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Protocol for Study M18-816

Psoriasis: A Multicenter, Randomized, Double-blind, Placebo-controlled Dose-Ranging Study of Cedirogant (ABBV-157) in Subjects with Psoriasis

VERSION:	2.0	DATE:	13 May 2022
SPONSOR:	AbbVie*	PLANNED NUMBER OF SITES:	Approximately 50
ABBVIE INVESTIGATIONAL PRODUCT:	Cedirogant (ABBV-157)	EudraCT:	Not Applicable

FULL TITLE: 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.

Incorporating Versions 1.0, 1.1 (Japan Only), and 2.0

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1 Synopsis

Title: 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.	
Background and Rationale:	Retinoic acid-related orphan receptor gamma, thymus (RORγt) is a key transcription factor responsible for interleukin (IL)-17 synthesis. Targeting RORγt has the potential to directly block cellular function via RORγt-dependent genes. Cedirogant (ABBV-157) is an inverse agonist of RORγt being developed for chronic plaque psoriasis. There is an unmet medical need for effective treatments in chronic plaque psoriasis. This study is being conducted to evaluate cedirogant in adult subjects with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Objective and Endpoints:	The 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 adults who are candidates for systemic therapy or phototherapy. The following primary endpoint will be evaluated: • Achievement of ≥ 75% reduction from baseline in Psoriasis Area Severity Index (PASI) score (PASI 75) at Week 16 The following secondary endpoints will be evaluated: • 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
Investigators:	Multicenter
Study Sites:	Approximately 50 sites in the United States, Canada, and Japan.
Study Population and Number of Subjects to be Enrolled:	A total of approximately 200 subjects with moderate to severe plaque psoriasis.
Investigational Plan:	This is a multicenter, Phase 2, randomized, double-blind, parallel-group, placebo-controlled dose ranging study.

Key Eligibility Criteria:	Adult subjects with stable moderate to severe plaque psoriasis (as defined by body surface area [BSA] psoriasis involvement ≥ 10%, scores of ≥ 12 on the PASI, and scores of 3 or 4 on the sPGA) of at least 6 months duration and who are candidates for systemic therapy or phototherapy.
Study Drug and Duration of Treatment:	Study duration will be approximately 16 weeks. Subjects will be randomized in a 1:1:1:1 ratio to 1 of 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)
Date of Protocol Synopsis:	13 May 2022

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

Psoriasis is a chronic debilitating immunologic disease characterized by marked inflammation and thickening of the epidermis that result in thick, scaly skin plaques. In most developed countries, the prevalence in adults is between approximately 1.5 and 5%.[1] About 20% of patients have moderate to severe disease with a considerable negative impact on psychosocial and economic status.[2,3] It is increasingly recognized that psoriasis is more than a superficial disease, with 30% of patients having joint involvement; additionally, high correlations exist between psoriasis and obesity, diabetes, depression, metabolic syndrome, and cardiovascular events.[4,5]

Currently available oral systemic agents provide modest efficacy in plaque psoriasis patients; therefore, patients are increasingly being treated with biologic agents, such as Tumor Necrosis Factor-alpha inhibitors (etanercept and adalimumab), an interleukin (IL)-12/23 inhibitor (ustekinumab),[5] and IL-17A inhibitors (secukinumab and ixekizumab). In addition, other recently approved systemic agents for the treatment of psoriasis include an IL-17RA inhibitor (brodalumab) and IL-23p19 inhibitors (risankizumab, guselkumab and tildrakizumab).

While the clinical efficacy of ustekinumab indicates a role for both IL-12 and IL-23 in the pathogenesis of psoriasis,[6] more recent data suggest that IL-23 is disproportionately involved in the maintenance of chronic psoriasis.[7] IL-23 is thought to be involved in the pathophysiology of psoriasis via induction and maintenance of T helper 17 (Th17) type cells, and other IL-23 responsive cells. This is supported by recent clinical data indicating that monoclonal antibodies that block IL-17A (the cytokine produced by Th17 cells), IL-17RA, and direct blockade of IL-23 with IL-23p19 inhibitors, have high efficacy in psoriasis.[6,8-10]

There is still clinical need for increased efficacy as the most effective anti-TNF and anti-IL-12/23 agents provide approximately 75% improvement in psoriasis in about 50 to 80% of patients and these responses can be lost over time. Although the anti-IL-17A, -IL-17RA, and -IL-23p19 agents (i.e., secukinumab, ixekizumab, brodalumab and guselkumab) may provide better efficacy than anti-TNF therapies and ustekinumab, they require monthly, every other month, or quarterly injections.[6,8-10] There remains an unmet medical need for an oral medication targeting the validated IL-17 pathway to potentially deliver efficacious intervention in dermatological indications.

Cedirogant is an inverse agonist of retinoic acid-related orphan receptor gamma, thymus (RORγt), a key transcription factor responsible for IL-17 synthesis in vivo and the master regulator of the Th17 cell lineage program. RORγt expression is driven by IL-23 and directly supports IL-17 production in multiple immune cell types, particularly Th17 cells; thus, RORγt bridges the gap between these 2 important cytokines. Targeting RORγt has the potential to directly block cellular function (i.e., RORγt-dependent genes), a different strategy from the neutralization of effector molecules (such as IL-17) by biologics.

This dose ranging study is designed to explore the range of efficacious and tolerated doses in adult subjects with moderate to severe chronic plaque psoriasis for determination of the dose(s) to be selected for a pivotal Phase 3 program in psoriasis.

Clinical Hypothesis

Cedirogant is superior to placebo in achieving ≥ 75% reduction from baseline in the Psoriasis Area and Severity Index score (PASI 75) at Week 16 in patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

2.2 Benefits and Risks to Subjects

Based on the available preclinical and clinical data, cedirogant is expected to demonstrate therapeutic benefit in the treatment of chronic plaque psoriasis. Study drugs may be associated with adverse events (AEs) as detailed in the subject informed consent form(s). Not all of the potential side effects of the study drugs may be known. In addition, subjects may experience discomfort or inconvenience related to study procedures.

Medical review of the safety data from the Phase 1 program with cedirogant (including Study M17-239, a single ascending dose study; Study M17-238, a multiple ascending dose [MAD] study; Study M18-809, a multiple dose study; and Study M19-371, a single and multiple dose study) did not identify any unexpected risk or trend in the healthy volunteer population or patients with chronic plaque psoriasis. No drug related ocular events, such as those observed in a different compound of the same chemical class, have been observed in the Phase 1 studies of cedirogant.

In Study M21-560, conducted in healthy volunteers to evaluate the effects of cedirogant on QT interval, no clinically relevant QT prolongation was observed following the administration of 375 mg or 750 mg doses of cedirogant, with mean placebo-corrected change from baseline in Fridericia-corrected QT interval of 4 and 6 milliseconds, respectively. Based on these results, standard electrocardiogram (ECG) eligibility criteria (Section 5.1) are considered appropriate.

