1.0 Title Page

Clinical Study Protocol M15-988

A Phase 3, Randomized, Open-Label Study to Assess Efficacy and Safety of Two Different Dose Regimens of Risankizumab Administered Subcutaneously in Japanese Subjects with Generalized Pustular Psoriasis or Erythrodermic Psoriasis

Incorporating Amendment 1

AbbVie Investigational Product:	Risankizumab
Date:	18 January 2017
Development Phase:	3
Investigators:	Multicenter Trial (Investigator information is on file at AbbVie)
Sponsor:	AbbVie GK, [redacted]
Sponsor/Emergency Contact:	[redacted]

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Protocol	Date
Original	21 October 2016

The purpose of this amendment is to:

- Update emergency contact information on Title Page.

  Rationale: *Reflect correct AbbVie personnel information.*
- Revise verbiage in Section 3.2, Benefits and Risks, Section 5.1, Overall Study Design and Plan, Section 5.2.2, Exclusion Criteria, Section 5.3.1.1, Study Procedures and Appendix C, Study Activities, to add an optional PPD skin test.

  Rationale: *To provide an alternative test if QuantiFERON-TB test is not available.*
- Revise verbiage in Section 5.1, Overall Study Design and Plan to add a more detailed description to the rescreening process.

  Rationale: *To provide more details regarding the time frame and the assessments to allow for a patient to rescreen.*
- Revise verbiage in Section 5.2.4, Contraception Recommendations and Pregnancy Testing, to match Standard Safety Risk language.

  Rationale: *To ensure that the elements match.*
- To clarify the time frame for follow-up TB testing in Section 5.3.1.1, Study Procedures and Appendix C, Study Activities.

  Rationale: *To have the TB assessments annually and at EOT visit rather than Week 188 visit.*
- Revise the pre-dose time frame for PK and ADA blood sample collection from 30 minutes prior to dosing to 60 minutes prior to dosing in Section 5.3.2.1, Collection of Samples for Analysis and Appendix C, Study Activities.

  Rationale: *To provide a larger window of time for the assessment to be performed.*
- Add the source documents required for adjudication in Section 5.3.4, Safety Variables.

Rationale: *For Japan sites, the process and the list of source documents to be reported to CCVT adjudication committee should be mentioned in the protocol.*

- Revise and check the assessments in Appendix C, Study Activities, to correlate with the text in the body of the protocol.

  Rationale: *To ensure that all the assessment time points accurately reflect the text in the protocol.*

- Revise the pregnancy testing language in Section 5.3.1.1, Study Procedures, Table 2, Laboratory Tests, and Appendix C, Study Activities.

  Rationale: *To ensure consistency in pregnancy testing language for all females subjects and for female subjects of child-bearing potential.*

- Revise the text throughout the protocol to correct clerical errors and provide clarification.

An itemized list of all changes made to this protocol under this amendment can be found in Appendix J.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-988
Name of Study Drug: ABBV-066	**Phase of Development:** 3
Name of Active Ingredient: Risankizumab	**Date of Protocol Synopsis:** 18 January 2017
Protocol Title: A Phase 3, Randomized, Open-Label Study to Assess Efficacy and Safety of Two Different Dose Regimens of Risankizumab Administered Subcutaneously in Japanese Subjects with Generalized Pustular Psoriasis or Erythrodermic Psoriasis	
Objective: The objective of this trial is to assess the long-term safety and efficacy of two different dose regimens of risankizumab in Japanese subjects with generalized pustular psoriasis (GPP) or erythrodermic psoriasis (EP).	
Investigator: Multicenter	
Study Sites: Multi-centre trial in Japan	
Study Population: Adult male or female subjects with a diagnosis of generalized pustular psoriasis or erythrodermic psoriasis.	
Number of Subjects to be Enrolled: Approximately 16 subjects will be randomized, 8 with generalized pustular psoriasis and 8 with erythrodermic psoriasis.	
Methodology: This is a 172 week randomized, open-label, parallel design study with two substudies, Substudy GPP and Substudy EP for subjects with generalized pustular psoriasis and subjects with erythrodermic psoriasis, respectively. In each Substudy, subjects will be randomized in 1:1 ratio to one of the two dose regimens of risankizumab. Subjects in each group will receive either 150 mg or 75 mg of risankizumab at Week 0, 4 and every 12 weeks after. From Week 16, subjects in the 75 mg group with no clinical response will be uptitrated to 150 mg. The primary efficacy evaluation will be performed at Week 16 and an assessment of long-term maintenance of response will be performed over 52 weeks.	
Diagnosis and Main Criteria for Inclusion/Exclusion: **Main Inclusion:** 1. Male or female subjects, age ≥ 20 years at screening. 2. Signed and dated written informed consent prior to admission to the study in accordance with Good Clinical Practice (GCP) and local legislation. <u>For generalized pustular psoriasis</u> • Have a diagnosis of generalized pustular psoriasis for at least 60 days prior to informed consent based on the diagnostic criteria of the Japanese Dermatological Association (JDA). Subjects not fulfilling one of the diagnostic criteria i.e., "accompanying systemic symptoms including fever or malaise" at the time of screening can be entered. • Subjects with an erythema area with pustules accounting for ≥ 10% of the body surface area (BSA), and with a severity assessment criteria score (JDA total score) specified by the JDA of less than 14. • Must be candidates for systemic therapy or phototherapy for generalized pustular psoriasis, as assessed by the investigator.	

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

For erythrodermic psoriasis

- Have a diagnosis of erythrodermic psoriasis prior to informed consent.
- Subjects with an inflammatory erythema area accounting for ≥ 80% of the BSA at screening and at the time of the first administration of the study drug.
- Must be candidates for systemic therapy or phototherapy for erythrodermic psoriasis, as assessed by the investigator.

Main Exclusion:

1. Previous exposure to risankizumab.
2. Currently enrolled in another investigational study or less than 30 days (from screening) since completing another investigational study (participation in observational studies is permitted).

For generalized pustular psoriasis

- Subjects with active ongoing inflammatory diseases other than generalized pustular psoriasis that might confound trial evaluations according to investigator's judgment.

For erythrodermic psoriasis

- Subjects with active ongoing inflammatory diseases other than erythrodermic psoriasis that might confound trial evaluations according to investigator's judgment.
- Subject diagnosed with medication-induced or medication-exacerbated EP.

Investigational Product:	Risankizumab (ABBV-066): 75 mg pre-filled syringe, 90 mg/mL, 0.83 mL dispensed volume, 0.87 mL fill volume
Doses:	Risankizumab (ABBV-066): 150 mg (2 syringes, 75 mg each) or 75 mg (1 syringe) administered at Week 0, 4 and every 12 weeks
Mode of Administration:	Subcutaneous injection

Duration of Treatment: 172 weeks

Criteria for Evaluation:

Efficacy:

The primary endpoint for Substudy GPP is the proportion of subjects achieving a GPP Clinical Response, defined as at least "Slightly Improved" in the overall improvement rating from baseline, at Week 16, according to JDA total score for GPP.

The primary endpoint for Substudy EP is the proportion of subjects achieving an EP Clinical Response, defined as at least "Minimally Improved" in Clinical Global Impression-Global Improvement (CGI-GI) for EP at Week 16.

In addition, JDA total score and components as well as, Physician Global Assessment-Generalized pustular psoriasis (PGA-GPP), Clinical Global Impression-Global Improvement (CGI-GI), Psoriasis Area and Severity Index (PASI), BSA and Dermatology Life Quality Index (DLQI) will be assessed.

Pharmacokinetics and Immunogenicity:

Blood samples will be collected for measurement of risankizumab concentration and anti-drug antibody (ADA) during the treatment period and also at the follow up visit.

Criteria for Evaluation (Continued):

Safety:

- Adverse events (AE)
- Serious adverse events (SAE)
- Physical examination
- Vital signs
- Clinical laboratory values (hematology, clinical chemistry and urinalysis)
- Local tolerability

Statistical Methods:

Descriptive statistics will be provided for all efficacy endpoints by treatment group for Substudy GPP and Substudy EP separately.

Efficacy:

The efficacy analyses will be performed on the Intent-to-treat and Safety populations, defined as all randomized subjects with at least one dose of study drug. No formal hypothesis testing will be conducted. Summary statistics will be provided.

Primary Endpoint

The primary endpoint for Substudy GPP is the proportion of subjects achieving a GPP Clinical Response, defined as at least "Slightly Improved" in the overall improvement rating from baseline, at Week 16, according to JDA total score for GPP.

The primary endpoint for Substudy EP is the proportion of subjects achieving an EP Clinical Response, defined as at least "Minimally Improved" in CGI-GI for EP at Week 16.

Secondary Endpoint(s)

For generalized pustular psoriasis:

- Proportion of subjects achieving a GPP Clinical Response, defined at least "Slightly Improved" in the overall improvement rating from baseline, at Week 52, according to JDA total score for GPP at Week 52
- Proportion of subjects achieving ≥ 90% reduction from baseline Psoriasis Area Severity Index (PASI) score (PASI 90) at Week 16
- Proportion of subjects achieving PASI 90 at Week 52

For erythrodermic psoriasis:

- Proportion of subjects achieving an EP Clinical Response, defined at least "Minimally Improved" in CGI-GI for EP at Week 52
- Proportion of subjects achieving PASI 90 at Week 16
- Proportion of subjects achieving PASI 90 at Week 52

Statistical Methods (Continued):

Pharmacokinetics (PK) and Immunogenicity:

Risankizumab plasma concentrations will be determined. Descriptive statistics will be calculated for each sampling time. PK and ADA data may be combined with data from other studies and analyzed using a mixed-effects modeling approach. This analysis will estimate the population central value and the empirical Bayesian estimates of the individual values for risankizumab apparent clearance (CL/F) and volume of distribution (Vss/F). Additional parameters may be estimated if useful in the interpretation of the data. Relationships between exposure and clinical observations (efficacy or safety variables of interest) may be explored.

The number and percentage of subjects with ADA will be calculated.

Safety:

All AEs, SAEs, AEs leading to discontinuation, and pre-specified AEs of special interest will be collected during the study. A treatment-emergent AE (TEAE) is defined as an event with onset or worsening after the first study dose of risankizumab and within 15 weeks after the last risankizumab injection. The number and percentages of subjects experiencing TEAE will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term. Summaries (including percentages and event per 100 subject-years) of SAEs, deaths, AEs leading to discontinuation from the study, and pre-specified AEs of special interest will be provided as well. Mean change in laboratory variables, and vital signs variables will be summarized. For selected parameters, a listing of all subjects with clinically significant laboratory values, or vital sign determinations will be provided. Shift tables for changes from baseline according to the normal range will also be provided.

The sample size of this study is not estimated based on powering for any hypothesis testing. There are only approximately 1600 and 40000 Japanese subjects with generalized pustular psoriasis and erythrodermic psoriasis respectively, thus finding subjects to participate in the trial will be difficult. Therefore, the sample size is determined based on feasibility. In total, at least 16 subjects will be enrolled: at least 8 subjects for GPP and EP separately.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
BSA	Body surface area
CASPAr	ClASsification of Psoriatic Arthritis
CCVT	Cardiac, Cerebrovascular and Thrombotic Events
CGI-GI	Clinical Global Impression-Global Improvement
CL/F	Apparent total clearance
CRF	Case report form
CRP	C-reactive protein
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EP	Erythrodermic Psoriasis
EudraCT	European Union Drug Regulatory Authority Clinical Trials
GCP	Good Clinical Practice
GPP	Generalized Pustular Psoriasis
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive response system

ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
JDA	Japanese Dermatological Association
mAb	Monoclonal antibody
MACE	Major Adverse Cardiac Events
MedDRA	Medical Dictionary for Drug Regulatory Activities
PASI	Psoriasis Area and Severity Index
PD	Premature discontinuation
PGA-GPP	Physician's Global Assessment of Generalized Pustular Psoriasis
PK	Pharmacokinetics
PMDA	Pharmaceutical and Medical Devices Agency
PRO	Patient reported outcome
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TEAE	Treatment –emergent adverse events
TNF	Tumor necrosis factor
ULN	Upper limit of normal
WBC	White blood cell count
VSS/F	Volume of distribution

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3.0 Introduction

Generalized pustular psoriasis (GPP) is a rare and severe skin disorder that presents with flares of widespread sterile pustules on a background of red and tender skin. It may in some cases require subject's hospitalization in intensive burn units and in rare cases be fatal.

There is no cure-all treatment for GPP, and as such, the mortality rate is high.

Erythrodermic psoriasis (EP) is a generalised erythema. It is also a very severe skin condition that can be fatal and difficult to treat. It is marked by widespread involvement (> ¾ of the body surface area) with redness and scaling and can be accompanied by systemic manifestations such as fever, chills, or malaise. It can be the first presentation of a subject's psoriasis or can result after many years of psoriasis, sometimes as the result of a poor control of subject's existing psoriasis. Erythrodermic psoriasis should be distinguished as much as possible from cutaneous manifestation of abrupt systemic medication withdrawal or response to malignancy.

Drug Profile

For a more detailed description of the risankizumab profile please refer to the current Investigator's Brochure.

Rationale for Performing the Trial

This study will randomize from two subtypes of subjects: Generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP).

Interleukin (IL)-23 plays a key role in the pathophysiology of psoriasis through induction and maintenance of Th-17 type cells that secrete inflammatory cytokines. Risankizumab is a humanized monoclonal antibody (mAB) that specifically neutralizes the IL-23 axis. About 10% of subjects with GPP have a preceding history of psoriasis, in which there are

persistent, circumscribed, red and scaly plaques. In considering with action of mechanism of risankizumab, this medicine might be effective for GPP and EP.

