occlusion
20000060	Carotid artery restenosis

SMQ Code	Preferred term
20000060	Carotid artery stenosis
20000060	Carotid artery stent insertion
20000060	Carotid artery stent removal
20000060	Carotid artery thrombosis
20000060	Carotid endarterectomy
20000060	Carotid revascularisation
20000060	Central nervous system haemorrhage
20000060	Central pain syndrome
20000060	Cerebellar artery occlusion
20000060	Cerebellar artery thrombosis
20000060	Cerebellar embolism
20000060	Cerebellar haematoma
20000060	Cerebellar haemorrhage
20000060	Cerebellar infarction
20000060	Cerebellar ischaemia
20000060	Cerebellar microhaemorrhage
20000060	Cerebral amyloid angiopathy
20000060	Cerebral aneurysm ruptured syphilitic
20000060	Cerebral arteriosclerosis
20000060	Cerebral arteriovenous malformation haemorrhagic
20000060	Cerebral arteritis
20000060	Cerebral artery embolism
20000060	Cerebral artery occlusion
20000060	Cerebral artery stenosis
20000060	Cerebral artery thrombosis
20000060	Cerebral circulatory failure
20000060	Cerebral gas embolism
20000060	Cerebral haematoma
20000060	Cerebral haemorrhage
20000060	Cerebral haemorrhage foetal
20000060	Cerebral haemorrhage neonatal
20000060	Cerebral haemosiderin deposition
20000060	Cerebral hypoperfusion
20000060	Cerebral infarction
20000060	Cerebral infarction foetal
20000060	Cerebral ischaemia

SMQ Code	Preferred term
20000060	Cerebral microangiopathy
20000060	Cerebral microhaemorrhage
20000060	Cerebral revascularisation
20000060	Cerebral septic infarct
20000060	Cerebral small vessel ischaemic disease
20000060	Cerebral thrombosis
20000060	Cerebral vasoconstriction
20000060	Cerebral venous thrombosis
20000060	Cerebrovascular accident
20000060	Cerebrovascular accident prophylaxis
20000060	Cerebrovascular arteriovenous malformation
20000060	Cerebrovascular disorder
20000060	Cerebrovascular insufficiency
20000060	Cerebrovascular stenosis
20000060	Charcot-Bouchard microaneurysms
20000060	Congenital cerebrovascular anomaly
20000060	Congenital hemiparesis
20000060	CSF bilirubin positive
20000060	Diplegia
20000060	Dural fistula
20000060	Dysarthria
20000060	Embolic cerebral infarction
20000060	Embolic stroke
20000060	Extradural haematoma
20000060	Fahr's disease
20000060	Foetal cerebrovascular disorder
20000060	Haemorrhage intracranial
20000060	Haemorrhagic cerebral infarction
20000060	Haemorrhagic stroke
20000060	Haemorrhagic transformation stroke
20000060	Hemiparesis
20000060	Hemiplegia
20000060	Hypoxic-ischaemic encephalopathy
20000060	Inner ear infarction
20000060	Internal carotid artery kinking
20000060	Intra-cerebral aneurysm operation

SMQ Code	Preferred term
20000060	Intracerebral haematoma evacuation
20000060	Intracranial aneurysm
20000060	Intracranial haematoma
20000060	Intracranial venous sinus thrombosis
20000060	Intraventricular haemorrhage
20000060	Intraventricular haemorrhage neonatal
20000060	Ischaemic cerebral infarction
20000060	Ischaemic stroke
20000060	Lacunar infarction
20000060	Lateral medullary syndrome
20000060	Meningorrhagia
20000060	Millard-Gubler syndrome
20000060	Modified Rankin score decreased
20000060	Modified Rankin score increased
20000060	Monoparesis
20000060	Monoplegia
20000060	Moyamoya disease
20000060	NIH stroke scale abnormal
20000060	NIH stroke scale score decreased
20000060	NIH stroke scale score increased
20000060	Paralysis
20000060	Paralysis flaccid
20000060	Paraparesis
20000060	Paraplegia
20000060	Paresis
20000060	Post procedural stroke
20000060	Post stroke depression
20000060	Precerebral artery occlusion
20000060	Putamen haemorrhage
20000060	Quadriparesis
20000060	Quadriplegia
20000060	Red blood cells CSF positive
20000060	Reversible ischaemic neurological deficit
20000060	Ruptured cerebral aneurysm
20000060	Sneddon's syndrome
20000060	Spastic paralysis