In Study M18-809, conducted in healthy volunteers to evaluate the modulatory effects of cedirogant on cytochrome P450 (CYP) enzymes, cedirogant showed moderate CYP3A and CYP2C19 induction potential with a 375 mg QD regimen, and a limited effect was observed on CYP2C9 while no clinically relevant effects were observed on CYP1A2 or CYP2D6.

In Study M20-115, conducted in healthy volunteers to evaluate potential drug-drug interactions between cedirogant and statins at steady state, co-administration of 375 mg QD cedirogant resulted in a 160% and 70% increase in C_{max} and AUC_{0-24} of rosuvastatin, respectively; resulted in no change in AUC and 40% increase in C_{max} of atorvastatin; and resulted in an 85% and 40% increase in C_{max} and AUC_{0-24} of the active metabolite of atorvastatin (ortho-hydroxy atorvastatin), respectively. Taken together, the safety and efficacy data from the Phase 1 program support further development of cedirogant in Phase 2 in subjects with psoriasis. Refer to Section 5.1 for instructions on daily use limits of concomitant statins.

For further details, please see findings from completed studies, including safety data, in the current cedirogant Investigator's Brochure.

In view of the Coronavirus Disease - 2019 (COVID-19) pandemic, the benefit: risk profile of various immunomodulatory therapies on COVID-19 is being evaluated. At this time, the effects of cedirogant on the course of COVID-19 are not well defined.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary Objective

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.

- Primary efficacy objective: The primary efficacy objective of the study is to demonstrate a higher rate of subjects achieving PASI 75 at Week 16 with cedirogant compared to placebo in the Intent-to-Treat (ITT) population, which consists of all randomized subjects (further described in Section 7.2).

The hypothesis corresponding to the primary endpoint is the proportion of subjects achieving PASI 75 at Week 16 with cedirogant is greater than that with placebo. The estimand corresponding to the primary endpoint is defined as the difference in the proportion of subjects achieving PASI 75 at Week 16, regardless of treatment discontinuation, between each of the cedirogant dose groups compared with placebo in the ITT Population.

Secondary Objectives

The secondary efficacy objectives are to demonstrate higher rates of subjects who achieve the secondary endpoints specified in Section 3.3 below in the ITT population.

3.2 Primary Endpoint

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

3.3 Secondary Endpoints

Secondary Endpoints

- 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

3.4 Additional 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). 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

3.5 Safety Measures

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.

3.6 Pharmacokinetic Endpoints

Plasma cedirogant concentrations, possible metabolite(s), and if warranted, relevant concomitant medications will be obtained at the visits indicated in the Activity Schedule (Appendix D). A nonlinear mixed effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of cedirogant oral clearance (apparent clearance) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

3.7 Biomarker Research Endpoints

Optional biospecimens (e.g., whole blood for plasma, serum, peripheral blood mononuclear cell [PBMC], RNA, DNA, and tissue biopsy) will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers in circulation or at tissue sites. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to: blood leukocyte subpopulations, serum and plasma cytokine evaluations, transcriptomic, genetic, epigenetic analysis, and tissue genomic and histopathological analysis to evaluate biomarker endpoints related to safety, disease state, response to treatment, and target pathway. The biomarker research results may not be included with the clinical study report. Further details regarding the biomarker research rationale and collection time points are located in the Operations Manual, Section 2.1 and Section 3.16.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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.

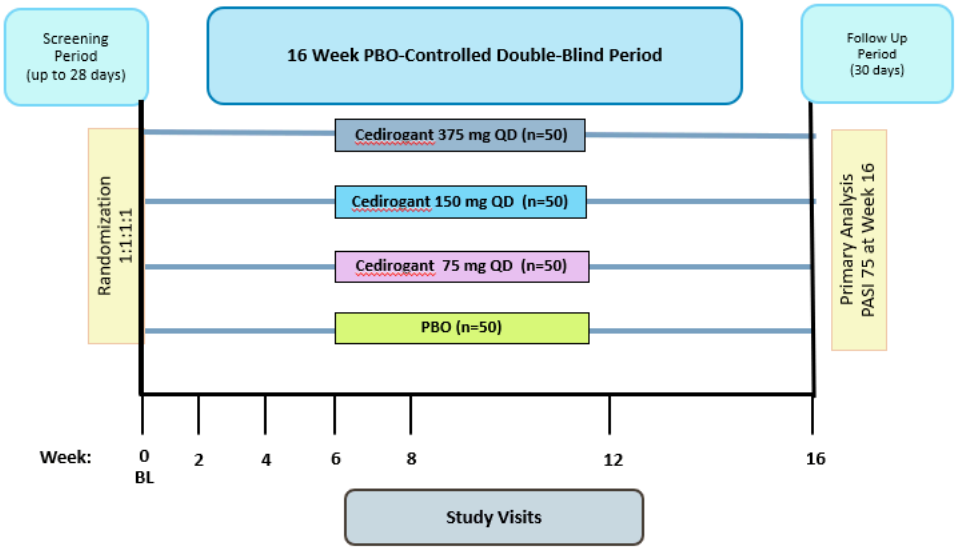
Subjects who meet eligibility criteria at Baseline will be randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups:

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

The schematic of the study is shown in Figure 1. Clinical assessments, laboratory tests, collection of samples for cedirogant concentration, optional biomarker samples and optional skin biopsies will be performed at specified clinic visits as noted in the Study Activities Table (Appendix D). Further details regarding study procedures are located in the Operations Manual (Appendix F). See Section 5 for information regarding eligibility criteria.

An interim analysis will be conducted after the first 140 subjects have either completed the Week 16 assessments or withdrawn from the study. Study sites and subjects will remain blinded for the duration of the study.

Figure 1. Study Schema



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

4.2 Discussion of Study Design

Choice of Control Group

Placebo has been selected as the appropriate control group to evaluate the efficacy endpoints as double-blind, placebo-controlled study designs are generally acknowledged as standard for unbiased estimates of treatment (cedirogant versus placebo) differences.

Appropriateness of Measurements

Standard (i.e., widely used and generally recognized as reliable, accurate, and relevant [able to discriminate between effective and ineffective agents]) statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for assessing disease activity in subjects with plaque psoriasis. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

This Phase 2 study will provide essential efficacy and safety data for cedirogant for the indication of moderate to severe plaque psoriasis. Efficacy results of cedirogant in a Phase 1 study of subjects with plaque psoriasis showed a potential therapeutic effect to improve disease activity. Safety results of cedirogant in healthy volunteers and subjects with plaque psoriasis indicate no safety issues of concern and no dose limiting toxicity.