[redacted]

therefore the aim of this trial is to obtain the efficacy, pharmacokinetic, safety, and tolerability data during a 52-week treatment period with two different dose regimens of risankizumab in Japanese subjects with GPP or EP.

The current trial is being performed to assess the safety and efficacy of risankizumab to support registration in Japan of subjects with GPP or EP.

3.1 Differences Statement

This study is specifically conducted to fulfill a requirement from the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and is focused on the most severe forms of psoriasis, for which the medical need is particularly high.

3.2 Benefits and Risks

Participation in this study may help to generate future benefit for larger groups of subjects with psoriasis if risankizumab proves to be successful in treating this disease. In Phase 1 and Phase 2 studies, risankizumab has been studied in approximately 200 subjects with moderate to severe plaque psoriasis. In these studies, the majority of subjects receiving risankizumab achieved 90% improvement of their disease. The most common adverse events (AE) reported in these trials were mild symptoms of the upper respiratory tract, including nasal stuffiness, sore throat, and influenza, and headache, that showed no dose dependency. These events were not considered to be related to drug treatment. Local

reactions following subcutaneous administration of risankizumab were uncommon, and limited to redness, swelling or induration at the injection site.

As with any immune modulating agent, risankizumab may impair immune function resulting in a risk of infection. This will be monitored by collection of all AEs during the treatment and observation periods. Subjects with clinically important active infection will not be included in the study. Subjects with positive QuantiFERON® tuberculosis (TB) test or a positive PPD (purified protein derivative) skin test must fulfill entry criteria as specified in Section 5.2.2, item 5, prior to receiving risankizumab. There is not enough information at this time to rule out a risk of cancer with risankizumab, but this risk is considered small with this type of compound as experience with the anti-IL-12/23 mAb ustekinumab has not suggested significant risk for cancer/serious infection. Subjects will be monitored for signs and symptoms of malignancy at each visit.

Increases in major adverse cardiovascular events (MACE) including myocardial infarction, cerebrovascular accident, and cardiovascular death, reported initially with anti-IL-12/23 agents, such as ustekinumab, have not been observed in longer term studies. While the likelihood of increased MACE is small, all suspected cardiovascular events (serious or non-serious) observed in this study will be adjudicated by an independent Cardiac, Cerebrovascular and Thrombotic Events (CCVT) Adjudication Committee.

The subjects will be administrated either 150 mg or 75 mg dose of risankizumab treatment during the clinical trial. From Week 16, subjects will be uptitrated to 150 mg if they have not achieved a clinical response.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects' safety.

In conclusion, the benefit-risk profile is considered appropriate for this stage of clinical development.

4.0 Study Objective

The primary objectives of this study are to investigate the safety and efficacy of two different dose regimens of risankizumab for Japanese subjects with GPP or EP.

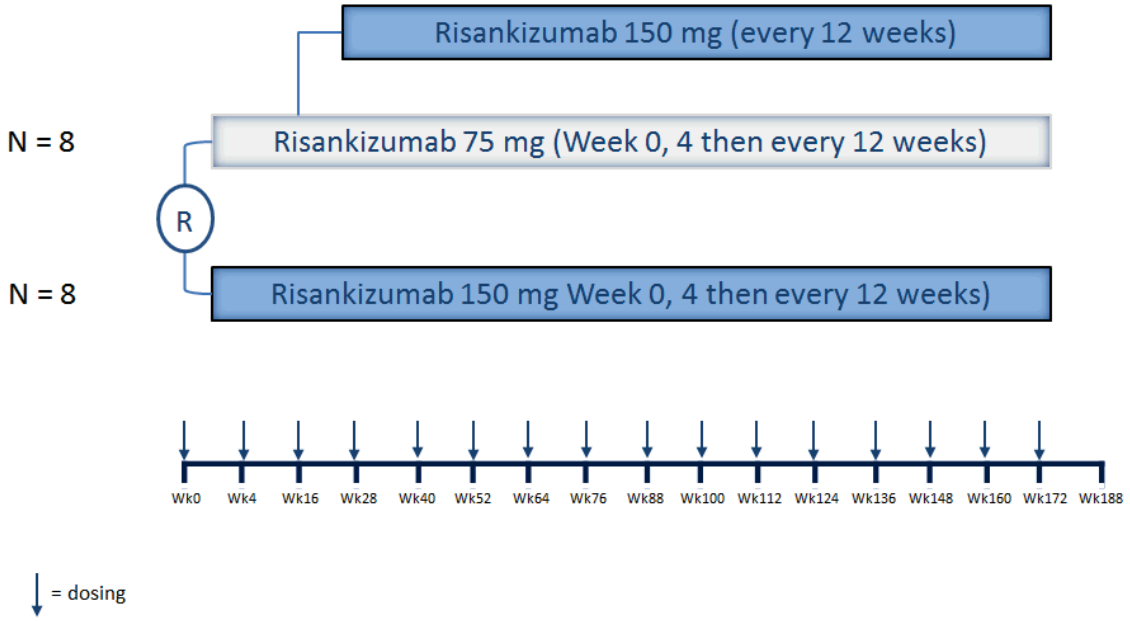
5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This trial is a randomized, open-label study of two different dose regimens of risankizumab, 150 mg (2 syringes, 75 mg each) or 75 mg (1 syringe) at Week 0, 4 and every 12 weeks in two populations (subjects with GPP and with EP). Starting after the Week 16 visit, subjects on 75 mg may increase dosage to 150 mg. In total, at least 16 subjects, 8 with generalized pustular psoriasis and 8 with erythrodermic psoriasis will be randomized in this trial.

Subjects are included in the trial once they have signed the informed consent. Subjects suitable after screening will be eligible to participate.

Figure 1. Trial Design



From Week 16, subjects will be uptitrated to 150 mg if they have not achieved a clinical response (for subjects with GPP: at least "Slightly Improved" in the overall improvement rating from baseline according to JDA total score; for subjects with EP: at least "Minimally Improved" in Clinical Global Impression-Global Improvement)

Visit Schedule

All subjects are to adhere to the visit schedule as specified in the Appendix C. Each visit date (with its window) is to be counted from Day 1. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

Details of Trial Procedures at Selected Visits

Study procedures to be performed at each visit are listed in Appendix C and the respective protocol sections. Refer to Section 5.3.1.1 for explanations of procedures. Additional details on procedures at selected visits are provided below.

Measurement of vital signs should precede blood sampling and be assessed pre-dose at all dosing visits.

Patient reported outcomes (PRO)s should be completed by the subject on his/her own in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the study team. At Visit 2 these questionnaires should be obtained before having the subject randomized.

Screening and Run-In Period(s)

No trial procedures should be done until the subject has consented to taking part in the trial.

Once consented, the subject is considered to be enrolled in the trial and has started screening. The subject number should be recorded on the enrollment log and registered in the Interactive Response System (IRT) as a screened subject.

The Screening Period (Visit 1) is from Day –42 to Day –1. Visit 1 procedures may be extended to two physical visits, if needed. Re-screening will be permitted.

Subjects that initially screen-fail for the study may be permitted to re-screen one time following re-consent and:

- a repeat of all screening procedures is needed with the possible exceptions noted below.
- If the subject had a complete initial screening evaluation including the assessment of an Interferon-Gamma Release Assay (IGRA; QuantiFERON Tuberculosis [TB] Gold In Tube test) or a PPD test (or equivalent), and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.2.2 and Section 5.3.1.1 are met.
- There is no minimum period of time a subject must wait to re-screen for the study. If there is an exclusionary laboratory result during screening or re-

screening within the 42 day screening window, one re-test of that particular value is allowed without repeating all other laboratory tests.

- The subject must meet all inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study.

Infection Screening

Refer to exclusion criteria Section 5.2.2 with study participation directive for subjects with a positive result for PPD or QuantiFERON® for TB, Hepatitis B, Hepatitis C, and Human Immunodeficiency Virus (HIV).

Medical History:

Cardiovascular and risk factors will be collected and reported in the Medical History electronic case report form (eCRF) page.

Baseline Conditions

Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, electrocardiogram (ECG), safety laboratory tests, and any condition requiring therapy (excluding psoriasis) will be reported on the Baseline Condition eCRF Page.

History of Psoriatic Arthritis

At Visit 1, all subjects at all sites will be evaluated via CASPAr (ClASsification of Psoriatic Arthritis) criteria for history of psoriatic arthritis.

Interactive Response System (IRT)

All subjects who are screened must be registered with IRT. If the subject must be designated as a screen failure, IRT should be notified as soon as possible and within the Screening Period. Details of IRT procedures can be found in the IRT manual located in the Investigator Site File (ISF).

For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to Appendix C.

Treatment Period(s)

The treatment period is from Visit 2 to EOT (End of Treatment) Visit.

Visits 2, 4, 6, 8, 10, 12, 16, 20, end of treatment (EOT), Week 184 follow-up visit and Week 188 follow-up visit will be performed in fasted state (8 hours no food and only water). If a subject comes in non-fasted where a fasting condition is required, the visit should be performed, the non-fasted condition documented on the laboratory requisition, and the subject reminded about the expected conditions. At Visits 3, 5, 7, 9, 11, 13, 14, 15, 17, 18, 19, 21, only white blood cell count (WBC), serum C-reactive protein (CRP) and serum albumin ("targeted" lab) will be collected and fasting is not required for these labs.

Urine pregnancy testing for all woman of child-bearing potential will be conducted on-site prior to every dosing and must be negative to further treat the subject. A positive urine test must be confirmed with a serum pregnancy test.

Randomization via IRT and administration of study medication should be the last activity at Visit 2.

Venipuncture (i.e., safety laboratories, PK, anti-drug antibody [ADA]), should be the last procedure prior to study drug administration.

Follow Up Period and Trial Completion

For all randomized subjects termination of trial medication and trial completion must be recorded on the corresponding eCRFs.

Early Treatment and Trial Termination

Subjects who prematurely discontinue (PD) treatment prior to the planned Appendix C visit schedule will complete EOT visit procedures instead of the planned treatment period

visit. If study medication is discontinued, every effort should be made to have the subject continue in the trial and complete all of the follow remaining trial and follow up visits. If a subject cannot or will not continue in the trial, these subjects should be registered as withdrawn/discontinued in IRT. These subjects should be registered as withdrawn in IRT and return to the clinic for Week 188 Follow-Up visit 16 weeks after last dose of study medication.

Trial Completion

Subjects who finish the randomized treatment period will return to the clinic for Week 184 Follow-Up Visit and Week 188 Follow-Up Visit. Completion is defined as a subject having completed the Week 188 Follow-Up visit.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

Subjects must have generalized pustular psoriasis or erythrodermic psoriasis.

General Inclusion Criteria

1. Male or female subjects, age ≥ 20 years at screening.
2. If female, subject must be either postmenopausal defined as:
   - 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 an FSH level > 40 IU/L OR
   - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy)

     OR
   - Women of Childbearing Potential (WOCBP) should be practicing at least one protocol specified method of birth control (Section 5.2.4) starting on Study Day 1 (or earlier) through at least 16 weeks after the last dose of study drug.

3. Females of childbearing potential must have a negative serum pregnancy test result at screening, and a negative urine pregnancy test at Study Day 1.

   Females of non-child bearing potential (either postmenopausal or permanently surgically sterile as defined above) at screening do not require pregnancy testing at study Day 1.

4. Signed and dated written informed consent prior to admission to the study in accordance with Good Clinical Practice and local legislation.

Disease Specific Inclusion Criteria

For Generalized Pustular Psoriasis

5. Have a diagnosis of generalized pustular psoriasis for at least 60 days prior to informed consent based on the diagnostic criteria of the Japanese Dermatological Association (JDA). Subjects not fulfilling one of the diagnostic criteria i.e., "accompanying systemic symptoms including fever or malaise" at the time of screening can be entered.
6. Subjects with an erythema area with pustules accounting for ≥ 10% of the body surface area (BSA), and with a severity assessment criteria score (JDA total score) specified by the JDA of less than 14 (Appendix D).
7. Must be candidates for systemic therapy or phototherapy for generalized pustular psoriasis, as assessed by the investigator.

For Erythrodermic Psoriasis

8. Have a diagnosis of erythrodermic psoriasis prior to informed consent.
9. Subjects with an inflammatory erythema area accounting for ≥ 80% of the BSA at screening and at the time of the first administration of the study drug.
10. Must be candidates for systemic therapy or phototherapy for erythrodermic psoriasis, as assessed by the investigator.

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

General Exclusion Criteria

1. Previous exposure to risankizumab.
2. Currently enrolled in another investigational study or less than 30 days (from screening) since completing another investigational study (participation in observational studies is permitted),
3. Use of any restricted medication as specified in Table 1 or any drug considered likely to interfere with the safe conduct of the study.
4. Major surgery performed within 12 weeks prior to assignment or planned within 12 months after baseline (e.g., hip replacement, aneurysm removal, stomach ligation).
5. Known chronic or relevant acute infections including HIV, viral hepatitis and/or tuberculosis as defined by either a positive QuantiFERON® TB test or a positive PPD (purified protein derivative) skin test. Subjects with a positive QuantiFERON® TB/PPD test result may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis.
6. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
7. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than psoriasis, surgical procedure (i.e., organ transplant), medical examination finding (including vital signs and ECG), or laboratory value at the Screening Visit outside the reference range that, in the opinion of the investigator, is clinically significant and would make the study

participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the subject, or compromise the quality of the data.

8. History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients.
9. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 16 weeks after the last dose of study drug.
10. Previous enrollment in this trial.

