Statistical Analysis Plan for Study M20-370

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Polymyalgia Rheumatica (PMR) Dependent on Glucocorticoid Treatment

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Version 2.0

Table of Contents

List of Tables

List of Figures

List of Appendices

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for ABBV-154 Study M20-370, "A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Polymyalgia Rheumatica (PMR) Dependent on Glucocorticoid Treatment."

Study M20-370 examines the efficacy and safety of ABBV-154 in Subjects with PMR dependent on glucocorticoid treatment.

The analyses of pharmacokinetic endpoints and pharmacodynamic biomarker endpoints will not be covered in this SAP.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the statistical analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

The primary objective is to assess the safety and efficacy of ABBV-154 versus placebo in subjects with PMR, who are dependent on treatment with glucocorticoids with doses of at least 5 mg/day prednisone equivalent (glucocorticoid-dependent PMR).

- Primary Efficacy Objective: The primary efficacy objective of the study is to demonstrate that ABBV-154 treatment results in a longer disease-free time when compared with placebo treatment in the Intent-to-Treat (ITT) population, which consists of all randomized subjects with at least one dose of study drug.

The hypothesis corresponding to the primary efficacy objective is that the time to flare with ABBV-154 treatment is longer than that with placebo treatment. The estimand for

the primary endpoint is defined as the median time to flare in the study for each ABBV-154 group versus the placebo group in the ITT population. Subjects will be censored at the time of the last available assessment, initiation of immunomodulator, or violation of protocol-allowed systemic glucocorticoid use.

- Secondary Efficacy Objectives: The secondary efficacy objectives of the study are to demonstrate greater efficacy with ABBV-154 treatment when compared with placebo treatment with respect to the secondary endpoints specified in Section 3.3, in the ITT population.

The estimands corresponding to the secondary efficacy objectives are:

- For each binary secondary endpoint: The difference in percentage of subjects achieving a response for each ABBV-154 group versus the placebo group in the ITT population.
- For each continuous endpoint: The mean difference between each ABBV-154 group versus the placebo group in the ITT population.

2.2 Study Design Overview

Study M20-370 is a randomized, double-blind, placebo-controlled, multicenter, 52-week Phase 2 study to assess the safety, tolerability, efficacy, PK, PD, and immunogenicity following multiple subcutaneous (SC) injections of ABBV-154 or placebo in 160 subjects with glucocorticoid-dependent PMR, as defined in Section 5.0.

The Primary Analysis will be performed after all subjects have either completed the Week 24 visit or withdrawn from the study. Interim analyses may be performed to reassess the treatment regimens in this study and to inform development of future studies.

A final analysis will be conducted after all subjects have either withdrawn from the study or completed Week 52 and the safety Follow-up Visit. To maintain integrity of the trial, the study sites and subjects will remain blinded until the final analysis is completed. Selected AbbVie personnel may be unblinded to treatment assignment to conduct interim

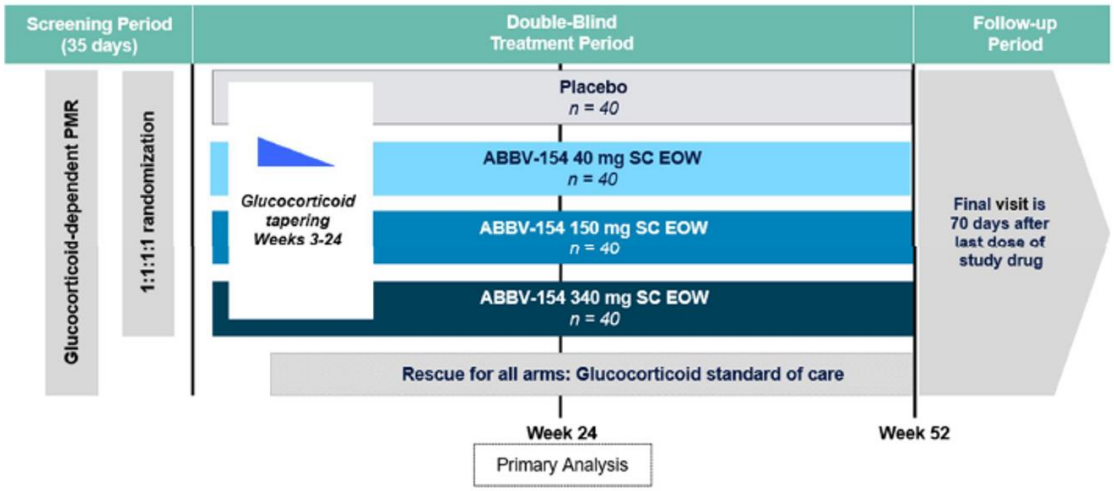
analyses or after an interim analysis to support regulatory interaction; details will be included in the interim unblinding plan (IUP).

Subjects in select countries and sites where the digital health technology device is deployed and available will also participate in a Wearable Device Substudy. Subjects participating in this substudy will wear a watch-like digital device on the wrist that will collect data reflecting the subject's UL-ROM and daily activity and sleep parameters. Enrollment will be capped at 96 subjects.