Selection of Doses in the Study

The cedirogant doses to be administered in this study are 75, 150, and 375 mg QD. Based on analyses of ex-vivo IL-17A inhibition by cedirogant in Phase 1 studies, the 75 mg QD dose is predicted to have a submaximal therapeutic effect. The 150 mg QD dose is predicted to approach the plateau and the 375 mg QD dose is predicted to be approximately at the plateau for inhibition of ex-vivo IL-17A by cedirogant. All three doses are expected to have plasma exposures in PsO patients which are within the exposures previously evaluated in Phase 1 single ascending dose and MAD studies, and those achieved in preclinical toxicology studies up to 16 weeks in duration.

Based on the pharmacokinetic (PK) data at cedirogant doses of 75 to 375 mg in the MAD study in healthy subjects (Study M17-238 Substudy 1), the cedirogant dose of 75 mg is expected to provide steady-state cedirogant AUC_{tau} of approximately 51 µg•hr/mL.

Based on the PK data from the multiple dose study in psoriasis patients (Study M17-238 Substudy 2), the highest planned dose of 375 mg QD is expected to provide steady-state cedirogant AUC_{tau} of approximately 206 µg•hr/mL.

Cedirogant safety margins at the highest planned dose of 375 QD are approximately 8-fold based on the exposure (area under the curve [AUC]) at the no-observed-adverse-effect-level (NOAEL) in the rat, and 11-fold based on the dog NOAEL in the 4-week toxicity study (no NOAEL defined in the 16-week dog study).

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects or their legally authorized representative must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, at least 18 years old and not more than 65 years of age at the time of Screening.
- 3. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum aspartate transaminase (AST) < 2 × upper limit of normal (ULN);
  - Serum alanine transaminase (ALT) < 2 × ULN;
  - Total Bilirubin ≤ 1.5 × ULN

- Total white blood cell (WBC) count > 3,000/µL;
- Absolute neutrophil count > 1,500/µL;
- Platelet count > 100,000/µL;
- Hemoglobin > 9 g/ (dL);

✔ 4. Are willing and able to comply with procedures required in this protocol.

Disease/Condition Activity

✔ 5. Subjects must have a clinical diagnosis of moderate to severe chronic plaque psoriasis with a disease duration of at least 6 months as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by the investigator.

✔ 6. Subjects must be a candidate for systemic therapy or phototherapy and meet the following disease activity criteria at both Screening and Baseline visits:

- Subjects must have a PASI score ≥ 12;
- Subjects must have a sPGA score of 3 or 4;
- Subjects must have a body surface area (BSA) affected by psoriasis ≥ 10%.

✔ 7. Subjects must not be primary non-responders to previous anti-IL-17 (e.g., secukinumab, ixekizumab, brodalumab), anti-IL-23 (e.g., guselkumab, tildrakizumab, risankizumab), or anti-IL-12/23 (e.g., ustekinumab) treatment for chronic plaque psoriasis.

✔ 8. Subjects must not be diagnosed with erythrodermic psoriasis, generalized or localized pustular psoriasis, medication-induced or medication exacerbated psoriasis, or new onset guttate psoriasis or any other active skin disease which may interfere with assessment of chronic plaque psoriasis.

Subject History

✔ 9. Subjects are judged to be in good health as determined by the Principal Investigator, based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead ECG performed during Screening.

✔ 10. No history of hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV), or active infection with tuberculosis (TB) or infections requiring intravenous (IV) treatment.

- No evidence of HBV or HCV infection defined as the following:
  - HBV: Hepatitis B surface antigen (HBs Ag) positive (+) test or detected sensitivity on the HBV DNA polymerase chain reaction (PCR) qualitative test for subjects who are HB core antibody (HBc Ab) positive (+) (and for HB surface antibody [Hbs Ab] positive (+) subjects where mandated by local requirements).
  - HCV: HCV RNA detectable in any subject with anti HCV antibody (HCV Ab).
- No evidence of HIV, defined as confirmed positive anti-HIV antibody test.

- No evidence of active TB: Subjects with a positive QuantiFERON-TB gold test (or interferon gamma release assay [IGRA] equivalent) or TB skin test may participate in the study if further work up (according to local practice / guidelines) establishes conclusively that the subject has no evidence of active TB. If the presence of latent TB is established, subjects are required to be treated with prophylactic anti-TB therapy for at least 2 weeks prior to initiation of cedirogant. Specific requirements for TB testing and prophylaxis are located in the Operations Manual, Section 3.14.
- No infections (bacterial, fungal or viral) requiring IV systemic treatment within 4 weeks of the Baseline Visit.

11. No known active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., PCR) test result or 2 negative antigen test results at least 24 hours apart. Note: SARS-CoV-2 diagnostic tests should be applied following local requirements/recommendations.

12. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:

- At least 10 days since first positive test result have passed in asymptomatic patients or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

13. No 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.

14. No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months, including medicinal or recreational cannabis or cannabinoids.

15. No evidence of uncontrolled thyroid disease.

16. No history of organ transplantation.

17. No major surgery performed within 12 weeks prior to randomization or planned during the conduct of the study (e.g., hip replacement, aneurysm removal, stomach ligation).

18. No history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.

19. No clinically relevant or significant ECG abnormalities or risk factors for torsade de pointes, including:

- Evidence of second or third degree atrioventricular block at Screening or Baseline;
- QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) is > 430 msec (males) or > 450 msec (females) at Screening or Baseline;
- History of QTc prolongation, bradyarrhythmia or clinically significant bradycardia or subjects with a resting heart rate of < 50 beats per minute;
- Family history of QTc prolongation or sudden cardiac death in immediate family members < 30 years of age.

- 20. No history of clinically significant medical conditions other than the indication being studied or any other reason that the investigator determines would interfere with the subject's participation in this study, would make the subject an unsuitable candidate to receive study drug, or would put the subject at risk by participating in the protocol.

Contraception

- 21. For all females of childbearing potential; a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug.
- 22. Females of childbearing potential must practice at least 1 protocol-specified method of birth control, that is effective from Baseline through at least 30 days after the last dose of study drug. If hormonal contraception is used, an additional barrier method (such as condoms with spermicide) must be used. Female subjects of non-childbearing potential do not need to use birth control.
- 23. Females who are not pregnant or breastfeeding, and are not considering becoming pregnant or donating eggs during the study or for approximately 30 days after the last dose of study drug.

Prior and Concomitant Medications

- 24. Subjects must not have been treated with any prohibited medications as specified in Section 5.3.
- 25. Subjects must not require daily use of rosuvastatin at doses higher than 10 mg, pitavastatin at doses higher than 2 mg, pravastatin at doses higher than 40 mg, fluvastatin at doses higher than 20 mg, atorvastatin at doses higher than 40 mg, or lovastatin at doses higher than 40 mg. Use of simvastatin at any dose is allowed.
- 26. Subjects must not have been treated with any investigational non-biologic drug within 30 days or 5 half-lives of the drug (whichever is longer) or 12 weeks for biologic investigational therapy prior to the first dose of study drug, or is currently enrolled in another clinical study. Examples of investigational non-biologic drugs include but are not limited to: phosphodiesterase 4 (PDE4) inhibitors such as orismilast, and Janus kinase (JAK) inhibitors (including JAK1-3 and tyrosine kinase 2 inhibitors such as tofacitinib or deucravacitinib).
- 27. Subjects must not have systemically used known strong CYP3A inhibitors (for example, clarithromycin or itraconazole) or inducers (for example, phenytoin or rifampin) from Screening through the end of the study.
- 28. Subjects must not have received any live vaccine within 28 days prior to the first dose of study drug (or longer if required locally) or expected need of live vaccination during study participation including at least 30 days after the last dose of study drug.