Disease Specific Exclusion Criteria

For Generalized Pustular Psoriasis

11. Subjects with active ongoing inflammatory diseases other than generalized pustular psoriasis that might confound trial evaluations according to investigator's judgment.

For Erythrodermic Psoriasis

12. Subjects with active ongoing inflammatory diseases other than erythrodermic psoriasis that might confound trial evaluations according to investigator's judgment.
13. Subject diagnosed with medication-induced or medication-exacerbated EP.

5.2.3 Prior and Concomitant Therapy

Any biologic or systemic medication or vaccine for psoriasis (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject has or is receiving at the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate eCRF.

Complete systemic psoriasis medication history, whether biologic or not, and including phototherapy will be captured as well as topical psoriasis medicine use should be captured for the past 5 years.

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the subject from participation are permissible. All concomitant medications should be carefully evaluated by the investigator and the AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prohibited Therapy

Uses of the following therapies are prohibited from administration in the time periods specified.

Table 1. Restricted Medications

Medication or Class of Medications	Restriction Duration (Through Week 188 Follow-Up Visit)
secukinumab (Cosentyx®), biologics targeting IL-12 except ustekinumab), IL-17 (except ixekizumab and brodalumab), and/or IL-23 directly	26 weeks prior to randomization
ustekinumab (Stelara®), Tumor Necrosis Factor (TNF)-α inhibitors except infliximab, adalimumab and etanercept	12 weeks prior to randomization
granulocyte and monocyte adsorptive apheresis (GMA)	12 weeks prior to randomization
brodalumab, ixekizumab	4 months prior to randomization
infliximab (Remicade®)	8 weeks prior to randomization
adalimumab (Humira®)	2 weeks prior to randomization
etanercept (Enbrel®) live virus vaccinations	6 weeks prior to randomization
Tofacitinib, apremilast	30 days prior to randomization
any investigational device or product (excludes psoriasis products)	30 days prior to randomization
investigational drug for psoriasis (biologics and non-biologics)	12 weeks prior to randomization, or five half-life if longer
other systemic immunomodulating treatments (e.g., methotrexate, cyclosporine A, corticosteroids,[a] cyclophosphamide) other systemic psoriasis treatments (e.g., retinoids, fumarates, any other drug known to possibly benefit psoriasis)	These therapies have to be unchanged for at least 4 weeks prior to randomization, and any change in the dose should be avoided. After Week 16, only dose decreasing will be permitted. Cyclosporine A and systemic corticosteroid will be tapered off after confirmation of a clinical improvement in the opinion of the investigator.
phototherapy (e.g., PUVA)	4 weeks prior to assignment
phototherapy (e.g., UVA, UVB)	2 weeks prior to assignment
topical treatment for psoriasis or any other skin condition (e.g., corticosteroids,[b] vitamin D analogues, vitamin A analogues, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea,α-hydroxy acid [fruit acids])	2 weeks prior to randomization

a. No restriction on corticosteroids with only a topical effect (e.g., inhalative corticosteroids to treat asthma or corticosteroid drops used in the eye or ear).

b. Exception: Topical steroids of mild potency such as locoid or weak potency such as prednisolone for use on the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to trial visit in which PASI is assessed.

5.2.3.2 Rescue Therapy

There are no special emergency procedures to be followed.

In the event that a subject experiences an intolerable worsening of GPP or EP, as deemed by the investigator, during the course of the trial the subject will be discontinued from the trial to receive rescue treatment.

In case of adverse events in need of treatment, symptomatic therapy according to investigator judgment will be permitted. All concomitant and/or rescue therapies will be recorded on the appropriate pages of the eCRF.

5.2.4 Contraception Recommendations and Pregnancy Testing

Women of child bearing potential should practice at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 16 weeks after the last dose of study drug.

Combined (estrogen and progestogen containing) hormonal contraception (oral) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1.

Progestogen-only hormonal contraception (oral) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.

Bilateral tubal occlusion/ligation.

Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.

Intrauterine device (IUD).

Intrauterine hormone-releasing system (IUS).

True abstinence: 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).

5.3 Efficacy, Pharmacokinetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

Informed Consent

The subject will sign and date a study specific, Independent Ethics Committee (IEC)/Independent Review Board (IRB) approved, informed consent form before any study specific procedures are performed in order to participate in this study. Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

Inclusion/Exclusion Criteria

Subjects will be evaluated to ensure they meet all inclusion criteria and have none of the exclusion criteria at both the Screening and the Week 0 visit.

Demographics

The subject's demographic data, including date of birth, gender, race, ethnicity, and disease status will be collected at the Screening Visit.

Physical Examination

Complete and targeted physical examinations will be performed at visits as described in Appendix C. Complete physical examination will include general appearance as well as

evaluation of all relevant organ systems. Targeted physical examination will include vital signs assessment and evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.

Physical examination findings that are related to subject's medical history will be captured on the appropriate medical history eCRF.

Vital Signs

Vital sign assessment includes temperature, pulse rate, sitting blood pressure, and respiratory rate, after subjects have been seated comfortably for at least 5 minutes.

Measurement of vital signs should precede blood sampling and be assessed pre-dose at all dosing visits. At Visit 2 and Visit 3 additional vital signs will be taken at 5 minutes post-dose and 60 minutes post-dose.

Subjects should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose administered and 1 hour following all other doses of study drug. Hypersensitivity reactions should be treated according to medical standards. Pre-medications for further injections might be considered and will be agreed on between investigator and AbbVie TA MD.

Body Weight and Waist Circumference

Waist circumference measurements should be made around a subject's bare midriff, after the subject exhales while standing without shoes and with both feet touching and arms hanging freely. The tape should be placed perpendicular to the long axis of the body and horizontal to the floor and applied with sufficient tension to conform to the measurement surface. Waist circumference should be determined by measuring the midpoint between the lowest rib and the iliac crest.

Body weight measurements should be done on the same scale for each subject. In order to get comparable body weight values, it should be performed in the following way:

- fasting (except for the Screening Visit)
- after the urine sampling (body weight after bladder voiding)
- shoes and coat/jackets should be taken off
- pockets should be emptied of heavy objects (i.e., keys, coins, etc.)

Electrocardiogram

The 12-lead ECGs will be performed as scheduled in Appendix C.

The ECG will be recorded after the subjects have rested for at least 5 minutes in a supine position and will always precede blood sampling. Six limb leads, as specified by Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF), and six pre-cordial leads (V1 – V6), according to Wilson, will be used.

The ECG may be repeated for quality reasons and the repeat used for analysis. Additional ECGs may be collected for safety reasons. Clinically relevant, abnormal findings will be reported as AEs.

Information about the details of ECG collection and the parameters assessed will be provided in the ISF.

The electronic version of the ECG is regarded as source data.

Pregnancy Testing

A serum pregnancy test will be performed for all female subjects at the Screening Visit. A urine pregnancy testing will be done on all women of child-bearing potential prior to administration of study drug at all dosing visits and at each Follow-Up Visit. Additional serum pregnancy testing will occur in case of a positive urine test result at any of the visits and must be negative to further treat the subject.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) do not require pregnancy testing after screening.

Safety Laboratory Parameters

The laboratory tests listed in Table 2 will be performed by the central laboratory service provider at Visits 1, 2, 4, 6, 8, 10, 12, 16, 20, EOT and at Week 188 follow-up visit ("complete" lab). At Visits 3, 5, 7, 9, 11, 13, 14, 15, 17, 18, 19, 21, only WBC, serum CRP and serum albumin will be collected ("targeted" lab). A local laboratory may be used for selected tests in exceptional cases. Subjects should be fasting for at least 8 hours prior to the blood sample being taken at the "complete" visits, except for screening (see Appendix C).

Instructions regarding sample collection, sample handling/processing and sample shipping are provided in the Laboratory Manual in the ISF. For time points of laboratory sampling, see Appendix C.

Laboratory results (i.e., all safety laboratory and clinical laboratory data relevant for current clinical practice) of the subjects will be available in real time to the respective investigator (via laboratory reports) and to the sponsor (via the central laboratory website) and selected abnormal laboratory alerts will be flagged to the site and sent to sponsor in real time.

A clinically relevant value may be either in or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed using an unscheduled visit laboratory kit and should be repeated until normalization or stabilization or until an alternative explanation has been found. Laboratory abnormalities are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

Table 2. Laboratory Tests

Category	Test Name
Hematology	Hematocrit (Hct) Hemoglobin (Hb) Red Blood Cell Count/Erythrocytes White Blood Cells/Leukocytes Platelet Count/Thrombocytes
Diff. Automatic	Neutrophils (relative count) Eosinophils (relative count) Basophils (relative count) Monocytes (relative count) Lymphocytes (relative count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Enzymes	AST(GOT) ALT(GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT)
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate

Table 2. Laboratory Tests (Continued)

Category	Test Name
Substrates	Glucose BUN Creatinine eGFR (estimated by CKD-EPI formula) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Albumin C-Reactive Protein (CRP) (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol
Urine Pregnancy test (only for female subjects of childbearing potential)[d]	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (in all female subjects at screening or if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Autoantibodies (only at screening)	Rheumatoid Factor
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/Erythrocytes Urine WBC/Leukocytes Urine pH Urine creatinine
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC/Erythrocytes Urine Sediment WBC/Leucocytes
Urine	Albumin (quantitative)

Table 2. Laboratory Tests (Continued)

Category	Test Name
Infection screening	Hepatitis B Surface Antigen (qualitative)[a] Hepatitis B Surface Antibody (qualitative)[a] Hepatitis B Core Antibodies total (qualitative)[a] Hepatitis B Virus DNA (quantitative)[a,b] Hepatitis C Antibodies (qualitative)[a] Hepatitis C Virus RNA (quantitative)[a] HIV-1, and HIV-2 Antibody (qualitative)[a] PPD or QuantiFERON®-TB[c]

a. Hepatitis B, Hepatitis C and HIV testing will be performed at screening.

b. If Hepatitis B Surface Antigen is negative but Hepatitis B Core Antibodies total is positive and/or Hepatitis B Surface Antibody is positive, Hepatitis B Virus DNA will be quantified. If Hepatitis B Virus DNA level is undetectable at screening, the subject can participate in this trial. In these cases, HBV DNA level will be monitored at least every 6 months. If positive, the subject's treatment will be discontinued. If Hepatitis C Virus Antibodies is positive, Hepatitis C Virus RNA will be quantified. If Hepatitis C RNA level is undetectable at screening, the subject can participate in this trial. In these cases, HCV RNA level will be monitored at least every 6 months. If positive, the subject's treatment will be discontinued.

c. TB testing will be performed at screening, Visit 12, 16, 20 and Week 184.

d. Urine pregnancy test will be performed at all dosing visits.

Other Safety Parameters

Local Tolerability

Local tolerability at the administration site of the subcutaneous injection will be assessed by the investigator according to "swelling," "induration," "heat," "redness," "pain," or "other findings" at the specified visits as noted in Appendix C. This assessment should be done pre-dose.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood Samples for Risankizumab Assay

Blood samples, approximately 3 mL, for risankizumab assay will be collected at the study visits at the time points specified in Appendix C by venipuncture into appropriately labeled collection tubes. The timing of blood collection will take priority over all other

scheduled study activities except for ECG, vital signs, and dosing. Blood samples for the PK assay should be collected as closely as possible relative to the time of dosing and within 60 minutes prior to dosing. Date and exact time (to the nearest minute) of drug administration will be recorded on eCRFs.

Eleven samples will be collected per subject for pharmacokinetic analysis during the treatment and follow-up periods.

Blood Samples for Risankizumab Anti-Drug Antibody (ADA) Assay:

Blood samples, approximately 3 mL, for risankizumab ADA assay will be collected at the study visits at the time points specified in Appendix C. Blood samples for the ADA assay should be collected as closely as possible relative to the time of dosing and within 60 minutes prior to dosing. Date and exact time (to the nearest minute) of drug administration will be recorded on eCRFs.

Eleven samples will be collected per subject for ADA analysis during the treatment and follow-up periods.

After completion of the study, PK and ADA plasma samples may be used for further methodological investigations, e.g., stability testing.

5.3.2.2 Handling/Processing of Samples

Details for the handling and processing of the samples will be provided outside this protocol, in the laboratory manual.

5.3.2.3 Disposition of Samples

The frozen plasma samples for risankizumab and risankizumab ADA assays will be packed and shipped from the study site to the Central Laboratory according to instructions in the central laboratory Lab Manual. An inventory of the samples included will accompany the package.

5.3.2.4 Measurement Methods

Plasma concentrations of risankizumab and relative titers of risankizumab ADA will be determined using validated methods under the supervision of the Bioanalysis department at AbbVie. Any additional analytes may be analyzed using non-validated methods. Plasma samples collected for risankizumab and risankizumab ADA analysis may be used for future assay development or validation activities.

The presence of ADA to risankizumab will be assessed via a tiered approach using a validated electrochemiluminescence assay (screening, confirmatory, and titration analysis as appropriate). Samples that are confirmed positive may be further characterized in a validated neutralizing antibody (NAb) assay.

5.3.3 Efficacy Variables

Primary Endpoint(s)

For generalized pustular psoriasis:

The primary endpoint for Substudy GPP is the proportion of subjects achieving a GPP Clinical Response, defined as at least "Slightly Improved" in the overall improvement rating from baseline, at Week 16, according to JDA total score (Appendix D) for GPP.

For erythrodermic psoriasis:

The primary endpoint for Substudy EP is the proportion of subjects achieving an EP Clinical Response, defined as at least "Minimally Improved" in Clinical Global Impression-Global Improvement (CGI-GI) (Appendix G) for EP at Week 16.