There will be optional serial photography for subjects who consent and at sites where photography is available.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



EOW = every other week; PMR = polymyalgia rheumatica; SC = subcutaneous

2.3 Treatment Assignment and Blinding

The Screening Period may be up to 35 days. At the Baseline Visit, subjects will be randomized to one of 4 treatment arms in a 1:1:1:1 ratio, as follows: placebo

administered SC in combination with a glucocorticoid taper or ABBV-154 administered as 40 mg every other week (EOW), 150 mg EOW, or 340 mg EOW in combination with a glucocorticoid taper. The glucocorticoid taper is identical for placebo and active treatment groups. Starting at Baseline, each subject will switch from oral glucocorticoids obtained from independent sources to oral prednisone/prednisolone provided by the Sponsor at the equivalent dose that the subject was taking just prior to the Baseline Visit, rounded up to the nearest 1 mg to a maximum of 15 mg. Beginning at Week 3, subjects will taper prednisone/prednisolone per the protocol-defined glucocorticoid taper schedule to 0 mg by Week 24 and remain off prednisone/prednisolone until the end of the Treatment Period, Week 52, unless a PMR flare is confirmed. A safety follow-up visit will be performed approximately 70 days after the last administration of ABBV-154/placebo.

If a subject has a suspected PMR flare at any time during the study, the flare should be confirmed according to the protocol-defined flare definition as soon as possible, prior to initiating glucocorticoid rescue treatment. Flare may be confirmed at either a scheduled visit or unscheduled visit. PMR must be confirmed as the cause of flare by eliminating other causes of the subject's symptoms/signs such as infection or other underlying disease. Once flare is confirmed at the visit, glucocorticoid rescue can be administered with the dose and subsequent tapering at the discretion of the investigator, taking into consideration local standard of care, the subject's preflare and/or baseline dose, and not exceeding 15 mg/day.

Addition of immunomodulators other than glucocorticoid rescue, as outlined above, are not permitted for rescue. If the investigator determines it is in the best interest of the subject to start an immunomodulator, the subject must discontinue study drug (ABBV-154/placebo and Sponsor-supplied prednisone/prednisolone; glucocorticoid will then be prescribed by the investigator as necessary, with dosing based on the investigator's judgement and in accordance with local standard of care).

2.4 Sample Size Determination

A total of 37 flares in the highest dose of ABBV-154 group and placebo group would provide more than 90% power to detect a hazard ratio of 0.296 at 2-sided significance level of 0.1. The hazard ratio of 0.296 is determined under the assumption that flares would occur during the tapering and within 12 weeks after the end of tapering (up to Week 36), and 70% and 30% of subjects will remain flare-free by Week 36 in the highest dose of ABBV-154 group and placebo group, respectively.

Based on an E_{max} model with ED_{50} of 150 mg, a total of 74 flares are expected for the Primary Analysis. A sample size of 40 subjects in each of the ABBV-154 and placebo arms is planned to ensure appropriate accrual of flares. A sample size re-estimation may be considered at an interim analysis prior to unblinding of the study team. The sample size increase will be capped at approximately 100 subjects.

3.0 Endpoints

3.1 Primary Endpoint(s)

The primary endpoint is the time to flare, where flare is defined as follows:

- Presence of clinical signs and symptoms of PMR

AND

- Requirement to increase the glucocorticoid dose per investigator.

Clinical signs and symptoms of PMR are defined as shoulder and/or hip girdle pain with inflammatory stiffness, neck pain with inflammatory stiffness, or new or worsened limited range of motion of hips and/or shoulders, as outlined in protocol.

3.2 Secondary Endpoint(s)

- Achievement of flare-free state up to Week 24
- Cumulative glucocorticoid dose by 24 weeks
- Change from Baseline in glucocorticoid dose at Week 24

3.3 Other Efficacy Endpoint(s)

The primary and/or secondary efficacy endpoints are listed in Section 3.1 and/or Section 3.2, respectively. All secondary endpoints will be analyzed at all visits other than those listed. In addition, the following endpoints will be analyzed at all visits assessed when applicable:

- Time to disease flare defined as Polymyalgia Rheumatica Activity Score (PMR-AS) increased from Baseline by ≥ 6.6.
  - PMR-AS = high-sensitivity CRP (hsCRP) (mg/dL) + Patient Assessment of Pain Severity (numeric rating scale [NRS], 0 – 10) + Physician Global Assessment of Disease Activity (NRS, 0 – 10) + (morning stiffness duration [MST] in minutes × 0.1) + elevation of upper limbs (EUL) (scale of 3 – 0)
- Time to disease flare defined as PMR-AS ≥ 9.35
- Achievement of PMR-AS < 1.5
- Achievement of PMR-AS < 7
- Achievement of ESR ≤ 30 mm/h at Week 24
- Achievement of hsCRP ≤ upper limit of normal (ULN) at Week 24
- Change from Baseline in hsCRP
- Change from Baseline in PMR-AS
- Change from Baseline in MST
- Change from Baseline in EUL
- Change from Baseline in Physician Global Assessment of Disease Activity NRS
- Change from Baseline in Patient Assessment of Pain Severity NRS
- Change from Baseline in Patient Assessment of Stiffness Severity NRS
- Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
- Change from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

- Change from Baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Item Bank v 1.0 – Sleep Disturbance
- Change from Baseline in Patient Assessment of Bruising Severity NRS
- Change from Baseline in EuroQol 5-dimension questionnaire, 5-level (EQ-5D-5L)
- Change from Baseline in Physician Assessment of Bruising Severity NRS
- For subjects participating in the Wearable Device Substudy:
    - Change from Baseline in the following sleep parameters: total sleep time, wake after sleep onset, sleep efficiency, and sleep onset latency
    - Change from Baseline in upper limbs range of motion (UL-ROM)

3.4 Safety Endpoint(s)

Safety measures monitored in the study include the following:

- Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation of study drug;
- Occurrence of potentially glucocorticoid-related AEs; and
- Potentially clinically significant laboratory, vital signs, and electrocardiogram (ECG) variables.