Other

- 29. Subjects must not have been previously exposed to cedirogant or any other RORγt inhibitors such as vimirogant.
- 30. Subjects must be willing and able to comply with procedures required in this protocol.

- 31. In the opinion of the investigator, the subjects are suitable candidates for enrollment in this study.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Premenopausal females with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
  2. Postmenopausal females
     - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
     - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level ≥ 30 IU/L.

- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 30 days after the last dose of study drug.
  - The efficacy of hormonal contraception is potentially decreased due to interaction with cedirogant; therefore, a barrier contraception, such as condoms with or without spermicide, must be used in addition to the hormonal contraception methods (combined oral contraception, progestogen only hormonal contraception and Intrauterine hormone-releasing system [IUS]) listed below. Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation-initiated at least 30 days prior to Baseline.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to Baseline.

- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure). For Japan: only bilateral tubal ligation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
- Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

- If required per local guidelines, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

5.3 Prohibited Medications and Therapy

The following medications are prohibited within the specified timeframe prior to Baseline Visit and through the duration of the study:

- Topical therapies for the treatment of chronic plaque psoriasis such as corticosteroids, vitamin D analogs, or retinoids, within 2 weeks.
- Phototherapy (e.g., UVA or UVB) and Psoralen + ultraviolet light A (PUVA) phototherapy, tanning beds, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks.
- Systemic non-biologic therapies for the treatment of chronic plaque psoriasis (including but not limited to corticosteroids, oral retinoids, methotrexate, apremilast, cyclosporine) or known to improve chronic plaque psoriasis within 4 weeks.
- Biologic therapies to treat psoriasis:
  - Etanercept or biosimilar versions within 6 weeks
  - Adalimumab, infliximab, or biosimilar versions within 12 weeks
  - Ixekizumab, brodalumab, or other IL-17 inhibitors (excluding secukinumab) within 16 weeks
  - Ustekinumab, secukinumab, risankizumab, guselkumab, tildrakizumab, bimekizumab, or other IL-23 inhibitors within 24 weeks.
- Any investigational non-biologic for the treatment of chronic plaque psoriasis within 4 weeks or 5 half-lives (whichever is longer).
- Any investigational biologic for psoriasis within 12 weeks or 5 half-lives (whichever is longer).

- Subjects may not use herbal therapies or other traditional medicines within 4 weeks.
- Subjects may not have systemic use of drugs that are strong CYP3A inhibitors (for example, clarithromycin or itraconazole) or inducers (for example, phenytoin or rifampin) within 4 weeks.
- Vaccines: Live vaccines are prohibited within 28 days prior to the first dose of study drug or during study participation and including at least 30 days (or longer if required locally) after the last dose of study drug. If the subject and investigator choose to receive / administer live vaccines, these vaccinations must be completed at least 28 days (or longer if required locally) before the first dose of study drug with appropriate precautions. Although not mandated by the protocol, vaccines recommended by local guidelines should be considered. Examples of live vaccines include but are not limited to the following:
  - Monovalent live attenuated influenza A (H1N1) (intranasal);
  - Seasonal trivalent live attenuated influenza (intranasal);
  - Zostavax (herpes zoster, live attenuated);
  - Rotavirus;
  - Varicella (chicken pox);
  - Measles-mumps-rubella or measles-mumps-rubella varicella;
  - Oral polio vaccine;
  - Smallpox;
  - Yellow fever;
  - Bacille Calmette-Guérin;
  - Typhoid (oral)
- Administration of inactivated (non-live) vaccines is permitted prior to or during the study according to local practice guidelines. Examples of common vaccines that are inactivated, toxoid or biosynthetic include but are not limited to the following:
  - Injectable influenza vaccine;
  - Pneumococcal;
  - Shingrix (zoster vaccine, recombinant, adjuvanted);
  - Pertussis (Tdap) vaccine

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded from 30 days prior to study drug administration through the post-treatment visit (30 day Follow-up Visit).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with cedirogant can be located in the cedirogant Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited medications within 30 days or 5 half-lives (whichever is longer) prior to initial study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Cedirogant showed moderate induction of CYP3A and CYP2C19 at a dose of 375 mg QD. Therefore, concomitant administration of cedirogant may decrease the plasma concentrations and efficacy of drugs that are sensitive substrates for CYP3A or CYP2C19 (e.g., simvastatin, omeprazole).

SARS CoV-2 Vaccination

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., messenger RNA [mRNA], non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of cedirogant on SARS-CoV-2 vaccination is unknown.

COVID-19 Vaccine: Whenever-possible, subjects should not have received a COVID-19 vaccination in the 7 days prior to randomization or plan to receive a COVID-19 vaccination within the first 7 days after initiation of study drug.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete treatment course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with psoriasis and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine electronic case report form (eCRF). Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

AbbVie may terminate this study prematurely, either in its entirety or partially (discontinue one or more treatment group[s]), at any site. The study may be discontinued or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. This might include the occurrence of AEs with a character, severity or frequency that is new in comparison to the existing risk profile. In addition, data derived from other clinical trials or toxicological studies which negatively influence the benefit-risk assessment might cause discontinuation or termination of the study. In the event the study is partially terminated, all subjects in the terminated arm(s) will be asked to return for a PD visit and to perform a 30-day follow-up phone call after the last dose of study drug.

The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator. Advance notice is not required by either party if the study is stopped due to safety concerns.

A subject may voluntarily withdraw or be withdrawn from the study at any time for any reason. An investigator may discontinue a subject's participation at any time for any reason. The AbbVie Therapeutic Area Medical Director (TA MD) may mandate individual subject discontinuation from study drug in case of a safety concern. Subjects may be discontinued for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie TA MD.
- Grade 2 or higher ocular AEs considered related to study drug administration (this is referenced in the 6.2 toxicity management section of the protocol).
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk. Note: intentional/prospective deviations from the protocol are NOT allowed, see Section 5.9.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- Subject is diagnosed with a malignancy; exception localized NMSC or carcinoma in situ of the cervix where discontinuation is at the discretion of the investigator.
- Subject is noncompliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- The subject becomes pregnant while on study drug.
- Subject is significantly noncompliant with study procedures.
- Any subject administered study drug having confirmed ECG changes that are considered clinically significant and considered related to study drug, or a confirmed absolute QTcF value > 500 msec, or a confirmed absolute QTcF value change from baseline > 60 msec.

