Statistical Analysis Plan for Study M18-816

Phase 2b, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of Cedirogant (ABBV-157) in Adult Subjects with Moderate to Severe Psoriasis

Date: 15 December 2022

Version 2.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for ABBV-157 Study M18-816 A Phase 2b, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of Cedirogant (ABBV-157) in Adult Subjects with Moderate to Severe Psoriasis.

Study M18-816 examines the efficacy and safety of ABBV-157 in adult subjects with moderate to severe psoriasis.

The analyses of pharmacokinetic 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 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 of this study is to assess the safety and efficacy of cedirogant versus placebo for the treatment of moderate to severe plaque psoriasis in adult subjects who are candidates for systemic therapy or phototherapy.

The primary objective of the study is to demonstrate a higher rate of subjects achieving Psoriasis Area and Severity Index (PASI) 75 (defined as ≥ 75% reduction from Baseline in PASI) at Week 16 with at least one cedirogant dosing group compared to placebo in the Intent-to-Treat (ITT) population, which consists of all randomized subjects.

The primary endpoint is the achievement of PASI 75 at Week 16.

The secondary efficacy objective of the study is to demonstrate a higher rate of subjects achieving static Physicians Global Assessment (sPGA) score of clear or almost clear,

PASI 50/90/100, Psoriasis Symptoms Scale (PSS) total score of 0 for subjects with PSS>0 at Baseline, and itch Numerical Rating Scale (NRS)≥4-point improvement from Baseline for subjects with itch NRS≥4 at Baseline, at Week 16 with cedirogant compared to placebo in the ITT population.

As the study was terminated prematurely before the planned number of subjects could be randomized, all efficacy data will be summarized using descriptive summary statistics without statistical comparison or statistical testing. No hypotheses or estimands are defined for the primary and secondary efficacy endpoints.

2.2 Study Design Overview

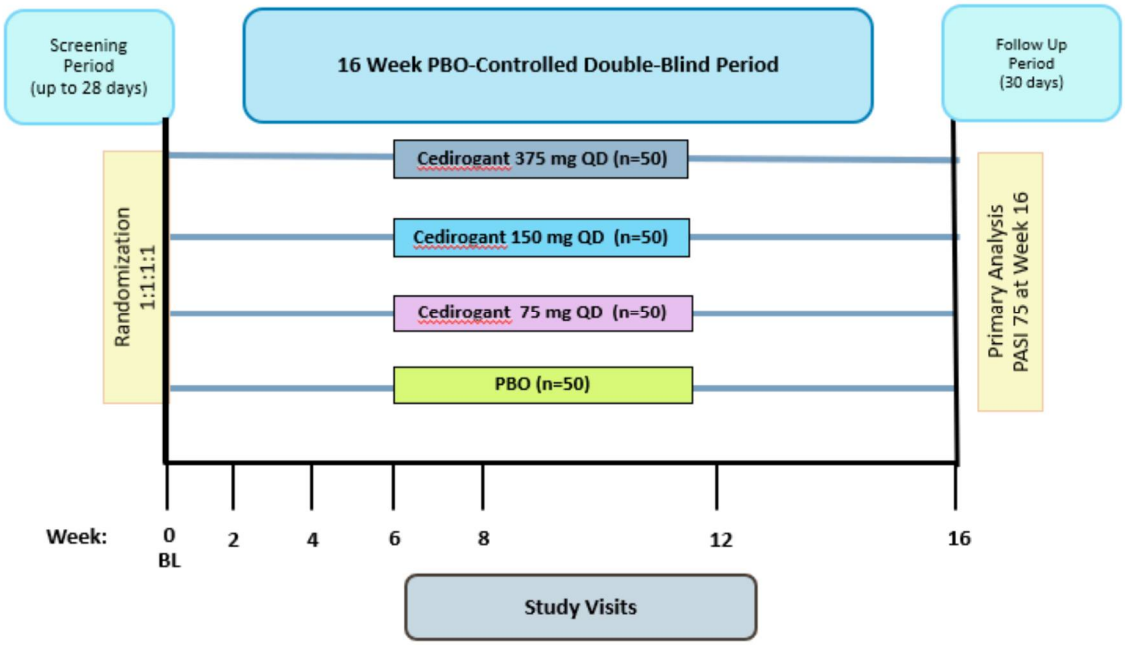
This is a Phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled dose ranging study that will evaluate the safety and efficacy of cedirogant in approximately 200 adult subjects with moderate to severe plaque psoriasis and who are candidates for systemic therapy or phototherapy.