SMQ Code	Preferred term
20000060	Spastic paraplegia
20000060	Spinal artery embolism
20000060	Spinal artery thrombosis
20000060	Spinal cord haemorrhage
20000060	Spinal epidural haemorrhage
20000060	Spinal haematoma
20000060	Spinal vascular disorder
20000060	Spinal vessel congenital anomaly
20000060	Stroke in evolution
20000060	Subarachnoid haemorrhage
20000060	Subarachnoid haemorrhage neonatal
20000060	Subclavian steal syndrome
20000060	Subdural haematoma
20000060	Subdural haematoma evacuation
20000060	Subdural haemorrhage
20000060	Subdural haemorrhage neonatal
20000060	Superficial siderosis of central nervous system
20000060	Superior sagittal sinus thrombosis
20000060	Susac's syndrome
20000060	Thalamic infarction
20000060	Thalamus haemorrhage
20000060	Thrombotic cerebral infarction
20000060	Thrombotic stroke
20000060	Transient ischaemic attack
20000060	Transverse sinus thrombosis
20000060	Vascular encephalopathy
20000060	Vasculitis cerebral
20000060	Vertebral artery dissection
20000060	Vertebral artery occlusion
20000060	Vertebral artery stenosis
20000060	Vertebral artery thrombosis
20000060	Vertebrobasilar dolichoectasia
20000060	Vertebrobasilar insufficiency
20000060	Visual midline shift syndrome
20000060	Wallenberg syndrome

10.3.3. Medical history of ischemic heart disease /Myocardial Infarction: defined by MSSO SMO 20000047

PBMQ 'Myocardial Infarction' is defined by selected PTs only (from MSSO SMQs below):

20000043: Ischaemic heart disease (MSSO SMQ)

20000047: Myocardial infarction (MSSO SMQ)

Ischaemic heart disease (SMQ)	20000043	Acute coronary syndrome
Ischaemic heart disease (SMQ)	20000043	Acute myocardial infarction
Ischaemic heart disease (SMQ)	20000043	Angina pectoris
Ischaemic heart disease (SMQ)	20000043	Angina unstable
Ischaemic heart disease (SMQ)	20000043	Arteriogram coronary abnormal
Ischaemic heart disease (SMQ)	20000043	Arteriosclerosis coronary artery
Ischaemic heart disease (SMQ)	20000043	Arteriospasm coronary
Ischaemic heart disease (SMQ)	20000043	Blood creatine phosphokinase MB abnormal
Ischaemic heart disease (SMQ)	20000043	Blood creatine phosphokinase MB increased
Ischaemic heart disease (SMQ)	20000043	Blood creatine phosphokinase abnormal
Ischaemic heart disease (SMQ)	20000043	Blood creatine phosphokinase increased
Ischaemic heart disease (SMQ)	20000043	Cardiac enzymes increased
Ischaemic heart disease (SMQ)	20000043	Cardiac stress test abnormal
Ischaemic heart disease (SMQ)	20000043	Computerised tomogram coronary artery abnormal
Ischaemic heart disease (SMQ)	20000043	Coronary angioplasty
Ischaemic heart disease (SMQ)	20000043	Coronary arterial stent insertion
Ischaemic heart disease (SMQ)	20000043	Coronary artery bypass
Ischaemic heart disease (SMQ)	20000043	Coronary artery disease
Ischaemic heart disease (SMQ)	20000043	Coronary artery dissection
Ischaemic heart disease (SMQ)	20000043	Coronary artery embolism
Ischaemic heart disease (SMQ)	20000043	Coronary artery insufficiency
Ischaemic heart disease (SMQ)	20000043	Coronary artery occlusion
Ischaemic heart disease (SMQ)	20000043	Coronary artery reocclusion
Ischaemic heart disease (SMQ)	20000043	Coronary artery restenosis
Ischaemic heart disease (SMQ)	20000043	Coronary artery stenosis
Ischaemic heart disease (SMQ)	20000043	Coronary artery thrombosis
Ischaemic heart disease (SMQ)	20000043	Coronary bypass thrombosis
Ischaemic heart disease (SMQ)	20000043	Coronary endarterectomy
Ischaemic heart disease (SMQ)	20000043	Coronary no-reflow phenomenon
Ischaemic heart disease (SMQ)	20000043	Coronary ostial stenosis