Subjects who withdraw from the study will not be replaced.

State of Emergency or Pandemic-Related Acceptable Protocol Modification

During states of emergency or pandemic situations, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

During the study drug dosing period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- At least 10 days since first positive test result have passed in asymptomatic patients or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Follow subsequent protocol Section 5.6 for subjects who discontinued study drug. Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

Discontinuation of Study Drug and Continuation of Study Participation

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits as outlined in the Protocol Activities Schedule in the Operations Manual (Appendix F, Section 2) and adhere to all study procedures except for administration of study drug and PK sample collection unless a subject decides to discontinue study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early. Subjects who prematurely discontinue study drug treatment should remain compliant with the prohibited medication requirements while participating in the study.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

If a subject prematurely discontinues study participation, the procedures outlined for the Premature Discontinuation Visit should be completed as soon as possible, preferably within 2 weeks. In addition, a 30-day follow-up phone call after the last dose of study drug will be completed to ensure all treatment-emergent AEs/serious adverse event (SAE) have been resolved.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the subject has withdrawn and no longer wishes biomarker samples research to continue, samples will not be analyzed, no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s), and the samples will be destroyed. A subject may withdraw consent for optional

biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

Cedirogant and matching placebo will be manufactured by AbbVie (Table 1). Each dose will be taken orally QD beginning on Day 1 (Baseline) and should be taken at approximately the same time each day. The study drug can be taken with or without food. If subjects should forget to take their cedirogant or matching placebo dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember as long as it is at least 12 hours before their next scheduled dose. Otherwise, they should skip the missed dose and take the next dose at the next scheduled dosing time. The phototoxic potential of cedirogant is unknown; therefore, pending further evaluation, subjects will be cautioned to limit sunlight exposure during the study and for 30 days after the last dose of study drug.

Subject dosing will be recorded on a subject dosing diary. The subject will be instructed to return all blister cards (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

AbbVie will provide study drug for cedirogant or matching placebo. If a subject is unable to come to the study site to pick up their study drug due to a pandemic or emergency situation, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual in Appendix F for details on DTP shipment of study drug.

Cedirogant and matching placebo will be packaged in blister cards with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

Table 1. Identity of Investigational Products

	Cedirogant	Placebo for Cedirogant
Dosage form	Capsule	Capsule
Strength	75 mg	N/A
Dosage	75, 150, and 375 mg	N/A
Route of administration	Oral	Oral
Manufacturer	AbbVie	AbbVie

N/A = not applicable

5.8 Randomization/Drug Assignment

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.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the cedirogant capsules and placebo capsules provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

In the event of a medical emergency that requires unblinding of the study drug assignment, the investigator is requested to contact the AbbVie TA MD prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie TA MD, the investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Subject Unblinding by Site transaction, which is available only to the investigator. If the IRT system is unavailable, unblinding may occur by contacting the technical support of the IRT vendor via either phone (preferred) or email (global.helpdesk@cenduit.com). For country-specific phone numbers, please see the following website: https://www.cenduit.com/support-247-global-help-desk.

In the event the blind is broken before notification to the AbbVie TA MD, the AbbVie TA MD should be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on appropriate eCRF.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to states of emergency or pandemic situations), the investigator is responsible for notifying IEC/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

5.10 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, with relevant expertise in their field will review unblinded data from the ongoing study. The DMC is responsible for safeguarding the interests of trial subjects by assessing the safety of the interventions during the trial, as well as for monitoring the integrity and interpretability of the trial. When needed, high-level unblinded efficacy data may also be requested by the DMC and reviewed so that the DMC can assess benefit/risk of any emerging safety differences. A separate DMC charter will be prepared outside of the protocol and will further describe

the roles and responsibilities of the DMC members, frequency and scope of the data reviews, and expectations for blinded communications. The DMC will provide recommendations to the study team regarding ongoing trial conduct or modifications to the trial as described in the separate DMC charter. Communications from the DMC to the study team will not contain information that could potentially unblind the primary study team to subject treatment assignments.

In order to maintain blinding, a statistical data analysis center (SDAC) is responsible for performing the analyses described in the DMC charter as well as additional analyses requested by the DMC and facilitating interpretation and answering questions that arise before, during or after DMC review.

The DMC will review unblinded safety data from the ongoing study according to the schedule provided in the DMC charter, including AEs, laboratory values, vitals sign values and ECG results.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness including chronic plaque psoriasis is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If any of the following Safety Topics of Interest events are reported, then the following supplemental report must be completed.

Event	Supplemental Report
Cardiac events **Myocardial infarction or unstable angina** **Heart failure** **Cerebral vascular accident and transient ischemic attack** **Cardiovascular procedures (SAE Supplemental Procedure eCRF)**	• Cardiovascular History and CV Risk Factors eCRF • Cardiovascular (Cardiac) AE eCRF • Myocardial Infarction and Unstable Angina AE eCRF • Heart Failure AE eCRF • Cerebral Vascular Accident and Transient Ischemic Attack AE eCRF • Arrhythmia AE eCRF
Discontinuation or interruption of study drug due to a hepatic-related AE **A hepatic-related SAE** **ALT/AST > 8 × ULN or ALT/AST > 3 × ULN with a total bilirubin > 2 × ULN**	Hepatic AE eCRF
TB Subjects with events of latent TB or suspected active TB after initiation of study drug should have a TB Supplemental Form completed.	TB Supplemental eCRF
COVID-19 infection	COVID-19 eCRF
Ocular events	Ophthalmologic eCRF
Herpes Zoster	Herpes Zoster eCRF
Hypersensitivity	Hypersensitivity Reaction Signs and Symptoms eCRF
Death	Death eCRF

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.3 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.

Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

Safety Topics of Interest

Adverse events will be monitored throughout the study to identify any safety topics of interest that may indicate a trend or risk.

The potential for abdominal distention, gastrointestinal pain, vomiting, diarrhea and eye pain, redness or blurred vision has been identified.

No ocular findings were seen in the preclinical studies conducted with cedirogant and no ocular AEs considered related to drug have been reported in the cedirogant Phase 1 studies to date. There have been no reports of ocular findings in the literature with other products in development of the same mechanism of action.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0).

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Toxicity Management

The toxicity management of the AEs including safety topics of interest consists of safety monitoring (review of AEs on an ongoing basis, and periodic/ad hoc review of safety issues by an independent Data Monitoring Committee), and, if applicable, interruption of study drug dosing with appropriate clinical management and/or discontinuation of the subjects from study drug. The management of specific AEs and laboratory parameters is described below.

Serious Infections: Study drug should be interrupted if a subject develops a serious infection. Study drug may be restarted once the infection has been successfully treated. Subjects who develop active TB must be permanently discontinued from study drug.