Secondary Efficacy Endpoint(s) in Substudy GPP

- Proportion of subjects achieving a GPP Clinical Response at Week 52
- Proportion of subjects achieving ≥ 90% reduction from baseline Psoriasis Area Severity Index (PASI) score (PASI 90) at Week 16
- Proportion of subjects achieving PASI 90 at Week 52

Secondary Efficacy Endpoint(s) in Substudy EP

- Proportion of subjects achieving an EP Clinical Response at Week 52
- Proportion of subjects achieving PASI 90 at Week 16
- Proportion of subjects achieving PASI 90 at Week 52

Other Efficacy Endpoint(s) in Substudy GPP

The following endpoints will be summarized at each scheduled visit that the respective variable is collected:

- Proportion of subjects achieving a GPP Clinical Response, defined at least "Slightly Improved" in the overall improvement rating from baseline according to JDA total score for GPP.
- Change from baseline in each of the JDA component scores
- Change and Percent change from baseline in JDA score
- Change and Percent change from baseline in PASI
- Change from baseline in BSA
- Proportion of subjects achieving PASI 50/75/90/100 response
- Proportion of subjects achieving Dermatology Life Quality Index (DLQI) of 0/0 or 1
- Change from baseline in DLQI
- Proportion of subjects achieving at least two grades of improvement in Physician's Global Assessment of Generalized Pustular Psoriasis (PGA-GPP).

Other Efficacy Endpoint(s) in Substudy EP

The following endpoints will be summarized at each scheduled visit that the respective variable is collected:

- Proportion of subjects achieving an EP Clinical Response, defined at least "Minimally Improved" in CGI-GI for EP
- Proportion of subjects achieving at least "Much Improved" in CGI-GI for EP

- Percent change from baseline in PASI
- Change from baseline in PASI
- Proportion of subjects achieving PASI 50/75/90/100 response
- Change from baseline in BSA
- Proportion of subjects achieving DLQI of 0/0 or 1
- Change from baseline in DLQI

5.3.4 Safety Variables

Safety will be assessed descriptively based on:

- Adverse events (AE)
- Serious adverse events (SAE)
- Clinical laboratory values (hematology, clinical chemistry and urinalysis)
- Vital signs
- Local tolerability

Major Cardiac, Cerebrovascular and Thrombotic Events Adjudication Committee

An independent adjudication committee will be used to adjudicate all observed cardio- and cerebro-vascular events reported during the conduct of the study to assure consistent assessment of major cardiac, cerebrovascular and thrombotic events. The events that are adjudicated and the adjudication process will be detailed in the CCVT Adjudication Committee Charter. Site personnel will collect source documentation for the identified events and submit to the CCVT Adjudication Committee. Source documentation should be obscured before submission by site personnel.

Source documentation: (below types of source may be included with the case and will vary depending on type of event and available source):

- SAE form or narrative
- Hospital Discharge Summary

- Death Summary/Details of death note
- Local Lab Values (e.g., normal ranges; cardiac biomarkers)
- Imaging reports (e.g., X-Ray, CT, MRI, MRA, Angiography, Ultrasonography)
- Consultation Notes (e.g., Cardiology, Neurology)
- Procedure Reports (e.g., cardiac catheterization, PCI, CABG)
- Echocardiography
- Admission History/Emergency Room report
- Autopsy result
- Death Certificate
- Clinical Course (e.g., progress notes, doctor visit notes)
- Narrative Form
- ECG
- Other Source (specified)

Details to perform the assessments and complete the necessary documentation will be available in the adjudication charter and investigator training material.

5.3.5 Pharmacokinetic Variables

Risankizumab plasma concentrations will be determined. Descriptive statistics will be calculated for each sampling time. PK and ADA data may be combined with data from other studies and analyzed using a mixed-effects modeling approach. This analysis will estimate the population central value and the empirical Bayesian estimates of the individual values for risankizumab apparent clearance (CL/F) and volume of distribution (Vss/F). Additional parameters may be estimated if useful in the interpretation of the data. Relationships between exposure and clinical observations (efficacy or safety variables of interest) may be explored.

The number and percentage of subjects with ADA will be calculated. As appropriate, the effect of ADA on risankizumab pharmacokinetics and efficacy may be explored.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

All subjects have the right to withdraw from the study at any time without the need to justify their decision. The investigator has the right to remove subjects from the study for noncompliance, administrative or other reasons. It should be clearly understood that an excessive rate of withdrawals can render the study results uninterpretable. The sponsor reserves the right to remove any study subject from the trial for non-compliance.

An individual subject is to be withdrawn from trial treatment if:

- The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision.
- The subject can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- Development of a toxicity or adverse event which warrants risankizumab discontinuation including but not limited to SAEs or Suspected Unexpected Serious Adverse Reactions (SUSAR)s.
- If prohibited treatment is used during the study for any indication, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study. In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment
- If a subject experiences an intolerable increase of psoriasis during the course of the trial the subject will be discontinued from the trial to receive rescue treatment as deemed appropriate by the investigator
- The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of the investigator, is not willing or able to stick to the trial requirements in the future.

Discontinuation of study medication should not lead to withdrawal from the study. If possible the subject should complete all study visits and procedures as initially planned.

Given the subject's agreement, the subject will undergo the procedures for premature discontinuation and follow up as outlined in Appendix C. If a subject becomes pregnant, refer to Section 6.1.6 for instructions on treatment termination.

For all subjects the reason for withdrawal (e.g., AE) must be recorded in the eCRF. These data will be included in the trial database and reported.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Subjects in each group will receive either 150 mg or 75 mg of risankizumab at Week 0, 4 and every 12 weeks after. All products will be supplied by BI.

5.5.2 Identity of Investigational Products

Information about the risankizumab formulation to be used in this study is presented in Table 3.

Table 3. Description of Test Product Risankizumab

Substance:	**Risankizumab**
Pharmaceutical form:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Anti-human IL-23p19 mAb
Molecular weight	Approximately 148 kDa
Unit Strength:	75 mg risankizumab in a pre-filled syringe, concentration 90 mg/mL
Route of administration:	Subcutaneous injection
Posology:	Week 0, Week 4, then every 12 weeks
Duration of use:	172 weeks

5.5.2.1 Packaging and Labeling

The investigational products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

For details of packaging and the description of the label, refer to the ISF.

5.5.2.2 Storage and Disposition of Study Drug

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the sponsor must be contacted immediately.

Trial medication must be securely stored, e.g., in a locked refrigerator or at a pharmacy. The medication may only be dispensed to trial subjects by authorized personnel as documented in the trial staff list.

5.5.3 Method of Assigning Subjects to Treatment Groups

Within each substudy, subjects will be randomized to receive risankizumab 75 mg or risankizumab 150 mg in a ratio of 1:1.

After the eligibility criteria are confirmed, the investigator or designee will randomize the subject on Day 1 (Visit 2) through IRT call or website entry. At visits where study medication is to be administered, study sites will be required to complete the medication resupply module in the IRT.

5.5.4 Selection and Timing of Dose for Each Subject

An IRT will be used to allocate medication to subjects through medication numbers. At visits where study medication is to be administered, study sites will be required to complete the medication resupply module in the IRT. These visits are specified in Appendix C.

At randomization as well as subsequent medication administration visits, IRT will assign medication numbers. At visits after Week 16, subjects in the 75 mg arm who do not achieve GPP or EP Clinical Response may be uptitrated to receive 150 mg; this process will be managed through IRT. Site personnel will enter the kit numbers in the eCRF.

Study drugs will be administered subcutaneously. Injections will be given with each subject receiving 1 or 2 injections of risankizumab at each dosing visit. Syringes will be administered per Appendix C schedule as assigned by IRT.

Risankizumab will be administered as a subcutaneous injection in the abdomen, thighs, gluteal regions, or upper arms (contra-lateral to that used for PK/ADA samples). Injections should be at least 2 cm apart and should not be close to a vein. The injection sites should avoid sites of psoriasis involvement as well as sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

In this open-label trial, treatment allocation will not be concealed throughout the trial. The eCRF will contain information on randomized treatment.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

5.5.7 Drug Accountability

The Investigator/Pharmacist/investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site,
- Notification of the regulatory authority, e.g., competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the principal Investigator

The investigator/pharmacist who is documented in the trial staff list/investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or warehouse/drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse/drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch/serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational product and trial subjects. The investigator/pharmacist who is documented in the trial staff list/investigational drug storage manager will maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational products received from the sponsor. At the time of return to the sponsor the investigator/pharmacist who is documented in the trial staff list/investigational drug storage manager must verify that all unused or partially used drug supplies are in the Investigator's possession.

All unused medication must be returned to the Sponsor.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is a randomized, open-label, parallel design trial. The trial design is appropriate for assessing the safety and efficacy of two different doses risankizumab for Japanese subjects with generalized pustular psoriasis or erythrodermic psoriasis. Since the population of subjects, especially GPP subjects, is very small, it is not feasible to have a control group. In addition to 150 mg, a 75 mg dose was also selected for this study to provide dose response information as well as evaluation of efficacy at a lower dose in Japanese subjects.

5.6.2 Appropriateness of Measurements

All measurements performed during this trial are standard measurements in GPP and/or EP treatment trials and will be performed in order to monitor safety aspects or assess treatment response in an appropriate way. Therefore, the appropriateness of all measurements applied in this trial is given.

5.6.3 Suitability of Subject Population

The subjects enrolled in the present study are subjects with GPP or EP, in agreement with the indication that is being pursued.

The inclusion and exclusion criteria, for most of them limit the factors of variability that could confuse efficacy and safety outcomes and/or have the purpose of protecting subject's safety.

Any active ongoing inflammatory disease other than GPP or EP that might confound efficacy evaluation according to investigator's judgment is exclusionary, as well as the intake of psoriasis medications that may interfere with risankizumab in the evaluation of the psoriatic disease.

GPP is a potentially severe disease and EP may lead to dehydration. Both diseases may be fatal. In order to protect subject's safety and control, medical conditions that could, in the opinion of the investigator, compromise the safety of the subjects are exclusionary. This is also the case for the exclusion criteria relating to GPP and EP.

Moreover, the restriction of the subject population will facilitate the interpretation of safety results.

5.6.4 Selection of Doses in the Study

A dose of 150 mg has been selected for global Phase 3 trials of risankizumab for psoriasis. The dose selection strategy for global Phase 3 involved analyses of data from the completed Phase 1 study (Trial 1311.1, c02434648), the Phase 2 study (Trial 1311.2, c03272682) and PK-Pharmacodynamic analysis of all available data from the Phase 1 and 2 studies. In Study 1311.16, following single dose administration of risankizumab 18 mg to 300 mg SC doses, [redacted] in the

Phase 2 study (Trial 1311.2). Therefore, the dose of 150 mg was selected in this trial, which is the same dose as being evaluated in other global Phase 3 trials of risankizumab for psoriasis.

In the Phase 2 study (Trial 1311.2), risankizumab 90 mg dose showed about 10% lower PASI90 response rate compared to the 180 mg dose. In addition to 150 mg, a 75 mg dose was also selected for this study to provide dose response information as well as evaluation of efficacy at a lower dose in Japanese subjects. The 75 mg dose in Japanese subjects is expected to provide risankizumab exposures comparable to the 90 mg dose evaluated in the Phase 2 study (Trial 1311.2) in Western subjects.

6.0 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 after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the

adverse event to study drug, and any action(s) taken. For SAEs considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (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 adverse event 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 accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and 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 adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a SAE within 24 hours of the site being made aware of the serious adverse event.

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.

For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.1.3 Adverse Events of Special Interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the compound level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g., the potential for AEs based on knowledge from other compounds in the same class. Ongoing evaluation of adverse events may identify future AESI.

The following are considered as AESI:

Hepatic Injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3-fold upper limit of normal (ULN combined with an elevation of total bilirubin > 2-fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10-fold ULN.

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to instructions from the sponsor including completion of the hepatic adverse events form.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary with an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, investigators are advised to provide a hepatic workup as directed by the Sponsor.

6.1.2 Adverse Event Severity

Intensity of AEs

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by OMERACT. Refer to the ISF for intensity/severity classification.

Intensity options are:

Grade 1	mild
Grade 2	moderate
Grade 3	severe
Grade 4	life-threatening

6.1.3 Relationship to Study Drug

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

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

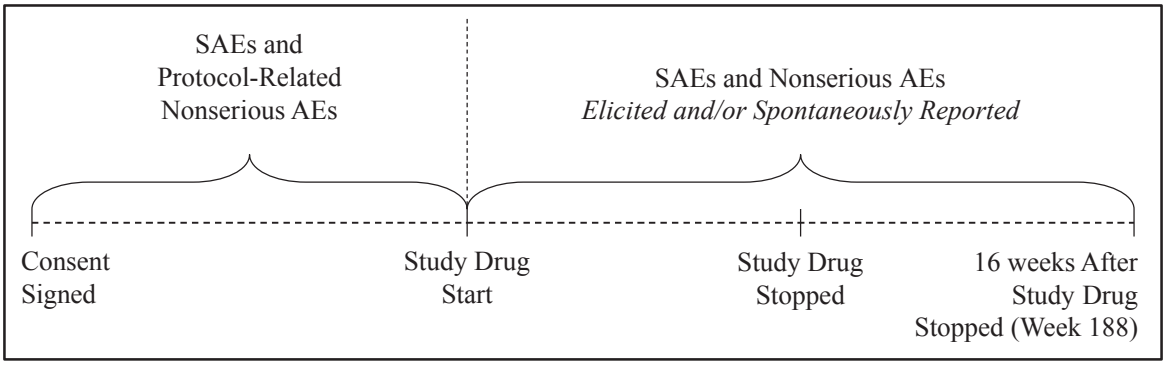
For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, an other cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All AEs reported from the time of study drug administration until 16 weeks following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related non-serious adverse events will be collected from the time the subject signed the study-specific informed consent.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-Case Report Forms (CRF) and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

[redacted]

For safety concerns, contact the Medical Science Group at:

[redacted]

For any subject safety concerns, please contact the physician listed below:

[redacted]

In emergency situations involving study subjects when the primary TA MD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: [redacted]

The sponsor will be responsible for SUSAR reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

In Japan, the principal investigator will provide documentation of all SAEs to the Director of the investigative site and the Sponsor.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Supplemental Safety CRFs

Supplemental CRFs have been developed to facilitate the routine and consistent collection of information for events including hepatic injury (see also Section 6.1.1.3) and MACE (to facilitate the work of the CCVT adjudication committee, see Section 5.3.4), systemic hypersensitivity/anaphylactic reactions, and tuberculosis.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) 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 (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a subject using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The objective of this study is to assess the long term safety and efficacy of two different dose regimens of risankizumab for Japanese subjects with generalized pustular psoriasis or erythrodermic psoriasis.