Ischaemic heart disease (SMQ)	20000043	Coronary revascularisation
Ischaemic heart disease (SMQ)	20000043	Dissecting coronary artery aneurysm
Ischaemic heart disease (SMQ)	20000043	ECG electrically inactive area
Ischaemic heart disease (SMQ)	20000043	ECG signs of myocardial ischaemia
Ischaemic heart disease (SMQ)	20000043	Electrocardiogram Q wave abnormal
Ischaemic heart disease (SMQ)	20000043	Electrocardiogram ST segment abnormal
Ischaemic heart disease (SMQ)	20000043	Electrocardiogram ST segment depression
Ischaemic heart disease (SMQ)	20000043	Electrocardiogram ST segment elevation
Ischaemic heart disease (SMQ)	20000043	Electrocardiogram ST-T segment abnormal
Ischaemic heart disease (SMQ)	20000043	Electrocardiogram ST-T segment depression
Ischaemic heart disease (SMQ)	20000043	Electrocardiogram ST-T segment elevation
Ischaemic heart disease (SMQ)	20000043	Electrocardiogram T wave abnormal
Ischaemic heart disease (SMQ)	20000043	Electrocardiogram T wave inversion
Ischaemic heart disease (SMQ)	20000043	Exercise electrocardiogram abnormal
Ischaemic heart disease (SMQ)	20000043	Exercise test abnormal
Ischaemic heart disease (SMQ)	20000043	External counterpulsation
Ischaemic heart disease (SMQ)	20000043	Haemorrhage coronary artery
Ischaemic heart disease (SMQ)	20000043	Infarction
Ischaemic heart disease (SMQ)	20000043	Ischaemic cardiomyopathy
Ischaemic heart disease (SMQ)	20000043	Kounis syndrome
Ischaemic heart disease (SMQ)	20000043	Microvascular coronary artery disease
Ischaemic heart disease (SMQ)	20000043	Myocardial infarction
Ischaemic heart disease (SMQ)	20000043	Myocardial ischaemia
Ischaemic heart disease (SMQ)	20000043	Myocardial reperfusion injury
Ischaemic heart disease (SMQ)	20000043	Myocardial stunning
Ischaemic heart disease (SMQ)	20000043	Papillary muscle infarction
Ischaemic heart disease (SMQ)	20000043	Percutaneous coronary intervention
Ischaemic heart disease (SMQ)	20000043	Post procedural myocardial infarction
Ischaemic heart disease (SMQ)	20000043	Postinfarction angina
Ischaemic heart disease (SMQ)	20000043	Prinzmetal angina
Ischaemic heart disease (SMQ)	20000043	Scan myocardial perfusion abnormal
Ischaemic heart disease (SMQ)	20000043	Silent myocardial infarction
Ischaemic heart disease (SMQ)	20000043	Stress cardiomyopathy
Ischaemic heart disease (SMQ)	20000043	Stress echocardiogram abnormal
Ischaemic heart disease (SMQ)	20000043	Subclavian coronary steal syndrome

Ischaemic heart disease (SMQ)	20000043	Subendocardial ischaemia
Ischaemic heart disease (SMQ)	20000043	Troponin I increased
Ischaemic heart disease (SMQ)	20000043	Troponin T increased
Ischaemic heart disease (SMQ)	20000043	Troponin increased
Ischaemic heart disease (SMQ)	20000043	Vascular graft occlusion
Medical history of myocardial infarction (aflibercept)	SMQ_1278	Acute coronary syndrome
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Acute myocardial infarction
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Angina pectoris
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Angina unstable
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Arteriogram coronary abnormal
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Arteriosclerosis coronary artery
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Arteriospasm coronary
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Computerised tomogram coronary artery abnormal
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary angioplasty
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary arterial stent insertion
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary artery bypass
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary artery disease
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary artery dissection
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary artery embolism
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary artery insufficiency
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary artery occlusion
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary artery reocclusion

Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary artery restenosis
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary artery stenosis
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary artery thrombosis
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary bypass thrombosis
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary endarterectomy
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary no-reflow phenomenon
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary ostial stenosis
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Coronary revascularisation
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Dissecting coronary artery aneurysm
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	ECG electrically inactive area
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	ECG signs of myocardial ischaemia
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Electrocardiogram ST segment abnormal
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Electrocardiogram ST segment depression
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Electrocardiogram ST segment elevation
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Electrocardiogram ST-T segment abnormal
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Electrocardiogram ST-T segment depression
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Electrocardiogram ST-T segment elevation
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	External counterpulsation
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Haemorrhage coronary artery
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Infarction

Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Ischaemic cardiomyopathy
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Ischaemic contracture of the left ventricle
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Kounis syndrome
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Myocardial infarction
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Myocardial ischaemia
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Myocardial reperfusion injury
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Myocardial stunning
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Papillary muscle infarction
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Percutaneous coronary intervention
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Post procedural myocardial infarction
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Postinfarction angina
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Prinzmetal angina
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Scan myocardial perfusion abnormal
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Silent myocardial infarction
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Stress cardiomyopathy
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Subclavian coronary steal syndrome
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Subendocardial ischaemia
Medical history of myocardial infarction (VEGF Trap-Eye)	SMQ_1278	Vascular graft occlusion

10.3.4. Renal Impairment

Renal impairment is defined by CRCL values.

Categories for renal impairment:

- CLCR >80ml/min (normal),
- CLCR >50-80ml/min (mild),
- CLCR >30-50 ml/min (moderate),
- CLCR <=30ml/min or 'requiring dialysis' (severe)

CLCR will be calculated using baseline values (creatinine, age, weight, sex) using the Cockcroft-Gault equation:

Males: CLCR = (140-age)*body weight / (72*creatinine)

Females: CLCR = (140-age)*body weight*0.85 / (72*creatinine)

'Requiring dialysis' is defined by PT from

MSSO SMQ	MSSO SMQ Code	Preferred term
renal impairment requiring dialysis	10061102	Dependence on enabling machine or device
renal impairment requiring dialysis	10061105	Dialysis
renal impairment requiring dialysis	10018875	Haemodialysis
renal impairment requiring dialysis	10034660	Peritoneal dialysis

10.4. Calculation of confidence intervals using Mantel-Haenszel weighting scheme

The confidence intervals using the Mantel-Haenszel weighting scheme will be calculated according to the formulas given by Koch et al. (1990, p. 415 ff.)[2], i.e. to compute confidence intervals for the difference in two binomial proportions obtained from a multicenter trial, we calculate a weighted difference and its associated variance using Mantel-Haenszel weighting scheme.

For a multicenter study with h 2x2 tables, the weighted difference is:

$$d = \left(\sum w_h(p_{he} - p_{hs})\right)/\left(\sum w_h\right)$$

where $w_h = n_{he}n_{hs}/(n_{he}+n_{hs})$

and p_{he} = success rate for experimental treatment in stratum h

p_{hs} = success rate for standard treatment in stratum h

n_{he} = number of patients under experimental treatment in stratum h

n_{hs} = number of patients under standard treatment in stratum h

The variance of the weighted difference is:

$$var(d) = \left(\sum w_h^2(p_{hs}(1-p_{hs})/(n_{hs}-1) + p_{he}(1-p_{he})/(n_{he}-1))\right)/\left(\sum w_h\right)^2$$

A large sample approximation is used to compute the confidence interval:

$$CI = d \pm z_{\alpha/2}\, SQRT(var(d))$$

Where z_α is the α quantile of the standard normal distribution and SQRT is the square root function.

10.5. Criteria for Predefined Lab Abnormalities

Parameter	PCSVs for phase 2/3 studies
Clinical chemistry	
ALT	By distribution analysis: > 3 ULN
AST	By distribution analysis: > 3 ULN
Alkaline Phosphatase	> 1.5 ULN
Total Bilirubin	> 1.5 ULN
Conjugated bilirubin	> 35% total bilirubin (when total bilirubin >1.5 ULN)
ALT and Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN
CPK	> 3 ULN
Creatinine	≥ 150 µmol/L (Adults) ≥ 30% from baseline
Uric Acid	Hyperuricemia: >408 µmol/L Hypouricemia: <120 µmol/L
Blood Urea Nitrogen	≥ 17 mmol/L
Chloride	< 80 mmol/L > 115 mmol/L
Sodium	≤ 129 mmol/L ≥ 160 mmol/L
Potassium	< 3 mmol/L ≥ 5.5 mmol/L
Total Cholesterol	≥ 7.74 mmol/L (3 g/L)
Triglycerides	≥ 4.6 mmol/L (4 g/L)
Lipasemia	≥ 3 ULN
Amylasemia	≥ 3 ULN
Glucose - Hypoglycaemia - Hyperglycaemia	 ≤ 3.9 mmol/L and < LLN ≥ 11.1 mmol/L (unfasted), ≥ 7 mmol/L (fasted)