Ocular Events: Any subject with CTCAE Grade 2 or higher AE ocular event or considered to be necessary by investigator must follow up with an ophthalmologist as soon as possible, but within 7 days at the latest. Grade 2 or higher ocular AEs considered related to study drug administration qualify for withdrawal criteria.

Management of Laboratory Abnormalities:

- All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution. If a repeat test is required, the repeat testing is to occur as soon as possible.
- In case of confirmed creatine phosphokinase > 5 × ULN accompanied by muscle related symptoms and without a clear alternate etiology (e.g., trauma), interrupt study drug and evaluate.
- Study drug should be discontinued for the following laboratory abnormalities:

- Occurrence of one or more of the following hepatic test abnormalities (confirmed on a second separate sample):
  - ALT or AST > 8 × ULN;
  - ALT or AST > 5 × ULN for more than 2 weeks;
  - ALT or AST > 3 × ULN and Total Bilirubin > 2 × ULN or international normalized ratio [INR] > 1.5;
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

Elective and Emergency Surgeries

For elective and emergency surgeries the following rules will apply:

If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that study drug may be safely restarted.

Elective surgery, and interruption of study drug for such a surgery, will not be allowed until after the Week 16 visit has been completed. If the subject undergoes elective surgery, the study drug should be interrupted at least 1 week prior to the planned surgery. Allow reintroduction of study drug once the physician has examined the surgical site and determined that study drug may be safely restarted.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on analyses of primary and secondary endpoints. Complete and specific details of the statistical analysis will be described in the statistical analysis plan (SAP).

The Primary Analysis will be conducted after all subjects have completed Week 16 of the treatment period or withdrawn from the study, data has been cleaned and a database lock has occurred.

An interim analysis will be conducted after the first 140 subjects have either completed the Week 16 assessments or withdrawn from the study. The study team will remain blinded during the conduct of the interim analysis and the analysis results will not be released to the study team. Study sites and subjects will remain blinded for the duration of the study.

7.2 Definition for Analysis Populations

The following populations will be used for analyses:

- Intent-to-Treat (ITT) Population: The 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.
- Safety Population: 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.

7.3 Handling Potential Intercurrent Events for the Primary Endpoint

The primary endpoint (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.

7.4 Statistical Analyses for Efficacy

The efficacy analysis will be conducted in the ITT Population and all statistical tests will be performed at a 2-sided significance level of 0.1. The 95% confidence interval of the treatment effect will be provided.

For categorical endpoints, comparisons will be made between each dose of cedirogant and placebo using Fisher's exact test. Non-responder imputation (NRI) incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-MI) will be the primary approach to handle missing values for categorical endpoints.

For continuous variables, comparisons of change and/or percent change from Baseline will be made between each dose of cedirogant and placebo based on the Mixed Model Repeated Measures (MMRM) adjusting for treatment, visit, and treatment-by-visit interaction as fixed factors, and Baseline value as a covariate. The MMRM will be the primary approach to handle missing values for continuous endpoints.

Summary and Analysis of the Primary Endpoint

The primary endpoint is the achievement of PASI 75 score at Week 16. Analysis of the primary endpoint will be conducted on the ITT Population based on treatment as randomized. Comparison of the primary endpoint will be made between each cedirogant dose and placebo using Fisher's exact test at a 2-sided significance level of 0.1.

The NRI-MI method will be the primary approach to handle missing values. A sensitivity analysis will be performed for the primary endpoint, using MI to handle all missing values.

Summary and Analysis of Secondary Endpoints

Categorical endpoints will be analyzed using Fisher's exact test. The comparisons of all the secondary endpoints will be made between each cedirogant dose and placebo at a 2-sided significance level of 0.1.

Summary and Analysis of Additional Efficacy Endpoints

Additional endpoints, as described in Section 3.4, will also be analyzed. Analysis details will be provided in the SAP.

Subgroup Analysis for Efficacy

To evaluate the consistency of efficacy across demographic and other baseline characteristics, summaries and analyses will be performed for selected subgroups for the primary endpoints. The subgroups will be defined in SAP.

7.5 Statistical Analyses for Pharmacokinetics

Plasma concentrations will be tabulated for each subject and summarized using descriptive statistics.

Data from this study may be combined with data from other studies for the population PK and exposure-response analyses. Population PK and exposure-response analyses of only data from this study may not be conducted.

7.6 Statistical Analyses for Safety

All safety analyses will be performed on the Safety Population, based on the actual treatment received. Treatment-emergent adverse events (TEAEs), laboratory assessments, and vital signs will be summarized. Details will be described in the SAP.

A TEAE for the Safety Population is defined as an AE newly occurred or worsened after the first dose of study drug and within 30 days after the last dose of study drug. The number and percentage of subjects experiencing TEAEs and exposure-adjusted number of events (events per 100 year) will be tabulated using the MedDRA system organ class and preferred term, by severity, and by relationship to the study drug as assessed by the investigator. Summaries (including percentages and events per 100 patient years) of SAEs, deaths, and AEs leading to discontinuation will also be provided.

Mean change in laboratory and vital signs variables will be summarized. For selected laboratory parameters, a listing of all subjects with any laboratory value that is Grade ≥ 3 of NCI CTCAE v4.03 will be provided. Additional details for the safety analysis will be provided in the SAP.

7.7 Interim Analysis

An interim analysis will be performed by an independent team at AbbVie after the first 140 subjects have either completed the Week 16 assessments or withdrawn from the study. The objective of this analysis is to assess the benefit and risk profile of the treatment regimens and initiate preparation of cedirogant to the next development stage. As this interim analysis is not intended for the claim of

success of this study, there will be no alpha spending for this interim analysis. An Interim Unblinding Plan will be developed to describe the analyses to be performed and will include execution logistics, unblinded analysis team, and the data chain of custody to protect the integrity of the study. An Internal Executive Review Committee (IERC) will review the interim unblinded results following the IERC charter. The study team will remain blinded.