3.5 Additional Endpoint(s)

Pharmacokinetic, immunogenicity, and biomarker research endpoints will be analyzed separately, and the corresponding analysis plan is not covered in this SAP.

4.0 Analysis Populations

The following population will be used for the efficacy analysis except for Wearable Device Substudy-related endpoints:

- Intent-to-Treat (ITT) Population: The ITT Population includes all subjects who were randomized and received at least 1 dose of study drug. The ITT

Population will be analyzed as randomized (i.e., according to the randomized treatment assignment).

The following population will be used for the safety analysis:

- Safety Population: The Safety Population includes all subjects who were randomized and received at least 1 dose of study drug. The Safety Population will be analyzed as treated (i.e., according to the actual treatment received).

The Per-Protocol Population will include ITT subjects with the exception of those who have major protocol deviations that are determined to have a potential impact on the primary efficacy endpoint up to Week 24. The final criteria and the exclusion of subjects for the per-protocol population will be finalized before unblinding data for the Primary Analysis.

5.0 Subject Disposition

The total number of subjects who were screened, enrolled (randomized), and treated will be summarized. Reasons for exclusion, including screen failure, will be summarized.

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for each treatment group:

- Subjects enrolled (randomized) in the study;
- Subjects who took at least one dose of study drug;
- Subjects who completed protocol-specified treatment;
- Subjects who prematurely discontinued study drug (all reasons and primary reason);
- Subjects in each analysis population, as applicable.

For end of study participation, the number and percentage of subjects who completed the protocol defined follow-up period (or did not with associated reasons) will be summarized overall and by treatment group.

6.0 Study Drug Duration and Compliance

For the Safety population, duration of treatment will be summarized for each treatment group and for all investigational study drug dose groups combined. Duration of treatment is defined for each subject as last dose date minus first dose date plus 14 days. Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of subjects in each treatment duration interval (< 2 weeks [14 days], ≥ 2 weeks [14 days], ≥ 4 weeks [28 days], ≥ 8 weeks [56 days], ≥ 12 weeks [84 days], ≥ 24 weeks [168 days], ≥ 36 weeks [252 days], and ≥ 52 weeks [364 days]) will be summarized.

Treatment compliance will be summarized for the entire treatment period by treatment group and total ABBV-154 group for the Safety population. Treatment compliance is defined as the number of injection actually taken divided by the number of injection that should have been taken. All placebo injections will be included in the calculation for treatment compliance. Percent compliance will be summarized.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the ITT overall and by treatment group. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Continuous demographic variables include age, weight, height, and body mass index (BMI). Categorical demographic variables include sex, ethnicity, race, age Group 1 (< 65, or ≥ 65 years), age Group 2 (< 65, ≥ 65 and < 75, or ≥ 75 years), weight Group 1

(< 60 or ≥ 60 kg), weight Group 2 (< 100 or ≥ 100 kg), BMI Group 1 (< 25 or ≥ 25 kg/m^2), BMI Group 2 (< 35 or ≥ 35 kg/m^2), region (Europe, North America, or rest of world), tobacco user (current, former, never, unknown), and alcohol user (current, former, never, unknown).

Disease characteristics that will be summarized as continuous and categorical variables are listed below:

PMR Medical History and Characteristics

- Duration of PMR diagnosis in years
- Duration of PMR diagnosis category (< 1, ≥ 1 and ≤ 2, or > 2 years)

Baseline PMR Disease Characteristics

- High sensitivity c-reactive protein (hs-CRP) (mg/L)
- Erythrocyte sedimentation rate (ESR) (mm/h)
- Patient Assessment of Pain Severity Numeric Rating Scale (NRS)
- Physician Global Assessment of Disease Activity NRS
- Morning Stiffness (MST) Duration
- Elevation of Upper Limbs (EUL)
- Polymyalgia Rheumatica Activity Score (PMR-AS)
- Polymyalgia Rheumatica Activity Score (PMR-AS) (< 1.5, ≥ 1.5 and < 7, ≥ 7 and < 17, or ≥ 17)
- Patient Assessment of Stiffness Severity NRS
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
- Health Assessment Questionnaire Disability Index (HAQ-DI)
- Patient-Reported Outcomes Measurement Information System (PROMIS) – Sleep Disturbance
- Patient Assessment of Bruising Severity NRS
- EuroQol 5-dimension questionnaire, 5-level (EQ-5D-5L)
- Physician Assessment of Bruising Severity NRS

- Rheumatoid factor (Positive (≥ 14 IU/mL), Negative (< 14 IU/mL))
- Time since most recent PMR flare prior to Baseline (≤ 12 weeks, > 12 weeks)

Prior and Concomitant Treatment use

- Length of prior glucocorticoid treatment for PMR* category (≤ 1 or > 1 year)
- Baseline glucocorticoid dose
- Baseline glucocorticoid dose categories 1 (< 10 or ≥ 10 mg/day prednisone equivalent)
- Baseline glucocorticoid dose categories 2 (< 7.5, ≥ 7.5 and < 10, ≥ 10 and ≤ 15, or > 15 mg/day prednisone equivalent)
- Prior biologic DMARD use (yes/no)
- Prior synthetic DMARD use (yes/no)
  - Prior conventional synthetic DMARD use (yes/no)
  - Prior targeted synthetic DMARD use (yes/no)
- Length of prior glucocorticoid use for PMR* (years)
- Prior cumulative glucocorticoid dose (mg)
- Prior cumulative glucocorticoid dose (mg) (within one year before randomization)

  *: Only consider glucocorticoid treatment use on or after confirmed PMR diagnosis date

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized overall and by treatment group. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical

order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug plus 70 days. The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

8.0 Handling of Potential Intercurrent Events for the Primary and Secondary Endpoints

The primary efficacy endpoint (defined in Section 3.1) will be analyzed based on the ITT population and subjects will be censored at the time of the last available assessment, initiation of immunomodulator, or violation of protocol-allowed systemic glucocorticoid use.