The study is comprised of a 28-day Screening Period, a 16-week double-blind Treatment Period, and a 30-day Follow-up Period.

The schematic of the study is shown in Figure 1.

This study was terminated early by AbbVie due to preclinical findings in the cedirogant 39-week dog toxicity study. The interim analysis pre-defined in the protocol will not be conducted. The final database lock will occur after the last on-going subject completes the follow-up phone call or withdraws from the study.

Figure 1. Study Schematic



PASI = Psoriasis Area Severity Index; PBO = placebo; QD = once daily

2.3 Treatment Assignment and Blinding

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule.

Subjects who meet eligibility criteria at Baseline will be randomized in a 1:1:1:1 ratio to 1 of the 4 treatment groups:

- Cedirogant 375 mg once daily (QD) (N = 50)
- Cedirogant 150 mg QD (N = 50)
- Cedirogant 75 mg QD (N = 50)

- Placebo QD (N = 50)

All active and placebo treatment will be taken orally (cedirogant 75 mg tablets and matching placebo). There is no stratification factor for the randomization.

2.4 Sample Size Determination

Given the planned total sample size of 200 subjects (50 subjects in each arm), the study has more than 95% power to detect the treatment differences of 60% in PASI 75 in at least one cedirogant group versus placebo (PASI 75 response rate of 11%) using a two-sided significance level of 0.1 based on the 2-sample Chi-Squared test.

3.0 Endpoints

3.1 Primary Endpoint

The primary endpoint is the achievement of ≥ 75% reduction from baseline in PASI score (PASI 75) at Week 16.

3.2 Secondary Endpoints

The secondary endpoints are:

- Achievement of a static Physician Global Assessment (sPGA) score of clear or almost clear at Week 16
- Achievement of ≥ 50% reduction from baseline in PASI score (PASI 50) at Week 16
- Achievement of ≥ 90% reduction from baseline in PASI score (PASI 90) at Week 16
- Achievement of 100% reduction from baseline in PASI score (PASI 100) at Week 16
- Achievement of Psoriasis Symptoms Scale (PSS) total score of 0 at Week 16 for subjects with PSS >0 at Baseline
- Achievement of itch Numerical Rating Scale (NRS) ≥ 4-point improvement from Baseline at Week 16 for subjects with itch NRS ≥ 4 at Baseline

3.3 Other Efficacy Endpoints

Additional efficacy endpoints include the primary and all secondary endpoints assessed at visits other than the Week 16 Visit as noted in the Study Activities table (Appendix D of the protocol). Additional efficacy endpoints include the following measurements assessed at visits as specified in the Study Activities table:

- Change from baseline in Dermatology Life Quality Index (DLQI) score
- Achievement of a DLQI score of 0 or 1
- Achieving a change of ≥ 4 points from baseline in DLQI score (for patients whose DLQI score at baseline is ≥ 4)
- Treatment Satisfaction Questionnaire for Medication Version 9 (TSQM-9) domain scores (effectiveness, convenience and global satisfaction domains)
- Change from baseline in Hospital Anxiety and Depression Scale (HADS)-Anxiety score
- Change from baseline in HADS-Depression score
- Change from Baseline in Work Productivity and Activity Impairment (WPAI): Psoriasis Questionnaire measures:
    - Percent work time missed (Absenteeism)
    - Percent impairment while working (Presenteeism)
    - Percent overall work impairment
    - Percent activity impairment

3.4 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG) variables, and clinical laboratory testing (hematology, chemistry, and urinalysis) as measures of safety and tolerability for the entire study duration.