There are two substudies. Substudy GPP will include subjects with GPP, and Substudy EP will include subjects with EP.

The primary endpoint for Substudy GPP is the proportion of subjects achieving a GPP Clinical Response, defined as at least "Slightly Improved" in the overall improvement rating from baseline, at Week 16, according to JDA total score for GPP.

The primary endpoint for Substudy EP is the proportion of subjects achieving an EP Clinical Response, defined as at least "Minimally Improved" in CGI-GI for EP at Week 16.

The summary tables will be presented separately for each Substudy and each risankizumab dose regimen. Integration across two doses for efficacy and safety within each study, and integration across the two Substudies for safety will be provided when appropriate.

Complete, specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock.

8.1.1 Analysis Population

The Intent-to-Treat (ITT) subject population in each Substudy is defined as all randomized subjects with at least one dose of study drug. The Safety population is the same as the ITT population.

8.1.2 Null and Alternative Hypotheses

Not applicable.

8.1.3 Planned Analyses

No formal hypothesis testing is planned for this trial.

The analysis will be performed using SAS® (SAS Institute Inc., Cary, NC, USA).

8.1.3.1 Demographics and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized for each arm of each Substudy and overall using descriptive statistics.

8.1.4 Primary Endpoint Analyses

For each Substudy and dose, the primary efficacy endpoint per Section 5.3.3 will be summarized descriptively, with count and proportion.

8.1.5 Secondary Endpoint Analyses

For each Substudy, descriptive statistics for secondary endpoints will be provided. These include the number of observations, min/max, range, median, 25th percentile, 75th percentile, median, mean, and standard deviation for continuous variables and counts and percentages for discrete variables.

8.1.6 Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) coding dictionary. Standard AbbVie summary tables and listings will be produced.

All AEs, SAEs, AEs leading to discontinuation, and pre-specified AEs of special interest will be collected during the study. A treatment-emergent AE (TEAE) is defined as an event with onset or worsening after the first study dose of risankizumab and within 15 weeks (105 days) after the last risankizumab injection. The number and percentages of subjects experiencing TEAE will be tabulated using the MedDRA system organ class and preferred term. Summaries (including percentages and event per 100 subject-years) of SAEs, deaths, AEs leading to discontinuation from the study, and pre-specified AEs of special interest will be provided as well. Mean change in laboratory variables, and vital signs determinations will be summarized. For selected parameters, a listing of all subjects with clinically significant laboratory values and vital sign determinations will be

provided. Shift tables for changes from baseline according to the normal range will also be provided.

8.1.7 Pharmacokinetic and Exposure-Response Analysis

Individual risankizumab plasma concentrations will be tabulated and summarized with appropriate statistical methods. In addition, ADA titers will be tabulated for each subject at the respective study visits. The number and percentage of subjects with ADA will be calculated.

Data from this study may be combined with data from other risankizumab studies for the population pharmacokinetic and exposure-response analyses or for external evaluation of pharmacokinetic or exposure-response models developed from other studies. Population pharmacokinetic and exposure-response analyses of only data from this study may not be conducted. The following general methodology will be used for the population pharmacokinetic analysis. Population pharmacokinetic analyses of risankizumab will be performed using [redacted]. Pharmacokinetic models will be built using a non-linear mixed-effects modeling approach with NONMEM software (Version 7, or a higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis data from previous studies. Apparent CL/F and apparent Vss/F of risankizumab will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be estimated if useful in the analysis.

Once an appropriate base pharmacokinetic model [redacted] is developed, [redacted] The relationship between [redacted] will be explored using [redacted] or another suitable regression/smoothing method at a significance [redacted] After identification of all

relevant covariates, a [redacted]

As appropriate, the effect of [redacted] on [redacted] as well as the relationships between exposure and clinical observations [redacted] may be explored. Results of the PK and exposure-response analyses may be summarized in a separate report rather than in the clinical study report.

8.1.8 Interim Analyses

An interim analysis will be conducted when the last subject completes the Week 28 visit and all data pertaining to Week 28 and earlier are cleaned. For this analysis all Week 16 efficacy endpoints will be analysed, and all safety as well as pharmacokinetic and anti-immunogenicity data received by cut-off date will be analysed. Another interim analysis will be conducted when the last subject completes the Week 52 visit. The analyses will be performed for the efficacy endpoints until Week 52, as well as all safety and pharmacokinetic and immunogenicity data received by cut-off date.

Additional interim analysis may be performed if deemed necessary for regulatory purpose.

8.1.9 Handling of Missing Data

Every effort should be made to collect complete data at all visits.

In addition to the as-observed analysis, the following rules will be used to impute for missing data:

- For continuous endpoints, LOCF (Last Observation Carried Forward) will be used to impute missing values
- For all binary endpoints (i.e., endpoints that are either 1 (subject responded) or 0 (subject did not respond):

- If no assessment after that visit*, then impute as failure (NRI [No Response Imputation])
- If there are assessments at visits* before and after, only impute as success if both visits are successes; else impute as failure

* Subjects that take prohibited medications to treat Psoriasis will be treated the same as those that discontinued from the trial – i.e., subsequent visits following start of prohibited medication will be considered as failure for binary endpoints.

8.2 Determination of Sample Size

The sample size is not estimated based on powering for any hypothesis testing. There are only approximately 1600 and 40000 Japanese subjects with generalized pustular psoriasis and erythrodermic psoriasis respectively, thus finding subjects to participate in the trial will be difficult. Therefore, the sample size is determined based on feasibility. In total, at least 16 subjects will be enrolled: at least 8 subjects for GPP and EP separately.

8.3 Randomization Methods

An IRT will be used to determine the randomization of subjects. Detailed instructions for using the IRT will be provided to the site personnel. Subjects who are eligible based on inclusion and exclusion criteria and have had all pre randomization procedures performed will be randomized in a 1:1 fashion in each group to either 150 mg (2 syringes, 75 mg each) or 75 mg (1 syringe) at Week 0, 4 and every 12 weeks. The randomization schedule will be prepared by the Statistics Department of AbbVie and provided to drug supply for adequate packaging. Randomization will be done using an adequate block size.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific

and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (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 clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source

documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the principal investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from

automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The

principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any research that may be done using optional exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or subject management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional exploratory research may be provided to investigators and used in scientific publications or presented at medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Director of the Site in Japan and AbbVie. Continuation of this study beyond this date must be mutually agreed

upon in writing by both the Director of the Site in Japan and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Director of the Site in Japan must retain any records related to the study according to local requirements. If the Director of the Site in Japan is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for ABBV-066.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Phase 3, Randomized, Open-Label Study to Assess Efficacy and Safety of Two Different Dose Regimens of Risankizumab Administered Subcutaneously in Japanese Subjects with Generalized Pustular Psoriasis or Erythrodermic Psoriasis
Protocol Date:	18 January 2017

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

Published References

	Treatment of erythrodermic psoriasis: from the medical board of the National Psoriasis Foundation. Rosenbach M, Hsu S, Korman NJ, et al; National Psoriasis Foundation Medical Board. J Am Acad Dermatol. 2010;62(4):655-62.
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R13-3515	Woodworth T, Furst DE, Alten, R, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol. 2007;34(6):1401-14.
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R96-3541	Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.

Unpublished References

c01569420	Investigator's Brochure Risankizumab, Psoriasis, Crohn's Disease, Ankylosing Spondylitis, Asthma, Psoriatic Arthritis 1311.P1/1311.P2/1311.P3/1311.P4/ 1311.P5, Current Version.
c02434648	Summary report of analysis, Trial 1311.1. 26 March 2015.
c03272682	Summary report of interim analysis at Week 48, Trial 1311.2. 05 May 2015.

Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. 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., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. 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).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. 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.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. 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.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		Clinical
		Statistics
		Pharmacokinetics
		Clinical
		Clinical

Appendix C. Study Activities

Trial Periods	Screening	Treatment																					Follow-Up	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18	V 19	V 20	V 21	EOT/ PD		
Week		0	4	8	12	16	22	28	34	40	46	52	64	76	88	100	112	124	136	148	160	172	184	188
Day	–42 to –1	1	28	56	84	112	154	196	238	280	322	364	448	532	616	700	784	868	952	1036	1120	1162	1246	1274
Visit window (days)			± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Informed consent	X																							
Demographics	X																							
Medical history	X																							
Smoking/alcohol history	X																							
Prior and ongoing medication	X																							
Psoriatic arthritis history[1]	X																							
In-/exclusion criteria	X	X																						
Height	X																							
Weight/waist circumference[2]	X					X				X														
Physical examination[3]	X^c	X^t	X^t	X^t	X^t	X^c	X^t	X^t	X^t	X^c	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^c
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Trial Periods	Screening	Treatment																					Follow-Up	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18	V 19	V 20	V 21	EOT/ PD		
Week		0	4	8	12	16	22	28	34	40	46	52	64	76	88	100	112	124	136	148	160	172	184	188
Day	–42 to –1	1	28	56	84	112	154	196	238	280	322	364	448	532	616	700	784	868	952	1036	1120	1162	1246	1274
Visit window (days)			± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Infection screening[5]	X											X				X				X			X	
Chest X-ray	X											X								X			X	
Pregnancy testing[6]	X	X	X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests[7]	X^c	X^c	X^t	X^c	X^t	X^c	X^t	X^c	X^t	X^c	X^t	X^c	X^t	X^t	X^t	X^c	X^t	X^t	X^t	X^c	X^t	X^c	X^c	X^c
12 lead-ECG	X																							
PK sampling[8]		X	X			X		X				X		X		X		X		X		X	X	X
ADA sampling[8]		X	X			X		X				X		X		X		X		X		X	X	X
Local tolerability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
JDA score and responder rating	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGA-GPP[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-GI[10]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI		X			X	X						X	X	X	X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X	X			X		X		X		X	X	X	X	X	X	X	X	X	X	X		
Administration of trial drugs		X	X			X		X		X		X	X	X	X	X	X	X	X	X	X	X		

Trial Periods	Screening	Treatment																					Follow-Up	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18	V 19	V 20	V 21	EOT/ PD		
Week		0	4	8	12	16	22	28	34	40	46	52	64	76	88	100	112	124	136	148	160	172	184	188
Day	–42 to –1	1	28	56	84	112	154	196	238	280	322	364	448	532	616	700	784	868	952	1036	1120	1162	1246	1274
Visit window (days)			± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Last injection of trial medication[11]																						X		
Trial completion																								X
Vital status[12]																								X

1. At Visit 1, all subjects at all sites will be evaluated via CASPAr for history of psoriatic arthritis as detailed in Appendix F.
2. Refer to Section 5.3.1.1 for weight procedures.
3. Physical examination: C = complete, T = targeted. Refer to Section 5.3.1.
4. Vital signs should precede blood sampling and be assessed pre-dose at all dosing visits. At Visit 2 and Visit 3, additional vital sign assessments should be taken at 5 minutes post-dose and 60 minutes post-dose. Subjects should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose administered and 1 hour following all other doses of study drug.
5. Infection screening consists of Hepatitis B Surface Antigen (qualitative), Hepatitis B Surface Antibody (qualitative), Total Hepatitis B Core Antibodies (qualitative), Hepatitis B Virus DNA (Quantitative) reflex, Hepatitis C Antibodies (Qualitative), Hepatitis C Virus RNA (Quantitative) reflex, HIV-1 and HIV-2 Antibody (Qualitative), PPD or QuantiFERON-TB. Hepatitis B, Hepatitis C and HIV testing will be performed at screening. TB testing will be performed at screening, Visit 12, 16, 20 and Week 184.
6. Serum pregnancy testing in all female subjects at screening and if urine pregnancy test is positive. Urine pregnancy testing will be done in women of child-bearing potential prior to administration of study drug at all dosing visits and at each Follow-Up Visit.
7. C = complete, T = targeted. Targeted lab samples should be limited to WBC, serum CRP and serum albumin for the measurement of JDA. Subjects should be fasting for at least 8 hours prior to the blood sample being taken at the "complete" visits, except for screening. If not fasted mark on laboratory requisition form.
8. On dosing visits, PK and ADA sampling should be taken approximately within 1 hour prior to administration of study drug.
9. Collected for Substudy GPP.
10. Collected for Substudy EP.

11. Subjects that terminate trial medication early will complete EOT Visit procedures instead of the planned treatment period visit and return for Week 188 Follow-up Visit, 16 weeks after last dose of study medication.
12. Vital Status should be collected for subjects leaving the study before the planned Week 188 Follow-up visit.