The categorical secondary efficacy endpoint (defined in Section 3.2) will be analyzed based on the ITT population and the following methods will be used to address the potential intercurrent events:

- Subjects will be considered as not achieving the response after the initiation of rescue medication, immunomodulator or violation of protocol-allowed systemic glucocorticoid use.

The continuous secondary efficacy endpoints (defined in Section 3.2) will be analyzed based on the ITT population and the following methods will be used to address the potential intercurrent events:

- No intercurrent event will be considered in the analysis of glucocorticoid dose.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted in the ITT Population in each period. In addition, Per-protocol analysis for the primary endpoint will be performed. All tests will be 2-sided at an alpha level of 0.1.

The Primary Analysis will be performed after all subjects have either completed the Week 24 visit or withdrawn from the study. This analysis will be the only and final analysis for the primary and secondary efficacy endpoints.

The primary endpoint will be analyzed using logrank test stratified by baseline stratification factors [Glucocorticoid use at Baseline (≥ 10 mg/day; < 10 mg/day prednisone equivalent); Length of prior glucocorticoid treatment for PMR (≤ 1 year; > 1 year)]. The point and 95% confidence interval (CI) estimate of median time to event and event-free rate for each group will be reported based on Kaplan-Meier curves. Hazard ratio and its corresponding 95% CI for each ABBV-154 group compared with placebo will be estimated using Cox regression analysis adjusting for Baseline stratification factors [Glucocorticoid use at Baseline (≥ 10 mg/day; < 10 mg/day prednisone equivalent); Length of prior glucocorticoid treatment for PMR (≤ 1 year; > 1 year)]. For all analyses of time-to-event endpoints, 1) subject without an event at the time of the analysis will be administratively censored at the time of the last available assessment or cutoff, whichever is later; 2) a flare at Baseline will not be counted as an event; 3) if a flare event and an intercurrent event happen on the same day, subject will be counted as having a flare event.

Unless otherwise specified, the categorical endpoints and continuous endpoints will be analyzed by Cochran-Mantel-Haenszel (CMH) and Mixed-Effect Model Repeat

Measurement (MMRM), respectively, and the corresponding analyses are specified in Section 9.2.

Unless otherwise specified, any subject who is randomized based on a wrong stratum will be analyzed according to the actual stratum the subject belongs to.

"Baseline" refers to the last non-missing observation on or before the day of the first administration of study drug or randomization if no study drug is given. Observation on the same day as the first administration of study drug will be considered for the baseline, regardless of whether observation time (if available) was before or after the first administration of study drug time.

9.2 Handling of Missing Data

For time-to-event endpoints, event and censoring details will be described in Section 9.3.

9.2.1 Missing Data due to COVID-19

Missing data could occur due to various reasons, including missing visits/assessments, early withdrawal from the study, or missing due to COVID-19 infection or logistic restriction.

The COVID-19 pandemic is interfering with the conduct of many ongoing trials, with potential impacts on treatment duration and the collection, analysis, and the interpretation of clinical trial data. Some protocol-specified visits in the clinical trials may be impacted due to COVID-19 infection or logistical restrictions during the pandemic. Impacted visits due to COVID-19 will be recorded in the database. The probability of having missed visits and missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic can be reasonably assumed to be unrelated to the unobserved values. Therefore, for the purpose of statistical analysis, it is reasonable to assume that these missing data are missing at random (MAR) and the statistical models that require MAR assumption are appropriate. Sensitivity analyses will be performed to assess the impact of missing data and the robustness of the conclusion.

9.2.2 Handling of Intercurrent Events and Missing Data in Categorical and Continuous Endpoints

- Non-Responder Imputation incorporating multiple imputation to handle COVID-19 (NRI-MI) will be the primary approach to handle missing data for categorical endpoints. The NRI-MI will categorize any subject who does not have an evaluation during a pre-specified visit window (either due to missing assessment, due to early withdrawal from the study, or due to intercurrent event) as a non-responder for the visit. The only exceptions are: 1) when the subject is a responder both before and after the visit window, the subject will be categorized as a responder for the visit. 2) missing data due to COVID-19 infection or logistical restriction will be handled by Multiple Imputation. In addition, all assessments after the start of intercurrent events will not be included in the analyses; as a result, subjects will be counted as non-responders thereafter and will not be imputed by MI.
- Non-Responder Imputation (NRI): In the interim analyses, NRI may be used due to subjects being in the study for different durations which makes multiple imputation infeasible.
- Multiple Imputation (MI): Markov Chain Monte Carlo (MCMC) will be first applied to augment data into monotonic missing pattern and PROC MI will be used to generate 30 datasets using the regression method. The variables to be included in the imputation model are treatment group, stratification factors at randomization [Glucocorticoid use at Baseline (≥ 10 mg/day; < 10 mg/day prednisone equivalent); Length of prior glucocorticoid treatment for PMR (≤ 1 year; > 1 year)], Baseline, and measurements at each visit. The random seed for MCMC and the random seed for PROC MI are specified in Appendix C. The imputed post-baseline measurements will be rounded to the same precision as the observed data before the determination of responder status. Subjects will be characterized as responders or non-responders based on MI imputed datasets. Using the Cochran-Mantel-Haenszel (CMH) model adjusted by stratification factors [Glucocorticoid use at Baseline (≥ 10 mg/day; < 10 mg/day prednisone equivalent); Length of prior glucocorticoid treatment for PMR (≤ 1 year; > 1 year)], the imputed endpoints will be analyzed using each of the 30 datasets. SAS PROC MIANALYZE will be used to generate the final inferences of the risk difference between each ABBV-154 group and

placebo. Note that measurements will be considered as missing after the start of confounding medication before MI. Regardless of MI imputed values, subjects after receiving confounding medication will be counted as non-responders.