4.0 Analysis Populations

The following population sets will be used for the analyses.

The Intent-to-Treat (ITT) Population includes all randomized subjects. The efficacy analyses, summary of demographic, and baseline disease characteristics will be carried out with the ITT Population. Subjects will be analyzed as randomized.

The Safety Population includes all subjects who are randomized and received at least 1 dose of study drug. All safety analyses will use the Safety Population. Subjects will be analyzed as treated (i.e., according to the actual treatments received), regardless of the treatment assigned. The 'as-treated' treatment group is determined by the treatment the subject received during the majority of the subject's drug exposure time in the analysis period.

5.0 Subject Disposition

The number of subjects for each of the following categories will be summarized, for overall and for each group in ITT Population:

- Subjects randomized;
- Subjects who took at least one dose of study drug;
- Subjects who completed study;
- Subjects who completed study drug;
- Subjects who prematurely discontinued study drug;
- Subjects who prematurely discontinued study.

Number and percentage of subjects who discontinue study drug or who discontinue from study will be summarized by primary reason for each treatment group and overall.

In addition, the above summaries (except for the reason for premature discontinuation) will also be summarized by center in the accountability table.

6.0 Study Drug Duration and Compliance

For the Safety population, duration of treatment will be summarized for each treatment group and for all active investigational study drug dose groups combined. Duration of treatment is defined for each subject as last dose date minus first dose date +1. 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 (≥ 1 dose, ≥ 4 weeks, ≥ 12 weeks, ≥ 16 weeks) will be summarized.

Treatment compliance in the treatment period will be summarized by treatment group based on the Safety population. Treatment compliance for each subject is defined as the number of tablets actually taken divided by the number of tablets that should have been taken. For subjects who prematurely discontinued the study drug, the planned tablets will only be counted prior to that scheduled visit of discontinuation. The compliance rate will be summarized by treatment group.

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 population 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 (< 40, 40 – 65), weight (< 100 or ≥ 100 kg), BMI (< 25 or ≥ 25 kg/m^2), region (North America,

rest of world), tobacco user (current, former, never, unknown), and alcohol user (current, former, never, unknown).

Disease characteristics include the following: Baseline PASI, Baseline sPGA, Baseline PSS, Baseline BSA, Baseline NRS, Baseline DLQI, Baseline HADS, Baseline WPAI, history of psoriatic arthritis, prior biologic and disease duration in years as a continuous and categorical (< 5 or ≥ 5 years) variable.

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. 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 and secondary endpoints (Section 3.1 and Section 3.2) will be analyzed in the ITT Population and no intercurrent events will impact the analysis. All data collected, regardless of premature discontinuation of study drug, will be used in the analysis.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted in the ITT Population.

The only and final analysis for the primary and secondary efficacy endpoints as well as all other efficacy endpoints will be performed after the last on-going subject completes the follow-up phone call or withdraws from the study and the database has been locked.

Descriptive summary statistics will be provided for efficacy endpoints at each visit by treatment groups based on the ITT population. There will be no statistical testing.

Categorical efficacy endpoints at each visit will be summarized by number of subjects, the number and percentage of subjects who achieve the endpoint, as well as the 95% confidence interval (CI) based on normal approximation.

Continuous efficacy endpoints at each visit and change from baseline at each visit will be summarized by descriptive summary statistics including number of subjects, mean, standard deviation, median, minimum, maximum. The 95% CI based on normal approximation will be provided for the mean change from baseline.

"Baseline" refers to the last non-missing observation before the first administration of study drug or randomization if no study drug is given.

9.2 Handling of Missing Data

Observed Cases (OC) approach will be the only approach to handle missing data for both categorical and continuous efficacy endpoints in the study. The OC 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 OC analysis for that visit. OC will not include values after a subject prematurely discontinues from study treatment.

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

The primary endpoint is the achievement of ≥ 75% reduction from baseline in PASI score (PASI 75) at Week 16.