Appendix D. Severity Assessment Criteria Score

Severity assessment criteria score (JDA total score) specified by the Japanese Dermatological Association

A	Assessment of skin symptoms: erythema, pustules, Edema (0 – 9)			
B	Systemic symptoms/assessment of test findings: fever, WBC count, serum CRP, serum albumin (0 – 8)			
o	Severity:	Mild	Moderate	Severe
(Total score)		(0 – 6)	(7 – 10)	(11 – 17)

A Assessment of skin symptoms (0 – 9)

	Severe	Moderate	Mild	None
Erythema area (total)*	3	2	1	0
Erythema area with pustules **	3	2	1	0
Edema area **	3	2	1	0

* % vs. BSA (severe: ≥ 75%, moderate: ≥ 25% and < 75%, mild: < 25%

** % vs. BSA (severe: ≥ 50%, moderate: ≥ 10% and < 50%, mild: < 1 0%)

B Systemic symptoms/assessment of test findings (0 – 8)

Score	2	1	0
Fever (°C)	≥ 38.5	≥ 37 and < 38.5	< 37
WBC count (/μL)	≥ 15,000	≥ 10,000 and < 15,000	< 10,000
Serum CRP (mg/dL)	≥ 7.0	≥ 0.3 and < 7.0	< 0.3
Serum albumin (g/dL)	< 3.0	≥ 3.0 and < 3.8	≥ 3.8

Overall Improvement Rating Defined According to JDA Total Score

	JDA Total Score Change		Other Criteria
Markedly improved	Decreased by ≥ 3 points	or	No or little symptom of generalized pustular psoriasis
Moderately improved	Decreased by 1 or 2 points	or	≥ 30% reduction of erythema area with pustules compared to baseline, without reaching "no or little symptoms of generalized psoriasis" or, Clinically meaningful improvement in at least 2 of the other parameters of the severity assessment criteria (erythema area, oedema area, WBC count, CRP, fever, serum albumin) AND the sum of the changes in individual JDA components is < 3
Slightly improved	0 points (no change)	and	≥ 20% and < 30% reduction of erythema area with pustules compared to baseline, or, Clinically meaningful improvement in at least 1 of the other parameters of the severity assessment criteria (erythema area, oedema area, WBC count, CRP, fever, serum albumin)
Unchanged	0 points (no change)	and	Does not fulfil the other criteria of "slight improvement"
Worsened	Increased by ≥ 1 point	-	-

Appendix E. Psoriasis Area and Severity Index (PASI)

The PASI score is an established measure of clinical efficacy for psoriasis medications (Study R96-3541).

The PASI is a tool which provides a numeric scoring for subjects overall psoriasis disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin that is affected and the severity of erythema, infiltration, and desquamation over four body regions.

The endpoints used are based on the percent reduction from baseline, generally summarized as a dichotomous outcome based on achieving over an X% reduction (or PASI X), where X is 50, 75, 90 and 100.

To calculate the PASI score, the four main body areas are assessed: **head (h), trunk (t), upper extremities (u) and lower extremities (l)**. These correspond to 10, 30, 20 and 40% of the total body area respectively.

The area affected by psoriasis within a these four areas site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of psoriatic involvement as follows:

- 0 = no involvement
- 1 = < 10%
- 2 = 10% to < 30%
- 3 = 30% to < 50%
- 4 = 50% to < 70%
- 5 = 70% to < 90%
- 6 = 90% to 100%

The **signs of severity, erythema (E), infiltration (I) and desquamation (D)** of lesions are assessed using a numeric scale 0 – 4 where 0 is a complete lack of cutaneous involvement and 4 is the severest possible involvement; scores are made independently

for each of the areas, h, t, u and l and represents a composite score for each area. The signs of severity, **erythema (E), induration (I) and desquamation (D)** of lesions are assessed using a numeric scale 0 – 4:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked
- 4 = Very marked

The table below outlines the characteristics of each category.

	Erythema[a]	**Desquamation**	**Induration**
0 = none	No redness	No scaling	No elevation over normal skin
1 = slight	Faint redness	Fine scale partially covering lesions	Slight but definite elevation, typically edges indistinct or sloped
2 = moderate	Red coloration	Fine to coarse scale covering most of all of the lesions	Moderate elevation with rough or sloped edges
3 = marked	Very or bright red coloration	Coarse, non-tenacious scale predominates covering most or all of the lesions	Marked elevation typically with hard or sharp edges
4 = very marked	Extreme red coloration; dusky to deep red coloration	Coarse, thick, tenacious scale over most or all lesions; rough surface	Very marked elevation typically with hard sharp edges

a. Do not include residual hyperpigmentation or hypopigmentation as erythema.

Assignments for the following body regions are as follows:

- Neck: include with the head
- Buttocks: include with the lower extremities
- Axillae: include with the trunk
- Genitals: include with the trunk

- The inguinal canal separates the trunk and legs anteriorly

The PASI score for each body region is obtained by multiplying the sum of the severity scores by the area score, then multiplying the result by the constant weighted value assigned to that body region. Since the head, upper extremities, trunk, and lower extremities correspond to approximately 10%, 20%, 30%, and 40% of BSA, respectively, the PASI score is calculated using the formula.

The PASI score is calculated according to the following formula:

PASI = 0.1(Eh+Ih+Dh)Ah + 0.3(Et+It+Dt)At + 0.2(Eu+Iu+Du)Au + 0.4(El+Il+Dl)Al

where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and *h*, *u*, *t*, and *l* denote head, upper extremities, trunk, and lower extremities, respectively. PASI scores range from 0.0 to 72.0 with the highest score representing complete erythroderma of the severest degree.

Appendix F. Diagnosis and Assessments for Subjects with Psoriatic Arthritis

At Visit 1, subjects with a positive history of PsA or suspected to have PsA will be further evaluated for PsA diagnosis based on CASPAr (ClASsification of Psoriatic Arthritis) criteria (Study R15-1001). To be classified has having PsA, a subject must have inflammatory articular disease (joint, spine, or entheseal) with at least 3 points total from the 5 categories below. All trial participants will have 2 points assigned due to evidence of current psoriasis per trial entry criteria and require at least one additional point for diagnosis of PsA.

CASPAr Criteria

Category	Point Assignment
Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis	2 points
Typical psoriatic nail dystrophy, including onycholysis, pitting, or hyperkaratosis observed on current physical examination	1 point
A negative test result for rheumatoid factor by any method except latex	1 point
Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist	1 point
Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot	1 point

Appendix G. Clinical Global Impression-Global Improvement (CGI-GI)

Clinical Global Impression (CGI)

2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

0 = Not assessed	4 = No change
1 = Very much improved	5 = Minimally worse
2 = Much improved	6 = Much worse
3 = Minimally improved	7 = Very much worse

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

Appendix H. Patient Reported Outcomes

Dermatology Life Quality Index

The DLQI is a subject-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment (Study R05-2548). The DLQI has a 1-week recall period. Item scores range from 0 (not relevant) and 1 (not at all) to 3 (very much). Question 7 is a "yes"/"no" question where "yes" is scored as 3.

The DLQI will be self-administered by the subject at visits indicated in the Appendix C.

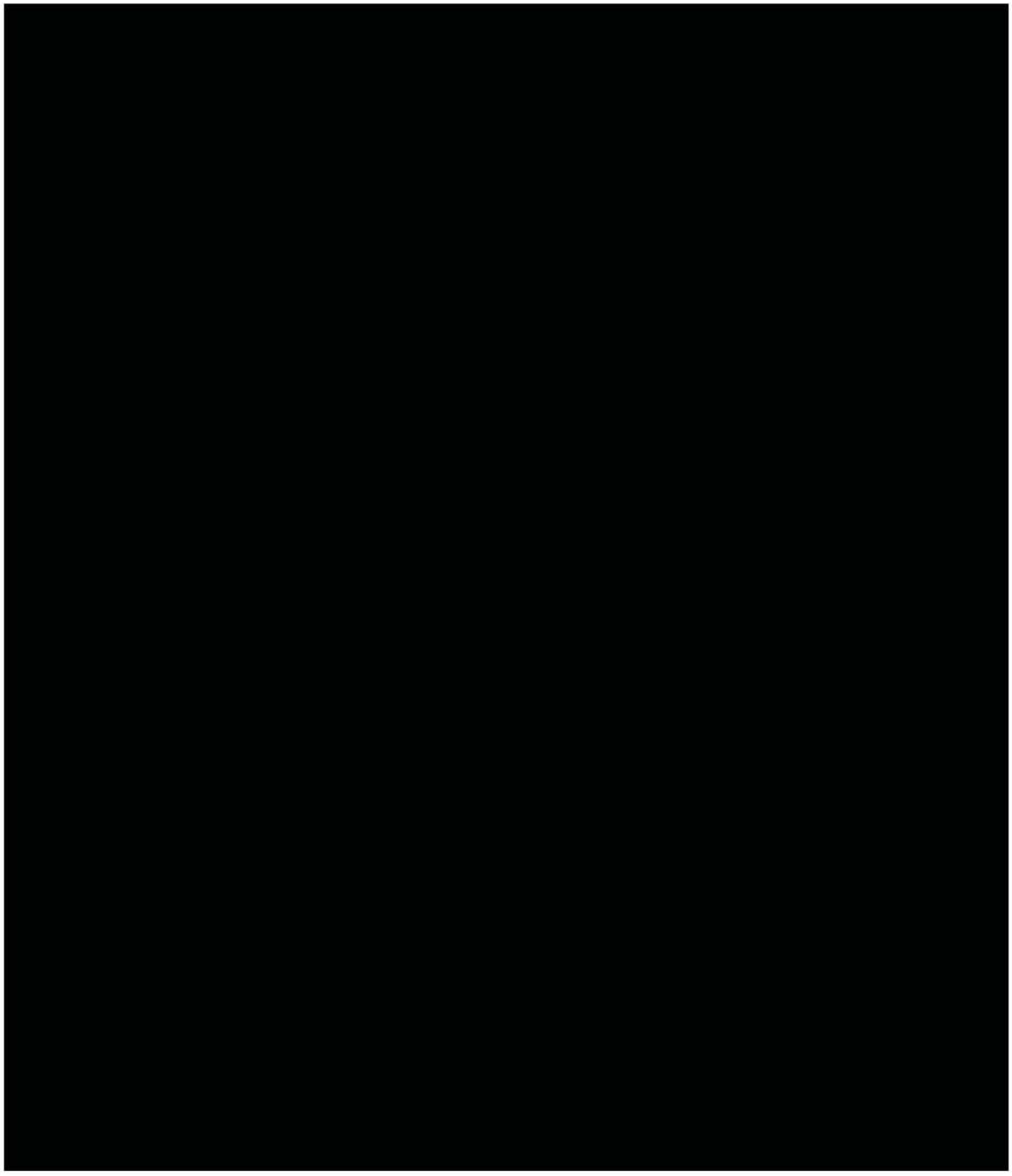
The DLQI will be analyzed under six headings as follows:

Domain	Question Number	Score
Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and school	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30 where 0 – 1 = no effect on subject's life, 2 – 5 = small effect, 6 – 10 = moderate effect, 11 – 20 = very large effect, and 21 – 30 = extremely large effect on subject's life. The higher the score, the more the quality of life is impaired. A 5-point change from baseline is considered a clinically important difference.

If the answer to one question in a domain is missing, that domain is treated as missing. If 2 or more questions are left unanswered (missing), DLQI total score is treated as missing.

The DLQI has been extensively used in clinical trials and has a large evidence base supporting reliability and validity (Study R15-3845).



Appendix I. PGA Scale for Generalized Pustular Psoriasis

The Physician's Global Assessment of Generalized Pustular Psoriasis is a 6-point scale used to measure the severity of skin disease at the time of the qualified investigator's evaluation of the subject. The degree of overall severity will be evaluated using the following categories: erythema, pustulation, and edema.

Scoring Instructions:

If a subject has signs of erythema, pustulation, or edema intermediate between two grades, then the subject's erythema, pustulation, or edema grade should be assigned the higher of the two grades. For example, if a subject's erythema is considered to be worse than 'mild' but less than 'moderate,' the subject's erythema grade should be considered 'moderate.'

The subject's score is an arithmetic average (mean) of the grades for erythema, pustulation, and edema, rounded to the nearest whole integer. For example, if a subject's erythema is moderate (3), **pustulation** is mild (2), and edema is moderate (3), the average grade is 2.67, which is rounded to the nearest whole integer of 3, giving the subject a score of 'moderate.'