Efficacy assessments after the initiation of rescue medication, immunomodulator or violation of protocol-allowed systemic glucocorticoid use will not be included in the analyses. As a result, the subjects will be considered as non-responders in the NRI-MI approach.

- Mixed-Effect Model Repeat Measurement (MMRM): MMRM will be the primary approach to the analysis of continuous variables except for glucocorticoid dose. The repeated measures analysis will be conducted using a mixed model including observed measurements at all visits. Subject's observations after intercurrent events will not be used in the MMRM. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, stratification factors at randomization [Glucocorticoid use at Baseline (≥ 10 mg/day; < 10 mg/day prednisone equivalent); Length of prior glucocorticoid treatment for PMR (≤ 1 year; > 1 year)], and the continuous fixed covariates of baseline measurement. An unstructured variance-covariance matrix (UN) will be used. If the model does not converge, an alternative variance-covariance structure matrix (e.g., autoregressive (1) or compound symmetry) will be used. Parameter estimation is based on the assumption of data being missing at random and the method of restricted maximum likelihood (REML) will be used.
- Analysis of covariance (ANCOVA): ANCOVA will be the primary approach for the analysis of glucocorticoid dose. No intercurrent event will be considered in the analysis of glucocorticoid dose. The ANCOVA model includes the categorical fixed effects of treatment and stratification factors at randomization [Glucocorticoid use at Baseline (≥ 10 mg/day; < 10 mg/day prednisone equivalent); Length of prior glucocorticoid treatment for PMR (≤ 1 year; > 1 year)], and baseline glucocorticoid dose as a covariate.
- As Observed (AO): The AO analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled

visit will be excluded from the AO analysis for that visit. AO will include all values collected in the study.

9.3 Primary Efficacy Endpoint(s) and Analyses

9.3.1 Primary Efficacy Endpoint(s)

The primary endpoint is the time to flare, where flare is defined as follows:

- Presence of clinical signs and symptoms of PMR

AND

- Requirement to increase the glucocorticoid dose per investigator.

Clinical signs and symptoms of PMR are defined as shoulder and/or hip girdle pain with inflammatory stiffness, neck pain with inflammatory stiffness, or new or worsened limited range of motion of hips and/or shoulders, as outlined in protocol.

9.3.2 Main Analysis of Primary Efficacy Endpoint(s)

The statistical null hypothesis corresponding to the primary endpoint is that there is no difference between an ABBV-154 group and the placebo group in time to flare.

Analysis of the primary endpoint will be conducted in the ITT Population based on treatment as randomized. Comparison of the primary endpoint will be made between each ABBV-154 group and the placebo group using logrank test stratified by baseline stratification factors [Glucocorticoid use at Baseline (≥ 10 mg/day; < 10 mg/day prednisone equivalent); Length of prior glucocorticoid treatment for PMR (≤ 1 year; > 1 year)].

The attributes of the estimands corresponding to the primary efficacy endpoint are summarized in Table 1.

Table 1. Summary of the Estimand Attributes of the Primary Efficacy Endpoint(s)

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events (IE)**	**Statistical Summary**
Primary: Time to flare (Composite)	ABBV-154 vs. Placebo	Time to flare	ITT	IE1: at the time of immunomodulator initiation IE2: at the time of violation of protocol-allowed systemic glucocorticoid use Subjects will be censored at the time of intercurrent event.	Between ABBV-154 and placebo: difference in number of events, difference in median time to event, event-free rate difference, hazard ratio and its corresponding CI

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint(s)

Not applicable.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Secondary Efficacy Endpoints

The categorical secondary endpoint is

- Achievement of flare-free state up to Week 24

The continuous secondary endpoints are

- Cumulative glucocorticoid dose by 24 weeks

- Change from Baseline in glucocorticoid dose at Week 24

For the analysis of glucocorticoid dose, all systemic glucocorticoid use will be included regardless of the indication.

9.4.2 Main Analyses of Secondary Efficacy Endpoints

The statistical null hypothesis corresponding to the secondary endpoint is that there is no difference between an ABBV-154 group and the placebo group.

Analysis of the secondary endpoint will be conducted in the ITT Population based on treatment as randomized. Comparison of the secondary endpoint will be made between each ABBV-154 group and the placebo group using:

- For categorical variable: CMH test adjusted by baseline randomization stratification factor [Glucocorticoid use at Baseline (≥ 10 mg/day; < 10 mg/day prednisone equivalent); Length of prior glucocorticoid treatment for PMR (≤ 1 year; > 1 year)].
- For analyses of glucocorticoid dose: ANCOVA mentioned in Section 9.2.

The attributes of the estimands corresponding to the secondary efficacy endpoints are summarized in Table 2.