9.3.2 Main Analysis of Primary Efficacy Endpoints

Descriptive summary statistics of the primary efficacy endpoint will be provided based on the ITT Population as described in Section 9.1.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

No sensitivity and supplementary analyses of the primary efficacy endpoint will be conducted.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Secondary Efficacy Endpoints

The secondary endpoints are as defined in Section 3.2.

9.4.2 Main Analyses of Secondary Efficacy Endpoints

Descriptive summary statistics of the secondary efficacy endpoints will be provided based on the ITT Population as described in Section 9.1.

9.4.3 Sensitivity and Supplementary Analyses for Secondary Efficacy Endpoints

There will be no sensitivity analysis for the secondary efficacy endpoints.

9.5 Additional Efficacy Analyses

Descriptive summary statistics of the additional efficacy endpoints will be provided based on the ITT Population as described in Section 9.1.

9.6 Efficacy Subgroup Analyses

Descriptive summary statistics of each subgroup defined below will be provided for PASI 75 at Week 16, among the ITT Population:

- Age group (< 40 years, ≥ 40)
- Sex (male, female)
- BMI (< 25, ≥ 25)
- Baseline PASI (< median, ≥ median)
- Baseline sPGA (3, 4)
- Baseline PSS (0, > 0)
- Baseline NRS (< 4, ≥ 4)
- Psoriatic arthritis (yes, no)
- Prior biologic (yes, no)

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.

The overview of TEAEs, and potentially clinically important (PCI) findings in laboratory variables and vital sign variables will also be summarized among the Safety Populations.

Missing safety data will not be imputed.

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 within 30 days after the last dose of study drug.

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 in the Safety Population:

- 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
- Any treatment-emergent Safety topic of interest (STI)

- All deaths
- Deaths occurring ≤ 30 days after last dose of study drug
- Deaths occurring > 30 days after last dose of study drug.

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

The number and percentage of subjects experiencing TEAEs will be tabulated using the MedDRA system organ class and preferred term, by maximum severity by SOC and PT, and by relationship to the study drug as assessed by the investigator by 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.

Note that one event per preferred term per day per subject will be counted in the calculation of the number of TEAEs (i.e., a preferred term will not be counted twice on the same day for the same subject). The exposure-adjusted TEAE rate per 100 patient-years is calculated as:

$$100 \times \frac{\text{Number of TEAEs}}{\text{Total Patient Years}},$$

where total patient years is defined as the sum of individual patient year, which is defined as the minimum of (the last dose date + 30 days, the end of study date) minus the first dose date +1, normalized by 365.25 and rounded to one decimal place.

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

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

A listing of pre-treatment SAEs with onset dates prior to the first dose of study drug will be provided.

10.2.6 Safety Topics of Interest

Safety topics of interest will be summarized according to the search criteria are provided in Appendix B.

The final list will be based on the most updated final version of cedirogant Product Safety Statistical Analysis Plan.

Treatment-emergent Safety Topics of Interest will be summarized by SOC and PT and listing format. Additionally, STI rates per 100 patient years of exposure will be provided for each STI category (Appendix B) in the AE overview summary.

Listings of safety topics of interest will also be provided.

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.

The raw laboratory variable values and change from baseline to each applicable post-baseline visit will be summarized by treatment group, with number of subjects, mean, standard deviation, median, minimum, maximum. The 95% CI based on normal approximation will be provided for the mean change from baseline.

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

Laboratory abnormalities will be evaluated based on Potentially Clinically Important (PCI) criteria (Appendix C). 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.

Assessment of Liver Enzyme and Bilirubin Elevations

The frequencies and percentages of subjects with post baseline liver specific function test values in ALT/SGPT, AST/SGOT, alkaline phosphatase, and total bilirubin meeting the following criteria will be summarized:

- ALT > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- AST > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- TBL > 1.5 × ULN, > 2 × ULN
- ALT and/or AST > 3 × ULN and TBL > 1.5 × ULN
- ALT and/or AST > 3 × ULN and TBL > 2 × ULN
- ALT > 3 × ULN and TBL > 1.5 × ULN
- ALT > 3 × ULN and TBL > 2 × ULN
- Alkaline phosphatase > 1.5 × 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 total bilirubin ≥ 2 × ULN and alkaline phosphatase < 2 × ULN.