7.8 Overall Type I Error Control

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

7.9 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.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators

should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial complies with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During states of emergency or pandemic situations, remote source data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as 30 days after the last study drug administration.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the curve
AUC_{inf}	area under the concentration-time curve from time 0 to infinite time
AUC_{tau}	area under the concentration-time curve over the dosing interval
BSA	body surface area
COVID-19	Coronavirus Disease – 2019
CTCAE	Common Terminology Criteria for Adverse Events
CXR	chest x-ray
CYP	cytochrome P450
CYP3A	cytochrome P450 3A isoform subfamily
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DTP	direct-to-patient
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FSH	follicle-stimulating hormone
GCP	Good clinical practice
HADS	Hospital Anxiety and Depression Scale
HB	hepatitis B
HBc Ab	hepatitis B core antibody
HBs Ab	hepatitis B surface antibody
HBs Ag	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	HCV antibody
HIV	human immunodeficiency virus

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IERC	Internal Executive Review Committee
IGRA	interferon gamma release assay
IL	interleukin
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-Treat
IUS	Intrauterine hormone-releasing system
IV	intravenous
JAK	Janus kinase
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	Mixed Model Repeated Measures
mRNA	messenger RNA
NCI	National Cancer Institute
NMSC	non-melanoma skin cancer
NRI	Non-Responder Imputation
NRS	Numerical Rating Scale
OR	odds ratio
PASI	Psoriasis Area Severity Index
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PDE4	phosphodiesterase 4
PK	pharmacokinetic(s)
PPD	purified protein derivative
PRO	patient-reported outcome
PSS	Psoriasis Symptoms Scale
PUVA	psoralen-UV-A
QD	once daily

QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	ribonucleic acid
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDAC	Statistical Data Analysis Center
SUSAR	Suspected Unexpected Serious Adverse Reactions
sPGA	static Physician Global Assessment
TA MD	Therapeutic Area Medical Director
TB	tuberculosis
TEAE	treatment-emergent adverse event(s)
Th17	T helper 17
TSH	thyroid-stimulating hormone
TSQM-9	Treatment Satisfaction Questionnaire for Medication Version 9
ULN	upper limit of normal
V/F	apparent volume of distribution
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol 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.

Protocol Date: 13 May 2022

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
1. Personally conducting or supervising the described investigation(s).
2. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
3. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
4. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
5. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
6. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
7. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
8. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
9. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Study Leadership
[redacted]	[redacted]	Clinical Study Leadership
[redacted]	[redacted]	Medical Writing
[redacted]	[redacted]	Therapeutic Area Medical Monitor
[redacted]	[redacted]	Global Pharmaceutical R & D
[redacted]	[redacted]	Statistics
[redacted]	[redacted]	Clinical Pharmacology and Pharmacometrics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the 11 subject encounters. The individual activities are described in detail in the Operations Manual (Appendix F). Allowed modifications due states of emergency or pandemic situations are detailed in the Operations Manual.

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Study Activities Table

Activity	Screening	Randomization/ Baseline	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Premature Discontinuation	30-Day Follow Up Call
INTERVIEWS & QUESTIONNAIRES										
Informed consent	✓									
Demographics	✓									
Medical history including disease specific history	✓									
Drug and alcohol history	✓									
Eligibility criteria	✓	✓								
TB Risk Assessment	✓									
AE assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Record prior and concomitant medication/therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medical history update		✓								
DLQI		✓		✓			✓	✓	✓	
HADS		✓		✓				✓	✓	
Itch NRS daily diary		✓	✓	✓	✓	✓	✓	✓	✓	
PSS daily diary		✓	✓	✓	✓	✓	✓	✓	✓	
TSQM-9				✓				✓	✓	
WPAI: Psoriasis		✓		✓				✓	✓	
Dispense subject diaries		✓								
Subject diary review			✓	✓	✓	✓	✓	✓	✓	
Phone visit										✓

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Activity	Screening	Randomization/ Baseline	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Premature Discontinuation	30-Day Follow Up Call
LOCAL LABS & EXAMS										
12-lead ECG (single)	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Complete physical exam (including height [at screening only] and weight)	✓	✓						✓	✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CXR	✓									
BSA	✓	✓						✓	✓	
sPGA	✓	✓	✓	✓	✓	✓	✓	✓	✓	
PASI	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Urine pregnancy test (WOCBP)		✓		✓		✓	✓			
Optional: Skin biopsy		✓		✓				✓		
Optional: Wound care after biopsy			✓		✓					
CENTRAL LABS										
Hepatitis panel	✓									
HIV test	✓									
FSH (for post-menopausal women)	✓									
TSH	✓									
TB testing (QuantiFERON-TB Gold test [or IGRA equivalent] and/or PPD skin test)	✓									
Chemistry (8 hour fast, excepting Screening)	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Hematology	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Urinalysis	✓	✓				✓		✓	✓	

Activity	Screening	Randomization/ Baseline	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Premature Discontinuation	30-Day Follow Up Call
Serum pregnancy test (WOCBP)	✓							✓	✓	
Phone call reminder for dosing instructions prior to the visit			✓	✓	✓					
PK sample (Central Lab shipping and handling)			✓	✓	✓		✓	✓	✓	
Optional Biomarker Sample: whole blood DNA		✓								
Optional Biomarker sample: PBMC		✓		✓		✓		✓		
Optional Biomarker sample: whole blood transcriptomics		✓	✓	✓		✓		✓		
Optional Biomarker sample: serum, plasma		✓	✓	✓		✓		✓		
Optional Biomarker sample: whole blood leukocyte subsets		✓		✓		✓		✓		
℞ TREATMENT										
Assign study drug		✓								
Dispense study drug		✓	✓	✓	✓	✓	✓			
Review study drug adherence and perform drug accountability			✓	✓	✓	✓	✓	✓	✓	

AE = adverse event; BSA = Body Surface Area; CXR = chest x-ray; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; FSH = follicle stimulating hormone; HADS = Hospital Anxiety and Depression Scale; HIV = human immunodeficiency virus; IGRA = Interferon-Gamma Release Assay; NRS = Numeric Rating Scale; PASI = Psoriasis Area Severity Index; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; PPD = purified protein derivative; PSS = Psoriasis Symptom Scale; sPGA = static Physician's Global Assessment; TB = tuberculosis; TSH = thyroid stimulating hormone; TSQM = Treatment Satisfaction Questionnaire for Medication; WOCBP = women of child bearing potential; WPAI = Work Productivity and Activity Impairment

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	28 July 2021
Version 1.1 (Japan Only)	02 December 2021
Protocol Appendix (Japan Only)	01 November 2021

The purpose of this version is to update the following sections below.

Summary of Protocol Changes:

- Protocol Title Page and Synopsis: Updated number of sites to approximately 50.

  Rationale: *To align with the number of sites currently participating.*

- Protocol Section 2.2, Benefits and Risks to Subjects: Revised Study M19-371 description to indicate that it is a single "and multiple" dose study.

  Rationale: *To correct the inadvertent omission.*

- Protocol Section 2.2, Benefits and Risks to Subjects: Added a paragraph regarding QT prolongation results from Study M21-560 to support the appropriateness of standard ECG eligibility criteria in Study M18-816.

  Rationale: *To justify the appropriateness of eligibility criteria #19, which includes exclusion of subjects with risk factors for torsade de pointes.*

- Protocol Section 2.2, Benefits and Risks to Subjects: Added a paragraph regarding results from Study M20-115, conducted in healthy volunteers to evaluate potential drug-drug interactions between cedirogant and statins at steady state.

  Rationale: *To provide current PK data regarding the interactions between cedirogant and studied statins to support the changes made to the daily use limits of concomitant statin in Section 5.1.*

- Protocol Section 2.2, Benefits and Risks to Subjects: Added a paragraph regarding results from Study M18-809, conducted in healthy volunteers to evaluate the modulatory effects of cedirogant on CYP enzymes.