Table 2. Summary of the Estimand Attributes of the Secondary Efficacy Endpoints

For binary endpoint:

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Binary Secondary Variable (Composite)	ABBV-154 vs. Placebo	Achievement of flare-free state up to Week 24	ITT	IE1: Initiation of rescue medication IE2: Initiation of immunomodulator IE3: Initiation of violation of protocol-allowed systemic glucocorticoid use Subjects will be considered as non-responders for visits after ICEs.	Difference in proportion of subjects achieving flare-free state up to Week 24

For analyses of glucocorticoid dose:

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Analyses of glucocorticoid dose (Treatment Policy)	ABBV-154 vs Placebo	Change from Baseline at Week 24 or cumulative assessment by Week 24	ITT	No IE.	Difference in the mean change from Baseline at Week 24 or cumulative assessment by Week 24

9.4.3 Sensitivity and Supplementary Analyses for Secondary Efficacy Endpoints

Not applicable.

9.4.4 Supportive Secondary Efficacy Endpoints and Analyses

Not applicable.

9.5 Additional Efficacy Analyses

Additional efficacy endpoints described in Section 3.3 will be analyzed at all visits assessed using the same methods listed in above and Section 9.2. The attributes of the estimands corresponding to the additional efficacy endpoints are summarized in Table 3.

Table 3. Summary of the Estimand Attributes of the Additional Efficacy Endpoints

For binary endpoint:

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Binary Additional Variable (Composite)	ABBV-154 vs. Placebo	Achievement of each binary additional endpoint respectively	ITT	IE1: Initiation of rescue medication IE2: Initiation of immunomodulator IE3: Initiation of violation of protocol-allowed systemic glucocorticoid use Subjects will be considered as non-responders for visits after ICEs.	Difference in proportion of subjects achieving each binary additional endpoint

For continuous endpoint:

Estimand Label	Attributes of the Estimand				
	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Continuous Additional Variable (Composite)	ABBV-154 vs. Placebo	Change from Baseline in each respective continuous additional endpoint	ITT	IE1: Initiation of rescue medication IE2: Initiation of immunomodulator IE3: Initiation of violation of protocol-allowed systemic glucocorticoid use Efficacy assessments after the start of IE will not be included in the analyses, and visits after IE will be handled by MMRM.	Difference in the mean change from Baseline in each continuous additional endpoint

9.6 Dose-Response Modeling for ABBV-154

The dose-response relationship among ABBV-154 dose groups and the placebo group will be characterized for the primary endpoint using the Multiple Comparison Procedure – Modeling (MCP-Mod) method [Pinheiro 2006, Bretz 2005]. The summary level response rates based on the primary analysis approach above will be used, and ADDPLAN DF software will be used to perform the MCP-Mod analyses.

A set of 6 pre-specified standardized candidate dose-response models, as described in Table 4 will be utilized to examine the dose-response relationship. A statistically significant dose-response relationship will be declared if at least one model is identified by the MCP-Mod method to be statistically significant at two-sided $\alpha = 0.1$. The fitted dose-response curves will be presented graphically for all statistically significant models along with 95% confidence bands. The minimum effective dose (MED) will be identified for each statistically significant model based on the pre-specified clinical meaningful

target of 22%. The weighted MED across all significant models will be calculated, with weight being the inverse of each candidate dose-response model AIC.

Table 4. Candidate Models

Model	$f(d,\theta)$ d = dose, θ = Model Parameters	$f^0(d,\theta)$ Standardized Model	Initial Value(s) for Parameter(s)*
Linear	$E_0 + \delta d$	d	NA
Exponential	$E_0 + E_1\left[exp\left(\frac{d}{\delta}\right) - 1\right]$	$exp\left(\frac{d}{\delta}\right) - 1$	δ = 680
Logistic	$E_0 + \frac{E_{max}}{1 + exp\left(\frac{ED_{50} - d}{\delta}\right)}$	$\frac{1}{1 + exp\left(\frac{ED_{50} - d}{\delta}\right)}$	ED_{50} = 150, δ = 64.5
Emax	$E_0 + \frac{E_{max} d}{ED_{50} + d}$	$\frac{d}{ED_{50} + d}$	ED_{50} = 83.9
sigEMax	$E_0 + \frac{E_{max} d^h}{{ED_{50}}^h + d^h}$	$\frac{d^h}{{ED_{50}}^h + d^h}$	ED_{50} = 150, h = 3.6
Quadratic	$E_0 + \beta_1 d + \beta_2 d^2$	$d + \frac{\beta_2}{\lvert\beta_1\rvert} d^2$	δ = –0.001

* For Exponential model, the initial value was determined based on the assumption that ABBV-154 340 mg EOW will achieve 95% of the maximum efficacy of ABBV-154. For Logistic, Emax, sigEMax, and Quadratic model, the initial values were determined based on the assumption that ABBV-154 340 mg EOW and ABBV-154 150 mg EOW will achieve 95% and 50% of the maximum efficacy of ABBV-154, respectively.

Steps of MCP-Mod:

1. Choose a candidate set of models as in Table 4.
2. Compute the optimum contrast for each model.
3. Use contrast test to find all significant models while preserving family-wise error rate (FWER).

4. Use all significant models to make inference about the weighted target dose of interest.

9.7 Efficacy Subgroup Analyses

Subgroup analysis for the primary endpoint will be conducted by the subgroups specified below. The difference in the primary efficacy endpoint between the treatment groups in each subgroup will be assessed using the same approach for primary endpoint.