Parameter	**PCSVs for phase 2/3 studies**
HbA1c	> 8 %
Albumin	≤ 25 g/L
CRP	> 2 ULN or > 10 mg/L (if ULN not provided)
Hematology	
WBC	< 3.0 GIGA/L (non-Black), < 2.0 GIGA/L (Black), ≥ 16.0 GIGA/L
Lymphocytes	> 4.0 GIGA/L
Neutrophils	< 1.5 GIGA/L (non-Black) < 1.0 GIGA/L (Black)
Monocytes	> 0.7 GIGA/L
Basophils	> 0.1 GIGA/L
Eosinophils	> 0.5 GIGA/L or > ULN if ULN ≥ 0.5 GIGA /L
Hemoglobin	Males : 115 g/L (≤ 7.14 mmol/L), ≥ 185 g/L (11.48 mmol/L) Females : ≤ 95 g/L (5.9 mmol/L), ≥ 165 g/L (10.24 mmol/L) Decrease from Baseline ≥ 20 g/L (1.24 mmol/L)
Hematocrit	Males : ≤ 0.37 v/v, ≥ 0.55 v/v Females : ≤ 0.32 v/v, ≥ 0.5 v/v
RBC	≥ 6 TERA/L
Platelets	< 100 GIGA/L ≥ 700 GIGA/L

10.6. Process to Derive Week 24 (Week 52) Data Cut-off

For Week 24 (Week 52) evaluations, a strategy for performing the data cut-off for the clinical database was developed, as described in the following:

10.6.1. Visit Dependent Data

All visit dependent data up to Week 24 (Week 52) [Visit 7 (Visit 11)] will be kept for the Week 24 (Week 52) analysis. All visit dependent data later than Week 24 (Week 52) [Visit 7 (Visit 11)] will not be included for the Week 24 (Week 52) analysis. Unscheduled visits with a date up to Week 24 (Week 52) [Visit 7 (Visit 11)] visit date will be kept for the Week 24 (Week 52) analysis data. If patients did not have Week 24 (Week 52) [Visit 7 (Visit 11)] visit date, unscheduled visit will be kept up to date of first injection + 168 days for the Week 24 (Week 52) analysis.

10.6.2. Visit Independent Data

Visit independent data (or event based data) include adverse events, concomitant/prior medication, and surgical/medical history.

Patients that discontinued study prematurely before or at Week 24 (Week 52) [Visit 7 (Visit 11)]

These patients are defined as having their end of study CRF page filled, and have either:

- a dropout date earlier or equal to date of first injection + 168 (364) days or
- a dropout date earlier or equal to Week 24 (Week 52) visit date

For such patients, all event based records are kept in the clinical database for Week 24 (Week 52) analysis without any change.

Patients who stayed longer than Week 24 (Week 52) [Visit 7 (Visit 11)] in the study

These patients are the patients who did not discontinue study prematurely at/before Week 24 (Week 52) [Visit 7 (Visit 11)]. Therefore, these patients are either:

- still ongoing after Week 24 (Week 52) [Visit 7 (Visit 11)],
- discontinued the study prematurely, but were in the study for longer than Week 24 (Week 52) [Visit 7 (Visit 11)].

For such patients, the following will be applied:

All event records with a start date later than the date of the Week 24 (Week 52) [Visit 7 (Visit 11)] will be censored. This includes the case that the incomplete date is without any doubt later than the Week 24 (Week 52) visit date, e.g. Week 24 (Week 52) [Visit 7 (Visit 11)] is 10 April 2010 and the incomplete date is May 2010 or only 2011. If Week 24 (Week 52) visit date is missing, then date of first injection + 168 (364) days will be used instead below.