  Rationale: *To provide current PK data regarding the modulatory effects of cedirogant on CYP enzymes, which provides support to the language added in Section 5.4 noting a potential decreased efficacy of concomitant CYP3A and CYP2C19 substrate medications.*

- Protocol Section 3.4, Additional Efficacy Endpoints; Operations Manual Section 3.19, Unscheduled Visits; Section 7.6, Skin Biopsy Procedure: Updated wording for the activities table to "Study Activities Table."

  Rationale: *Updated for consistency throughout both documents.*

- Protocol Section 3.6, Pharmacokinetic Endpoints; Operations Manual Section 3.15. Pharmacokinetic Sampling: Added ", possible metabolite(s), and if warranted, relevant concomitant medications" to plasma cedirogant concentrations.

  Rationale: *To provide clarification.*

- Protocol Section 3.7, Biomarker Research Endpoints: Corrected Operations Manual Section number from 3.8 to 3.16.

  Rationale: *To correct typographical error.*

- Protocol Section 4.1, Overall Study Design and Plan: Added "BL = baseline" to the abbreviations list for Figure 1, Study Schema.

  Rationale: *To add missing abbreviation.*

- Protocol Section 4.2, Selection of Doses in the Study: Updated the dose language based on final data from multiple ascending dose (MAD) Study M17-238, as well as safety margin based on most recent rat and dog toxicity results.

  Rationale: *To update language based on final data from completed MAD and animal studies.*

- Protocol Section 5.1, Eligibility Criteria: Added "at both Screening and Baseline visits" to criterion #6.

  Rationale: *To provide clarification.*

- Protocol Section 5.1, Eligibility Criteria: Added "active" to describe skin disease in criterion #8.

  Rationale: *To provide clarification.*

- Protocol Section 5.1, Eligibility Criteria: Added "or 2 negative antigen test results at least 24 hours apart" to criterion #11.

  Rationale: *Updated to reflect the current protocol template language regarding COVID-19 testing.*

- Protocol Section 5.1, Eligibility Criteria; Section 5.5, Interruption/Discontinuation of Study Drug Due to COVID-19 Infection: Revised criterion #12 to "at least 10 days since first positive molecular test result have passed in asymptomatic patients or at least 10 days since recovery…"

  Rationale: *To align with current SARS-CoV-2 guidelines.*

- Protocol Section 5.1 Eligibility Criteria: Updated pitavastatin dose from 1 mg to 2 mg and atorvastatin dose from 20 mg to 40 mg in criterion #25.

  Rationale: *Pitavastatin PK is mainly affected by OATP1B1 (organic anion transporting polypeptide 1B1). An estimated < 100% increase in OATP1B1 substrate by co-administered cedirogant (375 mg QD) is expected based on the results from the statin drug-drug interaction (DDI) Study M20-115. The atorvastatin dose was adjusted based on observed 85% increase in C_{max} of ortho-hydroxy atorvastatin (active metabolite of atorvastatin) by cedirogant (375 mg QD) in the statin DDI Study M20-115.*

- Protocol Section 5.1 Eligibility Criteria: Revised "cytochrome P450 (CYP) 3A" to "CYP3A" in criterion #27.

  Rationale: Changed to abbreviation since already defined at first use.

- Protocol Section 5.3, Prohibited Medications and Therapy: Added "including but not limited to corticosteroids, oral retinoids…" to the list of systemic non-biologic therapies for the treatment of chronic plaque psoriasis.

  Rationale: *To provide clarification.*

- Protocol Section 5.3, Prohibited Medications and Therapy: Deleted "with unknown effects on CYP3A" regarding the prohibition of herbal therapies or other traditional medicines.

  Rationale: *To ensure no potential DDI.*

- Protocol Section 5.4, Prior and Concomitant Therapy: Added language regarding moderate induction of CYP3A and CYP2C19 by cedirogant 375 mg QD, and the potential effects on drugs that are sensitive substrates with concomitant administration of cedirogant.

- **Rationale:** *To note a potential decreased efficacy of concomitant CYP3A and CYP2C19 substrate medications given the inductive effects of cedirogant on these two CYP enzymes observed in Study M18-809.*

- Protocol Section 5.5, Withdrawal of Subjects and Discontinuation of Study: Added "partially discontinue one or more treatment group(s)" regarding study termination. Added sentence to state that all subjects in the terminated arm(s) will be asked to return for a PD visit and to perform a 30-day follow-up phone call after the last dose of study drug.

  Rationale: *To provide clarification in the event that only partial termination of the study is required.*

- Protocol Section 6.1, Complaints and Adverse Events: Added herpes zoster and hypersensitivity to supplemental report form table.

  Rationale: *Herpes Zoster will be included as an additional search as an opportunistic infection as the risk is increased with subjects with psoriasis. Hypersensitivity reactions have been reported in healthy volunteer studies.*

- Protocol Section 6.2, Toxicity Management, Ocular Events: Expanded definition of AE ocular event to include investigator discretion when event does not meet the specified criterion of CTCAE Grade 2 or higher. Mandatory follow up with an ophthalmologist was changed from occurring within 7 days (± 1 day) to occurring as soon as possible, but within 7 days at the latest.

  Rationale: *Although current data demonstrates the risk of ocular toxicity with cedirogant to be low, a conservative approach for monitoring and reporting ocular AEs will be followed. Updated for consistency with Japan Only protocol amendment version 1.1.*

- Protocol Appendix B, Responsibilities of the Investigator: Updated title to include ABBV-157.

  Rationale: *Added for consistency with the title page.*

- Protocol Appendix C, List of Protocol Signatories: Updated list of protocol signatories.

  Rationale: *To reflect current personnel and roles.*

- Operations Manual Section 3.14, Tuberculosis Screening and Prophylaxis: For tuberculosis screening, added "which is the preferred testing method," to QuantiFERON-TB Gold Test (or IGRA equivalent). For tuberculosis testing, added "and the QUANTIFERON-TB Gold test should be utilized unless it is not possible or both tests are required by local regulations."

Rationale: *To provide clarification and clearer guidance for sites to follow.*

- Operations Manual Section 3.15, Pharmacokinetic Sampling: Added "The date and timing of the last two doses administered prior to the blood sample collection and the date and timing of the blood sample collection should be recorded to the nearest minute."

  Rationale: *To provide clarification.*

- Operations Manual Section 7.1, Static Physician Global Assessment (sPGA): Corrected the numbering from sequential to individual score values (0 through 4) by descriptor.

  Rationale: *To correct the typographical errors.*

- Operations Manual Section 7.2, Psoriasis Area and Severity Index (PASI) and Assessment of Total Body Surface Area: Corrected formula from "Dh" to "D_h."

  Rationale: *To correct the typographical error.*