- Baseline glucocorticoid use (≥ 10 mg/day; < 10 mg/day prednisone equivalent)
- Length of prior glucocorticoid treatment for PMR (≤ 1 year; > 1 year)
- Age (≤ median; > median)
- Sex (female; male)
- Race (white; nonwhite)
- Time since most recent PMR flare prior to Baseline (≤ 12 weeks; > 12 weeks)

In addition, change from Baseline in glucocorticoid dose at Week 24 will be analyzed by the following subgroup. The difference in this endpoint between the treatment groups in each subgroup will be assessed using ANCOVA approach. Treatment difference and corresponding confidence interval will be used to summarize the result.

- Glucocorticoid status at Week 24 (glucocorticoid free; not glucocorticoid free)

If any subgroup has fewer than 10% of the total subjects, then the analysis for this subgroup will not be performed.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety Population. Safety summaries will be presented by treatment group, including a total group for all subjects on active study drug.

For the safety analysis, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

A subject's actual treatment will be determined by the most frequent dose regimen received.

"Baseline" refers to the last non-missing observation on or before the day of the first administration of study drug or randomization if no study drug is given. Observation on the same day as the first administration of study drug will be considered for the baseline, regardless if observation time (if available) was after the first administration of study drug time.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with the onset that is after the first dose of study drug and with an onset date no more than 5 half-lives of the study drug (i.e., 70 days). Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless the study drug start time and the AE start time are collected and the AE start time is prior to the study drug start time. All treatment-emergent AEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing treatment-emergent AEs will be summarized.

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study drug according to the investigator
- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to discontinuation of study drug
- Any treatment-emergent AE leading to death
- Adverse events of special interest (AESI, formerly known as safety topics of interest)
- All deaths
- Deaths occurring ≤ 70 days after last dose of study drug
- Deaths occurring > 70 days after last dose of study drug.

An overview of treatment-emergent AEs per 100 patient-years of exposure will be presented by treatment group for the same AE categories listed above.

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency for the total active group.

10.2.4 Treatment-Emergent Adverse Events per Patient-Years of Exposure

Exposure-adjusted AEs per 100 patient-years will be provided, where AEs per 100 patient-years of exposure are defined as the number of AEs divided by the total exposure in 100 patient-years. The study drug exposure is defined as the last dose date plus 5 × half-life (70 days), minus the first dose date.

10.2.5 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format.

In addition, the event rate per 100 patient-years of exposure will also be provided by SOC and PT for each treatment-emergent SAE and TEAE leading to study drug discontinuation.

10.2.6 Adverse Events of Special Interest

AESI will be summarized by SOC and PT and will be based on standardized or company MedDRA queries (SMQs or CMQs), or based on adjudication results. AESI to be summarized will follow those indicated in the latest version of the Product Safety Statistical Analysis Plan (PSSAP) for ABBV-154 in the AESI section. Detailed information about search criteria for the AESI are also provided in a table in the same section.

Tabular listings of AESI will be provided.

In addition, the event rate per 100 patient-years of exposure will also be provided by SOC and PT for each AESI.

10.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. The clinical laboratory tests defined in the protocol operations manual (e.g., hematology and clinical chemistry) will be summarized.

Each laboratory variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group and difference between treatment groups (ABBV-154 vs. placebo).

Changes in laboratory parameters will be tabulated using shift tables either by NCI CTC criteria or categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline either to the worse value (based on NCI CTC criteria) during treatment or to minimum and maximum value (based on normal range), will be created. A similar shift table will be provided to summarize shifts from baseline to the final post-baseline value.

Laboratory abnormalities meeting CTC criteria grade 3 and 4 will be summarized.

Laboratory abnormalities will be evaluated based on Potentially Clinically Important (PCI) criteria (criteria in PSSAP will be used first, if the criteria are not available in PSSAP, then criteria in NCI CTC will be used). For each laboratory PCI criterion, the number and percentage of subjects who have a laboratory value meeting the criteria will be summarized. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCI criteria.

For the purpose of assessing for potential Hy's law cases, the frequencies and percentages of subjects with post baseline liver specific function test values that meet the following criteria of potential clinical interest will be summarized by "as treated" treatment group:

- ALT > 3 × ULN
- ALT > 5 × ULN
- ALT > 10 × ULN
- ALT > 20 × ULN
- AST > 3 × ULN
- AST > 5 × ULN
- AST > 10 × ULN
- AST > 20 × ULN
- TBL > 2 × ULN
- Alkaline phosphatase > 1.5 × ULN
- ALT and/or AST > 3 × ULN and concurrent INR > 1.5
- ALT and/or AST > 3 × ULN and concurrent TBL > 2 × ULN

A listing of possible Hy's Law cases, defined as those who meet all of the following conditions simultaneously, will be provided: ALT > 3 × ULN or AST > 3 × ULN that is associated with an increase in bilirubin > 2 × ULN.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be summarized.

Each vital sign variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95%

confidence interval will be presented for the mean change from baseline within each treatment group and difference between treatment groups (ABBV-154 vs. Placebo).

Vital sign variables will be evaluated based on PCI criteria. Pulse rate, body temperature, and respiratory rate will follow the criteria in Appendix B. All other vital sign measurements will follow criteria in PSSAP. For each vital sign PCI criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCI criteria.

10.5 Safety Subgroup Analyses

The AE Overview and AE by SOC and PT summaries will be provided for the following subgroups:

- Baseline Glucocorticoid dose Categories Group 1 (< 7.5, ≥ 7.5 and < 10, ≥ 10 and ≤ 15, or > 15 mg/day prednisone equivalent)
- Baseline Glucocorticoid dose Categories Group 2 (< 10 and ≥ 10 mg/day prednisone equivalent)
- Duration of PMR Diagnosis Categories (< 1, ≥ 1 and ≤ 2, or > 2 years)
- Length of prior glucocorticoid treatment for PMR (≤ 1 and > 1 year)

If any subgroup has fewer than 10% of the total subjects, then the analysis for this subgroup will not be performed.