An Evaluation of Drug Induced Serious Hepatotoxicity (eDISH) plot[1] of the maximum post-baseline ALT value (as a multiple of the ULN) vs. the maximum post-baseline total bilirubin value (as a multiple of the ULN), not necessarily concurrent, will also be created. Reference lines will be included at 3 × ULN for ALT and at 2 × ULN for total bilirubin. A similar eDISH plot will be provided for the maximum post-baseline AST value (as a multiple of the ULN) vs. the maximum post-baseline total bilirubin value (as a multiple of the ULN).

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure will be summarized.

The raw value of each vital sign variable and change from baseline at each time point will be summarized by treatment group with number of subjects, mean, standard deviation, median, minimum and maximum. The 95% CI based on normal approximation will be provided for the mean change from baseline.

Vital sign variables will be evaluated based on potentially clinically important (PCI) criteria (Appendix C) among the Safety Population. 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

There will be no safety subgroup analyses for this study.

10.6 Other Safety Analyses

There will be no other safety analyses for this study.

11.0 Other Analyses

There will be no other analyses for this study.

12.0 Interim Analyses

There were plans for an interim analysis which was to be conducted after the first 140 subjects had either completed the Week 16 assessments or withdrawn from the study. Due to preclinical findings in the cedirogant 39-week dog toxicity study, Study M18-816 was terminated early and no interim analysis will be conducted.

12.1 Data Monitoring Committee

An internal data monitoring committee (DMC) composed of clinicians and statisticians independent of any cedirogant clinical trials outside their role on the DMC, and with relevant expertise in their field will review unblinded safety data from the ongoing study. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A separate DMC charter describes the roles and responsibilities of the DMC members, frequency of data reviews, relevant data to be assessed, and general operations.

Since there are no efficacy analyses for early stopping, no alpha adjustment is needed.

13.0 Overall Type-I Error Control

There will be no comparison or statistical testing for this Phase 2 study. Overall type I error control is not applicable.

14.0 Version History

Table 1. SAP Version History Summary

Version	Date	Summary
1.0	18 Jan 2022	Original version
2.0	15 Dec 2022	1. Section 2.0 Study Objectives and Design, due to early termination of the study, the planned interim analysis will not be conducted. The Final database lock will occur after the last on-going subject completes the follow-up phone call. 2. Section 7.1 Demographics and Baseline Characteristics, removed Baseline TSQM-9, as TSQM-9 is not collected at baseline. 3. Section 9.0 Efficacy Analyses, due to early termination of the study, there will be no comparison or statistical testing for all efficacy endpoints, only summary statistics will be provided. OC will be the approach to handle missing data for categorical and continuous efficacy endpoints instead of NRI-MI and MMRM, respectively. 4. Section 10.2 Adverse Events, total patient years is defined as the sum of individual patient year, which is defined as the minimum of (the last dose date + 30 days, the end of study date) minus the first dose date +1, normalized by 365.25 and rounded to one decimal place. 5. Section 10.3 added eDISH Plot of AST and removed shift tables. 6. Section 12.0 Interim Analyses, due to early termination of the study, the planned interim analysis will not be conducted.

15.0 References

1. Watkins PB, Desai M, Berkowitz SD, et al. Evaluation of drug-induced serious hepatotoxicity (eDISH): application of this data organization approach to phase III clinical trials of rivaroxaban after total hip or knee replacement surgery. Drug Saf. 2011;34(3):243-52.