Grade	Erythema	Pustulation	Edema	Score
0	No evidence of erythema	No evidence of pustulation	No evidence of edema	Cleared, except for residual discoloration
1	Faint erythema	Scattered isolated pustules	Minimal edema	Minimal
2	Light red coloration	A cluster of non-confluent pustules involving 1 skin location	Mild edema	Mild
3	Moderate red coloration	Clusters of non-confluent pustules involving more than 1 skin location	Moderate edema	Moderate
4	Bright-red coloration	A confluent 'lake of pus' in 1 skin location	Marked edema	Severe
5	Dusky to deep-red coloration	Confluent 'lakes of pus' in more than 1 skin location	Severe edema	Very severe

Appendix J. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.0 Title Page
"Sponsor/Emergency Contact:"
Contact previously read:

[redacted]

Has been changed to read:

[redacted]

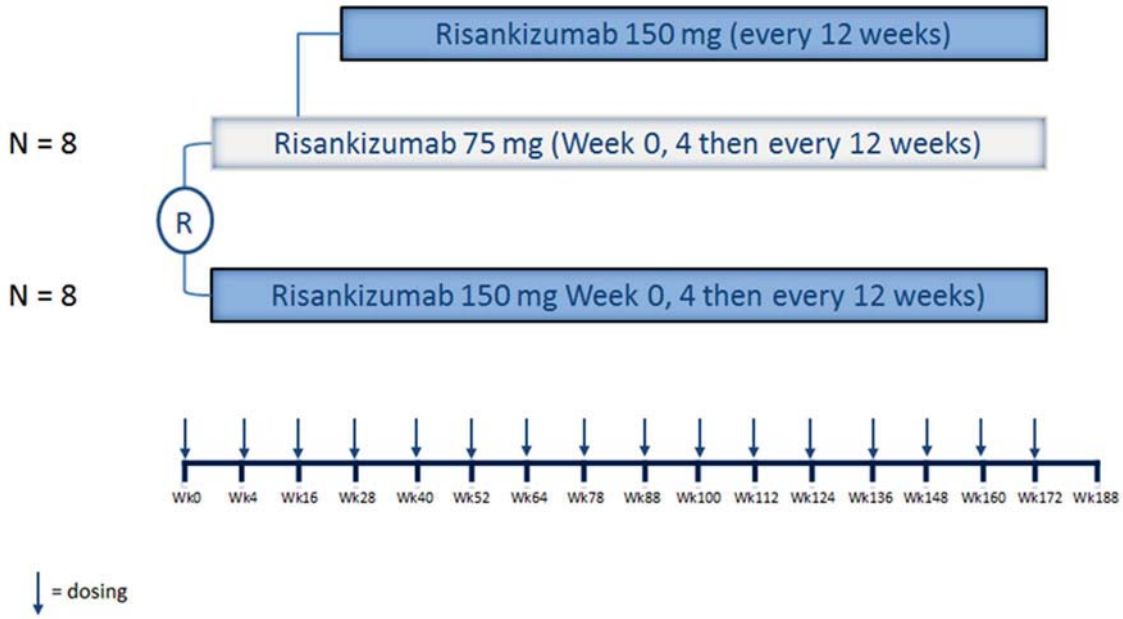
Section 3.2 Benefits and Risks
Second paragraph, fourth sentence previously read:

Subjects with positive QuantiFERON® tuberculosis (TB) test must fulfill entry criteria as specified in Section 5.2.2, item 5, prior to receiving risankizumab.

Has been changed to read:

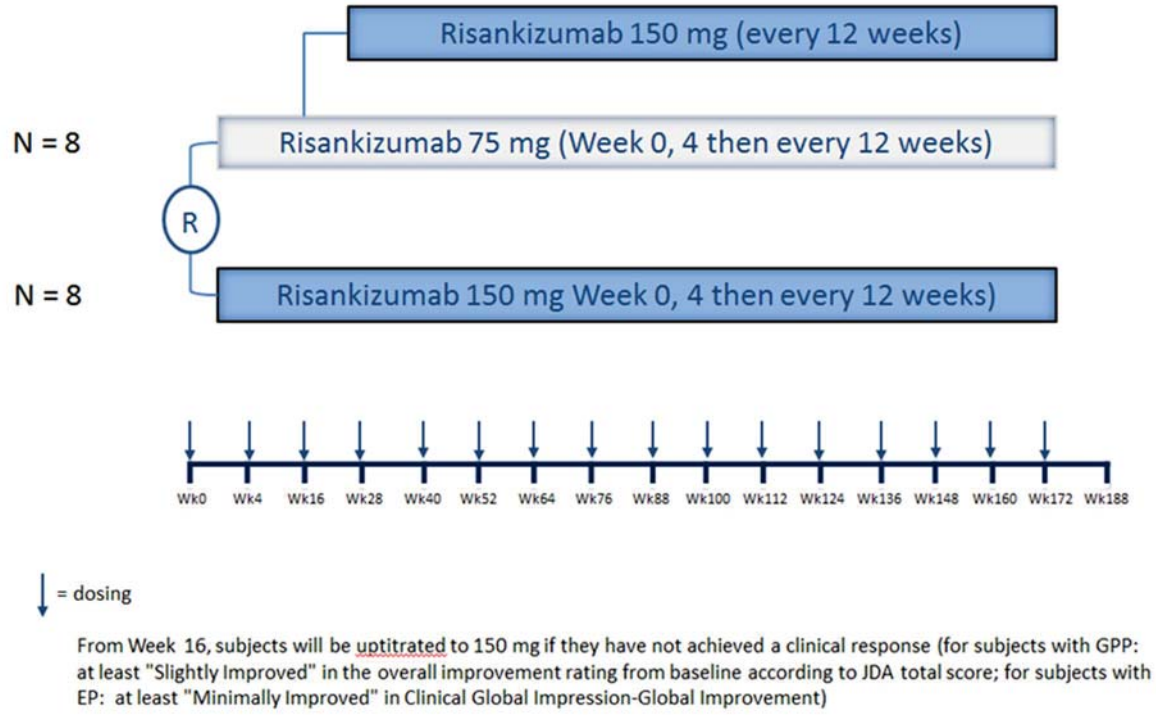
Subjects with positive QuantiFERON® tuberculosis (TB) test or a positive PPD (purified protein derivative) skin test must fulfill entry criteria as specified in Section 5.2.2, item 5, prior to receiving risankizumab.

Figure 1. Trial Design
Previously read:



From Week 16, subjects will be uptitrated to 150 mg if they have not achieved a clinical response (for subjects with GPP: at least "Slightly Improved" in the overall improvement rating from baseline according to JDA total score; for subjects with EP: at least "Minimally Improved" in Clinical Global Impression-Global Improvement)

Has been changed to read:



Section 5.1 Overall Study Design and Plan: Description
Subsection Screening and Run-In Period(s)
Add: new fourth paragraph

Subjects that initially screen-fail for the study may be permitted to re-screen one time following re-consent and:

- a repeat of all screening procedures is needed with the possible exceptions noted below.
- If the subject had a complete initial screening evaluation including the assessment of an Interferon-Gamma Release Assay (IGRA; QuantiFERON Tuberculosis [TB] Gold In Tube test) or a PPD test (or equivalent), and electrocardiogram (ECG), these tests will not be required to be repeated for re-

screening provided the conditions noted in Section 5.2.2 and Section 5.3.1.1 are met.

- There is no minimum period of time a subject must wait to re-screen for the study. If there is an exclusionary laboratory result during screening or re-screening within the 42 day screening window, one re-test of that particular value is allowed without repeating all other laboratory tests.
- The subject must meet all inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study.

Section 5.1 Overall Study Design and Plan: Description
Subsection Screening and Run-In Period(s)
Heading "Infection Screening"
Previously read:

Refer to exclusion criteria Section 5.2.2 with study participation directive for subjects with a positive result for QuantiFERON® for TB, Hepatitis B, Hepatitis C, and Human Immunodeficiency Virus (HIV).

Has been changed to read:

Refer to exclusion criteria Section 5.2.2 with study participation directive for subjects with a positive result for PPD or QuantiFERON® for TB, Hepatitis B, Hepatitis C, and Human Immunodeficiency Virus (HIV)

Section 5.1 Overall Study Design and Plan: Description
Subsection Treatment Period(s)
Second paragraph, first sentence previously read:

Visits 2, 4, 6, 8, 10, 12, 16, 20, end of treatment (EOT) and Week 188 follow-up visit will be performed in fasted state (8 hours no food and only water).

Has been changed to read:

Visits 2, 4, 6, 8, 10, 12, 16, 20, end of treatment (EOT), Week 184 follow-up visit and Week 188 follow-up visit will be performed in fasted state (8 hours no food and only water).

Section 5.2.3 Prior and Concomitant Therapy
Last paragraph, last sentence previously read:

All concomitant medications should be carefully evaluated by the investigator and the AbbVie Therapeutic Area Medical Director (TA MD) should be contacted if there are any questions regarding concomitant or prior therapy(ies).

Has been changed to read:

All concomitant medications should be carefully evaluated by the investigator and the AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapy(ies).

Table 1. Restricted Medications
Medication "brodalumab, ixekizumab" previously read:

Medication or Class of Medications	Restriction Duration (Through Week 188 Follow-Up Visit)
brodalumab, ixekizumab	4 months prior to assignment

Has been changed to read:

Medication or Class of Medications	Restriction Duration (Through Week 188 Follow-Up Visit)
brodalumab, ixekizumab	4 months prior to randomization

Section 5.2.4 Contraception Recommendations and Pregnancy Testing
Delete: eighth, ninth, tenth and eleventh paragraph

Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to Study Day 1.

Male or female condom with or without spermicide.

Cap, diaphragm or sponge with spermicide.

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier method).

Section 5.3.1.1 Study Procedures
Subsection Vital Signs
Second paragraph, last sentence previously read:

At Visit 2 and Visit 3 additional evaluations will be taken at 5 minutes post-dose and 60 minutes post-dose.

Has been changed to read:

At Visit 2 and Visit 3 additional vital signs will be taken at 5 minutes post-dose and 60 minutes post-dose.

Section 5.3.1.1 Study Procedures
Subsection Pregnancy Testing
Previously read:

A serum pregnancy test will be performed for all female subjects at the Screening Visit. A urine pregnancy test will occur at every other study visit for all women of child-bearing potential, prior to every dosing, and at the Week 188 follow-up visit. Additional serum pregnancy testing will occur in case of a positive urine test result at any of the visits and must be negative to further treat the subject.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) do not require pregnancy testing.

Has been changed to read:

A serum pregnancy test will be performed for all female subjects at the Screening Visit. A urine pregnancy testing will be done on all women of child-bearing potential prior to administration of study drug at all dosing visits and at each Follow-Up Visit. Additional serum pregnancy testing will occur in case of a positive urine test result at any of the visits and must be negative to further treat the subject.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) do not require pregnancy testing after screening.

Table 2. Laboratory Tests
Category "Urine Pregnancy test (only for female subjects of childbearing potential)[c]" and " Serum Pregnancy test (only for female subjects of childbearing potential at screening or if urine pregnancy test is positive)" previously read:

Category	Test Name
Urine Pregnancy test (only for female subjects of childbearing potential)[c]	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (only for female subjects of childbearing potential at screening or if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin

Has been changed to read:

Category	Test Name
Urine Pregnancy test (only for female subjects of childbearing potential)[d]	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (in all female subjects at screening or if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin

Table 2. Laboratory Tests
Category "Urine Pregnancy test (only for female subjects of childbearing potential)[c]" previously read:

Category	Test Name
Infection screening	Hepatitis B Surface Antigen (qualitative)[a] Hepatitis B Surface Antibody (qualitative)[a] Hepatitis B Core Antibodies total (qualitative)[a] Hepatitis B Virus DNA (quantitative)[a,b] Hepatitis C Antibodies (qualitative)[a] Hepatitis C Virus RNA (quantitative)[a] HIV-1, and HIV-2 Antibody (qualitative)[a] QuantiFERON®-TB[c] (if applicable)[b]

Has been changed to read:

Category	Test Name
Infection screening	Hepatitis B Surface Antigen (qualitative)[a] Hepatitis B Surface Antibody (qualitative)[a] Hepatitis B Core Antibodies total (qualitative)[a] Hepatitis B Virus DNA (quantitative)[a,b] Hepatitis C Antibodies (qualitative)[a] Hepatitis C Virus RNA (quantitative)[a] HIV-1, and HIV-2 Antibody (qualitative)[a] PPD or QuantiFERON®-TB[c]

Table 2. Laboratory Tests
Table note "b." and "c." previously read:

b. If Hepatitis B Surface Antigen is negative but Hepatitis B Core Antibodies total is positive and/or Hepatitis B Surface Antibody is positive, Hepatitis B Virus DNA will be quantified. If Hepatitis B Virus DNA level is undetectable at screening, the subject can participate in this trial. If Hepatitis C Virus Antibodies is positive, Hepatitis C Virus RNA will be quantified. If Hepatitis C RNA level is undetectable at screening, the subject can participate in this trial.

TB testing will be performed at screening Visit 12, 16, and Week 188 Follow-up Visit.

c. Urine pregnancy test performed at every visit.

Has been changed to read:

b. If Hepatitis B Surface Antigen is negative but Hepatitis B Core Antibodies total is positive and/or Hepatitis B Surface Antibody is positive, Hepatitis B Virus DNA will be quantified. If Hepatitis B Virus DNA level is undetectable at screening, the subject can participate in this trial. In these cases, HBV DNA level will be monitored at least every 6 months. If positive, the subject's treatment will be discontinued. If Hepatitis C Virus Antibodies is positive, Hepatitis C Virus RNA will be quantified. If Hepatitis C RNA level is undetectable at screening, the subject can participate in this trial. In these cases, HCV RNA level will be monitored at least every 6 months. If positive, the subject's treatment will be discontinued.

c. TB testing will be performed at screening, Visit 12, 16, 20 and Week 184.

d. Urine pregnancy test will be performed at all dosing visits.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection <u>Blood Samples for Risankizumab Assay</u>
First paragraph, third and fourth sentence previously read:

Blood samples for the PK assay should be collected as closely as possible relative to the time of dosing and within 30 minutes prior to dosing. Date and exact time (to the nearest minute) of drug administration and PK and ADA sampling will be recorded on eCRFs.

Has been changed to read:

Blood samples for the PK assay should be collected as closely as possible relative to the time of dosing and within 60 minutes prior to dosing. Date and exact time (to the nearest minute) of drug administration will be recorded on eCRFs.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Blood Samples for Risankizumab Anti-Drug Antibody (ADA) Assay:
First paragraph, second and third sentence previously read:

Blood samples for the ADA assay should be collected as closely as possible relative to the time of dosing and within 30 minutes prior to dosing. Date and exact time (to the nearest minute) of drug administration and PK and ADA sampling will be recorded on eCRFs.