10.6 Other Safety Analyses

ECG is collected at screening, Week 24, and Week 52. ECG findings will be summarized by treatment group for each parameter and visit.

Dual-energy X-ray absorptiometry (DXA) is collected at screening and Week 52. DXA measurements, including bone mineral density and the corresponding T-scores and Z-scores, will be summarized by treatment group for each visit and also in the following subgroups:

- Vitamin D status at baseline (< 30 and ≥ 30 nmol/L)
- Female patients' post-menopausal status at baseline (Yes and No)
- Bone protective agent status at baseline (Yes and No)

If available, body composition should be collected at screening and Week 52. Body composition measurements, including body fat mass (grams), lean body mass (grams), total body mass (grams), fat (%), and lean (%) will be summarized by treatment group for each visit.

11.0 Other Analyses

Not applicable.

12.0 Interim Analyses

An interim analysis will be conducted for this study approximately 3 weeks before the Primary Analysis for M20-466 (ABBV-154 Rheumatoid Arthritis [RA] Phase 2b study). Additional interim analyses may be performed to reassess the treatment regimens in this study and to inform development of future studies. The interim analysis result will not be reviewed by the Data Monitoring Committee (DMC).

A separate interim unblinding plan will be developed to describe the detailed interim analysis plan, including the interim unblinding team, decision rules, execution logistics, and data chain of custody to protect the integrity of the clinical study. The interim analysis result will not be reviewed by the Data Monitoring Committee (DMC) and the interim analysis plan will not be documented in the DMC charter.

These interim analyses will not impact the study conduct.

12.1 Data Monitoring Committee

An external data monitoring committee (DMC) will be established to safeguard the interest of trial subjects by assessing the safety of the interventions during the trial and well as for the monitoring the integrity and interpretability of the trial.

A separate DMC charter will be prepared to describe the roles and responsibilities of the DMC members, frequency and scope of the data reviews, and expectations for blinded communications.

An internal independent glucocorticoid adjudication committee will be established to adjudicate potentially glucocorticoid-related AEs. A separate charter describes the roles and responsibilities of the adjudication committee members, frequency of data reviews, and expectations for blinded communications.

13.0 Overall Type-I Error Control

Overall Type I error control is not planned in this Phase 2 study.

Since there are no efficacy analyses for early stopping planned for the DMC or IERC review, no alpha spending is needed due to the DMC or IERC review.

14.0 Version History

Table 5. SAP Version History Summary

Version	Date	Summary
1.0	29 November 2021	Original version
2.0	03 August 2022	• Section 2.2, Section 2.3, Section 2.4, and Section 12.0: update the sample size, interim analysis language, sample size for Wearable Device Substudy, study schematics, randomization ratio, to align with protocol version 3.0. • Section 7.1: update/add details for the age Group 1, Rheumatoid factor, and length of prior glucocorticoid use for PMR, add summarization for time since most recent PMR flare prior Baseline (≤ 12 weeks, > 12 weeks). • Section 9.1: add details for time-to-event (censoring, event at the Baseline, event and flare happen on the same day) and efficacy Baseline definition. • Section 9.2: add statements for NRI instead of NRI-MI will be used in the interim analysis. • Section 9.5: clarify the intercurrent event for the additional efficacy endpoint. • Section 9.7: add efficacy subgroup time since most recent PMR flare prior Baseline (≤ 12 weeks, > 12 weeks) • Section 10.1: add details for safety Baseline definition • Section 10.2: clarify the definition of Treatment-emergent AEs; use AESI instead of STI for terminology • Section 10.5: add new safety subgroup • Section 10.6: add details for BMD analysis • Appendix B: add PCI criteria for selected laboratory variables.

15.0 References

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5. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci. 2007;8(3):206-13.
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8. Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat. 2006;16(5):639-56.
9. Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61(3):738-48.

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.

Appendix B. Potentially Clinically Important Criteria for Safety Endpoints

The PCI criteria for selected laboratory variables are described in Table B1 instead of using NCI CTC.

Table B1. Potentially Clinically Important Criteria for Selected Laboratory Variables

Laboratory Variables	Definition of Potentially Clinically Important
HbA1c	< 6.5%
	>= 6.5% to < 8%
	>= 8%
HDL	< 1.03 mmol/L
	>= 1.03 mmol/L
LDL	< 3.36 mmol/L
	>= 3.36 to <4.14 mmol/L
	>= 4.14 mmol/L

The PCI criteria for selected vital sign variables are described in Table B2.

Table B2. Potentially Clinically Important Criteria for Selected Vital Sign Variables

Vital Signs Variables	Criterion	Definition of Potentially Clinically Important
Pulse rate	Low	Value ≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High	Value ≥ 120 bpm and increase ≥ 15 bpm from Baseline
Body temperature	High	> 39.0 degrees C (102.3 degrees F)
Respiratory rate	Low	< 10 breaths/min
	High	> 24 breaths/min

Appendix C. Random Seeds

In case of non-convergence, the random seed will be updated by adding 10000 at each attempt until convergence of model happens.

Random Seeds for NRI-MI

Endpoints	Random Seed	
	MCMC procedure	**PROC MI**
PMR-AS related binary endpoints	10001	20001
ESR	10002	20002
hsCRP	10003	20003