Records with a start date earlier or equal to the date of Week 24 (Week 52) (first injection + 168 (364) days if date of Week 24 (Week 52) is missing) will be kept (this includes incomplete dates when the incomplete date is earlier than the week 24 (week 52) date or in case of doubts,

e.g., Week 24 (visit 9) is 10 April 2010 and the incomplete date is March 2010, April 2010 or only 2010 or even a missing date, but several adaptions to the data will be made):

- Concomitant medication:

If a stop date is reported which is earlier than the date of Week 24 (Week 52) [Visit 7 (Visit 11)] (first injection + 168 (364) days if date of Week 24 (Week 52) is missing), the record will not be changed.

If a stop date is reported which is later than the date of Week 24 (Week 52) [Visit 7 (Visit 11)] (first injection + 168 (364) days if date of Week 24 (Week 52) is missing), the stop date will be set to missing and the variable CMONG will be set to 1 (yes).

- Adverse Events:

AEs with a start date on or after the date of the Week 24 (Week 52) [Visit 7 (Visit 11)] will be censored. Cut-off date will be first injection + 168 (364) days if date of Week 24 (Week 52) is missing.

If a stop date of adverse event is specified and earlier or equal to date of Week 24 (Week 52) [Visit 7 (Visit 11)] (first injection + 168 (364) days if date of Week 24 (Week 52) missing), then the record will not be changed.

If a stop date of adverse event is specified and later than the date of Week 24 (Week 52) [Visit 7 (Visit 11)] (first injection + 168 (364) days if date of Week 24 (Week 52) is missing), then the stop date will be deleted (set to missing) and the outcome of the adverse event (SAS variable AEOUT) will be set to missing.

If no stop date is specified and the outcome is either not yet reported (AEOUT is blank) or is reported (AEOUT" is 2-recovering/resolving, 4-not recovered/not resolved, 992-unknown), then the outcome will be set to missing (AEOUT is blank).

- Surgeries:

All surgeries with a date of surgery later than Week 24 (Week 52) [Visit 7 (Visit 11)] date will be deleted.

10.6.3. Study Medication Data

Study medication data (including real/sham injection) up to Week 16 (Week 48) [Visit 6 (Visit 10)] will be kept for the Week 24 (Week 52) analysis.

10.7. SAS Procedure for Multiple Imputation

Step 1. Imputation: Impute missing value using MCMC method and subsequently impute missing data by a regression model.

```
PROC MI DATA = <indata> SEED = 12345 OUT=mi01 NIMPUTE = 100;   *SEED = 12345;
   MCMC IMPUTE =MONOTONE;
   VAR v1 v2 v3 v4 v5 … ;
RUN;

PROC MI DATA=mi01 SEED=54321 OUT= mi02 NIMPUTE=1;
   CLASS <treatment> <factor>;
   MONOTONE REG ;
   VAR <treatment> <factor> v1 v2 v3 v4 v5 … ;
   BY _IMPUTATION_ ;
RUN;
```

Step 2. Analysis: After merge imputed data with the original data, define respond as ≥2 steps decrease from baseline in the DRSS score. Use PROC FREQ CMH to analyze data by _imputation_.

```
ODS OUTPUT CMH=cmh;
PROC FREQ DATA=<combined data>;
    BY _IMPUTATION_;
    TABLES <factor>*<treatment>*<respond>/CMH;
RUN;
```

Step 3. Polling

Apply Wilson-Hilferty transformation to the CMH statistic and standardize the resulting normal variable. Then combine results and Compute one-sided p-value.

```
DATA cmh_wh;
   SET cmh(WHERE=(AltHypothesis="General Association"));
   cmh_value_wh=((VALUE/DF)**(1/3) - (1-2/(9*DF)))/SQRT(2/(9*DF));
   cmh_sterr_wh = 1.0;
RUN;

ODS OUTPUT PARAMETERESTIMATES=mian_cmh_wh;
PROC MIANALYZE DATA=cmh_wh;
   MODELEFFECTS cmh_value_wh;
   STDERR cmh_sterr_wh;
RUN;

DATA pval (keep = PROBT_UPPER) ;
   SET mian_cmh_wh;
   IF tValue > 0 THEN Probt_upper = Probt/2;
   ELSE Probt_upper = 1-Probt/2;
RUN;
```

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