Has been changed to read:

Blood samples for the ADA assay should be collected as closely as possible relative to the time of dosing and within 60 minutes prior to dosing. Date and exact time (to the nearest minute) of drug administration will be recorded on eCRFs.

Section 5.3.4 Safety Variables
Subsection Major Cardiac, Cerebrovascular and Thrombotic Events Adjudication Committee
First paragraph previously read:

An independent adjudication committee will be used to adjudicate all observed cardio- and cerebro-vascular events reported during the conduct of the study to assure consistent assessment of major cardiac, cerebrovascular and thrombotic events. The events that are adjudicated and the adjudication process will be detailed in the CCVT Adjudication Committee Charter.

Has been changed to read:

An independent adjudication committee will be used to adjudicate all observed cardio- and cerebro-vascular events reported during the conduct of the study to assure consistent assessment of major cardiac, cerebrovascular and thrombotic events. The events that are

adjudicated and the adjudication process will be detailed in the CCVT Adjudication Committee Charter. Site personnel will collect source documentation for the identified events and submit to the CCVT Adjudication Committee. Source documentation should be obscured before submission by site personnel.

Source documentation: (below types of source may be included with the case and will vary depending on type of event and available source):

- SAE form or narrative
- Hospital Discharge Summary
- Death Summary/Details of death note
- Local Lab Values (e.g., normal ranges; cardiac biomarkers)
- Imaging reports (e.g., X-Ray, CT, MRI, MRA, Angiography, Ultrasonography)
- Consultation Notes (e.g., Cardiology, Neurology)
- Procedure Reports (e.g., cardiac catheterization, PCI, CABG)
- Echocardiography
- Admission History/Emergency Room report
- Autopsy result
- Death Certificate
- Clinical Course (e.g., progress notes, doctor visit notes)
- Narrative Form
- ECG
- Other Source (specified)

Section 5.5.4 Selection and Timing of Dose for Each Subject
Second paragraph, last sentence previously read:

Site personnel will enter the medication numbers in the eCRF.

Has been changed to read:

Site personnel will enter the kit numbers in the eCRF.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Clinical
		Statistics
		Pharmacokinetics
		Clinical
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Clinical
		Statistics
		Pharmacokinetics
		Clinical
		Clinical

Appendix C. Study Activities
Previously read:

Trial Periods	Screening	Treatment																					Follow-Up	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18	V 19	V 20	V 21	EOT/ PD		
Week		0	4	8	12	16	22	28	34	40	46	52	64	76	88	100	112	124	136	148	160	172	184	188
Day	–42 to –1	1	28	56	84	112	154	196	238	280	322	364	448	532	616	700	784	868	952	1036	1120	1162	1246	1274
Visit window (days)			± 3	± 7	± 7	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Informed consent	X																							
Demographics	X																							
Medical history	X																							
Smoking/alcohol history	X																							
Prior and ongoing medication	X																							
Psoriatic arthritis history[1]	X																							
In-/exclusion criteria	X	X																						
Height	X																							
Weight/waist circumference[2]	X					X				X														
Physical examination[3]	X^c	X^t	X^t	X^t	X^t	X^c	X^t	X^t	X^t	X^c	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t		X^c
Vital signs[4]	X	X	X	X	X	X	X	X^4	X	X	X	X	X	X	X	X	X	X^4	X	X	X	X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Trial Periods	**Screening**	**Treatment**																					**Follow-Up**	
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**	**V 16**	**V 17**	**V 18**	**V 19**	**V 20**	**V 21**	**EOT/ PD**		
Week		**0**	**4**	**8**	**12**	**16**	**22**	**28**	**34**	**40**	**46**	**52**	**64**	**76**	**88**	**100**	**112**	**124**	**136**	**148**	**160**	**172**	**184**	**188**
Day	**–42 to –1**	**1**	**28**	**56**	**84**	**112**	**154**	**196**	**238**	**280**	**322**	**364**	**448**	**532**	**616**	**700**	**784**	**868**	**952**	**1036**	**1120**	**1162**	**1246**	**1274**
Visit window (days)			**± 3**	**± 7**	**± 7**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Infection screening[5]	X											X				X						X		
Chest X-ray	X											X								X				
Pregnancy testing[6]	X	X	X			X		X		X		X		X		X		X		X		X		X
Safety laboratory tests[7]	X^c	X^c	X^t	X^c	X^t	X^c	X^t	X^c	X^t	X^c	X^t	X^c	X^t	X^t	X^t	X^c	X^t	X^t	X^t	X^c	X^t	X^c		X^c
12 lead-ECG	X																							
PK sampling[8]		X	X			X		X				X		X		X		X		X		X		X
ADA sampling[8]		X	X			X		X				X		X		X		X		X		X		X
Local tolerability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
JDA score and responder rating	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PGA-GPP[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
CGI-GI	X	X	X	X	X	X	X	X	X	X	X	X	X	X										
DLQI		X			X	X						X	X	X	X	X	X	X	X	X	X	X		X
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Contact IRT	X	X	X			X		X		X		X		X		X		X		X		X		
Administration of trial drugs		X	X			X		X		X		X		X		X		X		X		X		

Trial Periods	Screening	Treatment																					Follow-Up	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18	V 19	V 20	V 21	EOT/ PD		
Week		0	4	8	12	16	22	28	34	40	46	52	64	76	88	100	112	124	136	148	160	172	184	188
Day	–42 to –1	1	28	56	84	112	154	196	238	280	322	364	448	532	616	700	784	868	952	1036	1120	1162	1246	1274
Visit window (days)			± 3	± 7	± 7	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Last injection of trial medication[10]																						X		
Trial completion												X												
Vital status[11]																								X

1. At Visit 1, all subjects at all sites will be evaluated via CASPAr for history of psoriatic arthritis as detailed in Appendix F.
2. Refer to Section 5.3.1.1 for weight procedures.
3. Physical examination: C = complete, T = targeted. Refer to Section 5.3.1.
4. Vital signs should precede blood sampling and be assessed pre-dose at all dosing visits. Additional vital signs assessments at 5 minutes post-dose and 60 minutes post-dose at Visit 2 and Visit 3. Monitor for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose administered at Visit 2 and 1 hour following all other doses of study drug.
5. Infection screening consists in Hepatitis B Surface Antigen (qualitative), Hepatitis B Surface Antibody (qualitative), Total Hepatitis B Core Antibodies (qualitative), Hepatitis B Virus DNA (Quantitative) reflex, Hepatitis C Antibodies (Qualitative), Hepatitis C Virus RNA (Quantitative) reflex, HIV-1 and HIV-2 Antibody (Qualitative), QuantiFERON-TB. Refer to Appendix D.
6. Serum pregnancy testing at screening and if urine pregnancy test is positive. Urine pregnancy testing will be done prior to administration of study drug at all dosing visits and at each Follow-Up (FU) Visit.
7. C = complete, T = targeted. Targeted lab samples should be limited to WBC, serum CRP and serum albumin for the measurement of JDA. Subjects should be fasting for at least 8 hours prior to the blood sample being taken at the "complete" visits, except for screening. If not fasted mark on laboratory requisition form.
8. On dosing visits, PK and ADA sampling should be taken approximately within 1 hour prior to administration of study drug.
9. Collected for Substudy GPP.
10. Subjects that terminate trial medication early will complete EOT Visit procedures instead of the planned treatment period visit and return for Week 188 Follow-up Visit, 16 weeks after last dose of study medication.

11. Vital Status should be collected for subjects leaving the study before the planned Week 188 Follow-up visit.

Has been changed to read:

Trial Periods	Screening	Treatment																					Follow-Up	
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V 10**	**V 11**	**V 12**	**V 13**	**V 14**	**V 15**	**V 16**	**V 17**	**V 18**	**V 19**	**V 20**	**V 21**	**EOT/ PD**		
Week		**0**	**4**	**8**	**12**	**16**	**22**	**28**	**34**	**40**	**46**	**52**	**64**	**76**	**88**	**100**	**112**	**124**	**136**	**148**	**160**	**172**	**184**	**188**
Day	**–42 to –1**	**1**	**28**	**56**	**84**	**112**	**154**	**196**	**238**	**280**	**322**	**364**	**448**	**532**	**616**	**700**	**784**	**868**	**952**	**1036**	**1120**	**1162**	**1246**	**1274**
Visit window (days)			**± 3**	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Informed consent	X																							
Demographics	X																							
Medical history	X																							
Smoking/alcohol history	X																							
Prior and ongoing medication	X																							
Psoriatic arthritis history[1]	X																							
In-/exclusion criteria	X	X																						
Height	X																							
Weight/waist circumference[2]	X					X				X														
Physical examination[3]	X^c	X^t	X^t	X^t	X^t	X^c	X^t	X^t	X^t	X^c	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^c
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Trial Periods	Screening	Treatment																					Follow-Up	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18	V 19	V 20	V 21	EOT/ PD		
Week		0	4	8	12	16	22	28	34	40	46	52	64	76	88	100	112	124	136	148	160	172	184	188
Day	–42 to –1	1	28	56	84	112	154	196	238	280	322	364	448	532	616	700	784	868	952	1036	1120	1162	1246	1274
Visit window (days)			± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Infection screening[5]	X											X				X				X			X	
Chest X-ray	X											X								X			X	
Pregnancy testing[6]	X	X	X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests[7]	X[c]	X[c]	X[t]	X[c]	X[t]	X[c]	X[t]	X[c]	X[t]	X[c]	X[t]	X[c]	X[t]	X[t]	X[t]	X[c]	X[t]	X[t]	X[t]	X[c]	X[t]	X[c]	X[c]	X[c]
12 lead-ECG	X																							
PK sampling[8]		X	X			X		X				X		X		X		X		X		X	X	X
ADA sampling[8]		X	X			X		X				X		X		X		X		X		X	X	X
Local tolerability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
JDA score and responder rating	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGA-GPP[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-GI[10]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI		X			X	X						X	X	X	X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X	X			X		X		X		X	X	X	X	X	X	X	X	X	X	X		
Administration of trial drugs		X	X			X		X		X		X	X	X	X	X	X	X	X	X	X	X		

Trial Periods	Screening	Treatment																					Follow-Up	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18	V 19	V 20	V 21	EOT/ PD		
Week		0	4	8	12	16	22	28	34	40	46	52	64	76	88	100	112	124	136	148	160	172	184	188
Day	–42 to –1	1	28	56	84	112	154	196	238	280	322	364	448	532	616	700	784	868	952	1036	1120	1162	1246	1274
Visit window (days)			± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7
Last injection of trial medication[11]																						X		
Trial completion																								X
Vital status[12]																								X

1. At Visit 1, all subjects at all sites will be evaluated via CASPAr for history of psoriatic arthritis as detailed in Appendix F.
2. Refer to Section 5.3.1.1 for weight procedures.
3. Physical examination: C = complete, T = targeted. Refer to Section 5.3.1.
4. Vital signs should precede blood sampling and be assessed pre-dose at all dosing visits. At Visit 2 and Visit 3, additional vital sign assessments should be taken at 5 minutes post-dose and 60 minutes post-dose. Subjects should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose administered and 1 hour following all other doses of study drug.
5. Infection screening consists of Hepatitis B Surface Antigen (qualitative), Hepatitis B Surface Antibody (qualitative), Total Hepatitis B Core Antibodies (qualitative), Hepatitis B Virus DNA (Quantitative) reflex, Hepatitis C Antibodies (Qualitative), Hepatitis C Virus RNA (Quantitative) reflex, HIV-1 and HIV-2 Antibody (Qualitative), PPD or QuantiFERON-TB. Hepatitis B, Hepatitis C and HIV testing will be performed at screening. TB testing will be performed at screening, Visit 12, 16, 20 and Week 184.
6. Serum pregnancy testing in all female subjects at screening and if urine pregnancy test is positive. Urine pregnancy testing will be done in women of child-bearing potential prior to administration of study drug at all dosing visits and at each Follow-Up Visit.
7. C = complete, T = targeted. Targeted lab samples should be limited to WBC, serum CRP and serum albumin for the measurement of JDA. Subjects should be fasting for at least 8 hours prior to the blood sample being taken at the "complete" visits, except for screening. If not fasted mark on laboratory requisition form.
8. On dosing visits, PK and ADA sampling should be taken approximately within 1 hour prior to administration of study drug.
9. Collected for Substudy GPP.
10. Collected for Substudy EP.

11. Subjects that terminate trial medication early will complete EOT Visit procedures instead of the planned treatment period visit and return for Week 188 Follow-up Visit, 16 weeks after last dose of study medication.
12. Vital Status should be collected for subjects leaving the study before the planned Week 188 Follow-up visit.

Appendix D. Severity Assessment Criteria Score
Third paragraph, in-text table
Last row previously read:

Score	2	1	0
Serum albumin (mg/dL)	< 3.0	≥ 3.0 and < 3.8	≥ 3.8

Has been changed to read:

Score	2	1	0
Serum albumin (g/dL)	< 3.0	≥ 3.0 and < 3.8	≥ 3.8

Document Approval

Study M15988 - A Phase 3, Randomized, Open-Label Study to Assess Efficacy and Safety of Two Different Dose Regimens of Risankizumab Administered Subcutaneously in Japanese Subjects with Generalized Pustular Psoriasis or Erythrodermic Psoriasis - Amendment 1 - 18Jan2017

Version: 1.0 **Date:** 23-Jan-2017 03:46:55 PM **Company ID:** 01232017-00F9F68140A9A7-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	[redacted]	Approver
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		Approver
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		Approver
		Author
		Approver