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. Definition of Safety Topics of Interest for cedirogant

Safety topics of interest (STI) will be identified using the following search criteria:

Safety Topic of Interest	Basis for Inclusion	Criteria for Identification of Event	Are events adjudicated (yes/no)? If yes, external or internal adjudication?	Special Collection Forms or Safety Studies	Relevant Restrictions[#]
Identified Risks - None					
Important Potential Risks					
Serious infection*	Based on the mechanism of action and data from the biomedical literature, as well as information from nonclinical pharmacology and toxicity studies, ABBV-157 administration is expected to produce effects on white blood cells and cytokines. These immunomodulatory properties may result in an increased risk of infection.	Serious events only from the Infections and Infestations SOC	No	No	Exclusion of subjects with HIV, hepatitis B or hepatitis C viral infection. Exclusion of subjects with active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
Other Safety Topics of Interest					
GI tract altered mobility	In rats, GI effects were present at ≥ 100 mg/kg/day in the 4-week GLP study and led to marked body weight loss and dehydration, necessitating euthanasia in two animals due to moribund condition. There was also histopathologic evidence of intestinal tract dilation in rats. In the GLP dog study, ABBV-157 produced emesis and loose to watery stools that were well tolerated throughout the study at doses of 40, 120, and 300 mg/kg/day.	Gastrointestinal nonspecific symptoms and therapeutic procedures SMQ_Narrow	No	No	None
Herpes zoster	Manipulating the inflammation cascade with any immune-modulating biologic may increase the risk of infections. Cases of Herpes Zoster is not included in OI CMQ	Herpes Zoster CMQ	No	Yes	None

Safety Topic of Interest	Basis for Inclusion	Criteria for Identification of Event	Are events adjudicated (yes/no)? If yes, external or internal adjudication?	Special Collection Forms or Safety Studies	Relevant Restrictions[#]
Opportunistic infection excluding tuberculosis and herpes zoster	On the basis of MOA and data from the medical literature, as well as information from nonclinical pharmacology and toxicity studies, Cedirogant administration is expected to produce effects on white blood cells and cytokines. These immunomodulatory properties may result in an increased risk of infection.	Opportunistic Infection Excluding Tuberculosis and Herpes Zoster CMQ	No	No	Exclusion of subjects with infection (bacterial, fungal or viral) requiring systemic treatment within 4 weeks of the Baseline Visit.
Active tuberculosis	On the basis of MOA and data from the medical literature, as well as information from nonclinical pharmacology and toxicity studies, Cedirogant administration is expected to produce effects on white blood cells and cytokines. These immunomodulatory properties may result in an increased risk of infection.	Active Tuberculosis CMQ	No	Yes	Exclusion of subjects with active TB and prophylaxis of subjects with latent TB.
Hepatic Disorders	Though there are no signals, preclinical or clinical, of hepatotoxicity associated with ABBV-157 therapy to date, hepatic events are routinely monitored for any drug in development.	Drug Related Hepatic Disorders – Comprehensive Search SMQ _narrow	No	Yes	Exclusion of subjects with AST ≥2 x ULN or ALT ≥2 x ULN or total bilirubin > 1.5 x ULN. Exclusion of subjects with history or evidence of HBV or HCV infection.

Safety Topic of Interest	Basis for Inclusion	Criteria for Identification of Event	Are events adjudicated (yes/no)? If yes, external or internal adjudication?	Special Collection Forms or Safety Studies	Relevant Restrictions[#]
Lymphopenia	Non-clinical Findings: Decreased numbers of lymphocyte in the thymus, Peyer's patch, and lymph nodes, along with decreases in thymus weights, were present in rats and dogs and were related to ABBV-157 administration.	Hematological Toxicity - Lymphopenia (Upadacitinib Product Specific) CMQ	No	No	None.
Anemia	Non-clinical Findings: Minimal to mild decreases in RBC mass were present in dogs and rats and were reversible after 4 weeks of recovery.	Non-Hemolytic and Non-Aplastic Anemias CMQ	No	No	Exclusion of subjects with hemoglobin ≤ 9 g/dl.
MACE	There is an increased risk of cardiovascular disease in the psoriasis patient population.	Other Ischaemic heart disease SMQ_narrow Central nervous system hemorrhages and cerebrovascular conditions SMQ_narrow Myocardial infarction SMQ_narrow Death and Sudden Death - HLT	No	Yes	None

Safety Topic of Interest	Basis for Inclusion	Criteria for Identification of Event	Are events adjudicated (yes/no)? If yes, external or internal adjudication?	Special Collection Forms or Safety Studies	Relevant Restrictions[#]
Ocular events	In a healthy volunteer study of an RORγt compound related to ABBV-157, 3 of 9 subjects developed eye related events after multiple doses, including one subject who was seen by eye specialists and required prolonged treatment with steroid eye drops and an oral NSAID (aspirin-like drug).	Conjunctival disorders SMQ_narrow Corneal disorders SMQ Scleral disorders SMQ_narrow	No	Yes	Current phase 2b protocol requires any subject with CTCAE Grade 2 or higher AE ocular event must follow up with an ophthalmologist within 7 days. Grade 2 or higher ocular AEs considered related to study drug administration qualify for withdrawal criteria.
Possible malignancies	Comorbidity with patient population, NMSC most common. Theoretical possibility of decreased immune surveillance against malignancies with alteration of immune pathways.	- Malignant tumours SMQ - narrow	No	No	Exclusion of subjects with a history of any malignancy within the last 5 years or documented active malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.
Non-melanoma skin cancer (NMSC)	Comorbidity with patient population, NMSC most common. Theoretical possibility of decreased immune surveillance against malignancies with alteration of immune pathways.	Skin malignant tumours SMQ Broad excluding preferred terms identified by the Melanoma CMQ	No	No	Exclusion of subjects with a history of untreated non-melanoma skin cancer (NMSC).

Safety Topic of Interest	Basis for Inclusion	Criteria for Identification of Event	Are events adjudicated (yes/no)? If yes, external or internal adjudication?	Special Collection Forms or Safety Studies	Relevant Restrictions[#]
Malignant tumours excluding non-melanoma skin cancer (NMSC)	Comorbidity with patient population. Theoretical possibility of decreased immune surveillance against malignancies with alteration of immune pathways.	Malignant Tumours SMQ Narrow EXCLUDING (Skin malignant tumors SMQ Broad excluding PTs identified by Melanoma CMQ)	No	No	Exclusion of subjects with a history of any malignancy within the last 5 years or documented active malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.

* Important risk.

\# e.g., protocol exclusion criteria or risk minimization actions limiting data on certain patient populations.

Appendix C. Potentially Clinically Important Criteria for Safety Endpoints

The criteria for Potentially Clinically Important (PCI) laboratory findings are described in Table C-1 and Table C-2, and the PCI criteria for vital sign findings are described in Table C-3.

Table C-1. Criteria for Potentially Clinically Important Hematology Values

Hematology Variables	Units	Definition of Potentially Clinically Important NCI CTCAE (Version 4.03) Grade 3 or greater
		Very Low
Hemoglobin	g/dL	< 8.0
Platelets count	10^9/L	< 50.0
WBC count	10^9/L	< 2.0
Neutrophils	10^9/L	< 1.0
Lymphocytes	10^9/L	< 0.5

Note: A post-baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table C-2. Criteria for Potentially Clinically Important Chemistry Values

Chemistry Variables	Units	Definition of Potentially Clinically Important NCI CTCAE (Version 4.03) Grade 3 or greater	
		Very Low	Very High
TBL	mcmol/L		> 3.0 × ULN
ALP	U/L		> 5.0 × ULN
SGOT/AST	U/L		> 5.0 × ULN
SGPT/ALT	U/L		> 5.0 × ULN
Albumin	g/L	< 20	
Glucose	mmol/L	< 2.2	> 13.9
Triglycerides	mmol/L		> 5.7
Creatinine	mcmol/L		> 3.0 × ULN (> 3.0 × BL)
Sodium	mmol/L	< 130	> 155
Potassium	mmol/L	< 3.0	> 6.0
Calcium	mmol/L	< 1.75	> 3.1
CPK	U/L		> 5.0 × ULN
Total Cholesterol	mmol/L		> 10.34
GGT			> 5.0 × ULN

Note: A post-baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table C-3. Criteria for Potentially Clinically Important Vital Sign Values

Vital Signs Variables	Criterion	Definition of Potentially Clinically Important
Systolic Blood Pressure (mmHg)	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic Blood Pressure (mmHg)	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from Baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from Baseline