1.0 Title Page

Clinical Study Protocol M15-997

A multicenter, open Label study to assess the safety and efficacy of rIsankizuMab for MaInTenance in moderate to severe pLaquE type pSoriaSis (LIMMITLESS)

Incorporating Administrative Change 1, 2, 3, 4, 5, and 6 and Amendments 1, 2, 3, 4, 5, 6, 7, and 8

AbbVie Investigational Product:	Risankizumab/ABBV-066/previously BI-655066
Date:	18 October 2021
Development Phase:	3
Study Design:	Global, multicenter, single-arm, open label extension study in subjects with moderate to severe plaque type psoriasis
EudraCT Number:	2016-003046-87
Investigator(s):	Investigator information is on file at AbbVie
Sponsor:	AbbVie*

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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.

Confidential Information
No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	22 September 2016
Amendment 1	09 December 2016
Administrative Change 1	19 April 2017
Amendment 1.01 (France Only)	05 May 2017
Amendment 2	06 June 2017
Amendment 3	10 January 2018
Amendment 3.01 (France Only)	30 January 2018
Amendment 3.02 (Japan Only)	30 January 2018
Amendment 4	21 June 2018
Amendment 4.01 (France Only)	09 July 2018
Amendment 4.02 (Japan Only)	09 July 2018
Amendment 4.02.01 (Japan Only)	30 November 2018
Amendment 5	24 September 2019
Administrative Change 2	07 October 2019
Amendment 5.01 (France Only)	28 October 2019
Administrative Change 3	01 November 2019
Amendment 6	26 November 2019
Amendment 6.01 (France Only)	13 December 2019
Amendment 6.02 (Japan Only)	30 December 2019
Administrative Change 4	21 July 2020
Amendment 7	17 November 2020
Amendment 7.01 (France Only)	07 December 2020
Amendment 7.02 (Japan Only)	08 December 2020
Administrative Change 5	18 March 2021
Administrative Change 6	01 September 2021

The purpose of this amendment is to:

- Throughout the protocol, remove the requirement for the physical exam, clinical laboratory samples and efficacy assessments PASI, sPGA, NAPSI, PPASI, PSSI, and the DLQI at the End of Observation (EOO) visit and change the EOO visit from an in-person visit to a phone visit.

  Rationale: *Converting the EOO visit to a safety follow up call 20 weeks after the last study drug administration ensures that the safety monitoring measures in this study are consistent with all risankizumab trials in psoriasis and in other indications. All safety assessments that had not been scheduled for the EOT visit but cannot be performed during the EOO safety follow up call (i.e., annual TB testing and ECG) will now be completed at the EOT visit to ensure those parameters are assessed. Considering the availability of 5-year efficacy data from this study, the additional efficacy assessments at the EOO visit are not required and removing these will not impact the study objectives nor the scientific interpretation of the study results.*

- Change the End of Observation visit requirement to perform an ECG, TB testing and additional clinical laboratory testing to the EOT visit in Appendix C ("Study Activities Flow Chart").

  Rationale: *These procedures will no longer be performed at the End of Observation visit and will therefore be performed at the EOT visit to ensure that all appropriate safety monitoring is completed.*

- Clarify the analysis of the immunogenicity samples in Section 5.3.2.4 ("Measurement Methods").

  Rationale: *To provide clarity on which samples will be analyzed for antibodies.*

- Add INR test to be performed if ALT or AST > 3 x ULN to Table 1 Clinical Laboratory Test in Section 5.3.1.1 ("Study Procedures").

  Rationale: *Although mentioned in the discontinuation criteria, the INR test was Previously not included in the Clinical Laboratory Test table. The Clinical Laboratory Test table has been updated to add the INR test to coincide with the specified discontinuation criteria in Section 5.4.1 ("Discontinuation of Individual Subjects").*

- Update the definition of hepatic injury to include marked peak aminotransferase elevations ≥ 8-fold ULN, instead of ≥ 10-fold ULN in Section 6.1.1.3 ("Adverse Events of Special Interests").

Rationale: *To align with U.S. FDA Drug-Induced Liver Injury: Premarketing Clinical Evaluation guidelines.*

- Clarify in Section 6.1.1.3 Adverse Events of Special Interests, that the supplemental hepatic eCRFs have to be completed for any hepatic related AE leading to discontinuation or interruption of study drug or any hepatic related SAE, not meeting the hepatic injury definition.

  Rationale: *To align guidance on supplemental hepatic eCRFs completion in Section 6.1.1.3 ("Adverse Events of Special Interests") with the standardized approach across the risankizumab development programs, which is based on U.S. FDA Drug-Induced Liver Injury: Premarketing Clinical Evaluation guidelines.*

- Add language to address potential use of SARS-CoV-2 vaccines to Section 5.2.3 ("Prior and Concomitant Therapy") and Section 6.1.5 ("Adverse Event Reporting").

  Rationale: *To provide guidance on COVID-19 vaccinations to investigators.*

- Update the Sponsor/Emergency contact/Primary Therapeutic Area Medical Director and Alternate Contact for Protocol Deviations in Section 1.0 ("Title Page"), Section 6.1.5 ("Adverse Event Reporting") and Section 7.0 ("Protocol Deviations").

  Rationale: *Change in AbbVie company staff.*

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-997
Name of Study Drug: Risankizumab/ABBV-066 (previously known as BI 655066)	**Phase of Development:** 3
Name of Active Ingredient: Risankizumab/ABBV-066	**Date of Protocol Synopsis:** 18 October 2021
Protocol Title: A multicenter, open **L**abel study to assess the safety and efficacy of r**I**sankizu**M**ab for **Ma**l**In**T**e**nance in moderate to severe p**L**aqu**E** type p**S**oria**S**is (LIMMITLESS)	
Objectives: The primary objective of Study M15-997 is to investigate long-term safety and tolerability of risankizumab in subjects with psoriasis who have completed one of the preceding Phase 2/3 studies. The secondary objective of Study M15-997 is to investigate the long-term efficacy of risankizumab in the treatment of psoriasis.	
Investigators: Multicenter	
Study Sites: Approximately 235 sites globally	
Study Population: Adult subjects with a diagnosis of moderate to severe chronic plaque psoriasis who have completed one of the preceding Phase 2/3 Studies 1311.3, 1311.4, 1311.13, 1311.28, 1311.30, 1311.38 and M16-178.	
Number of Subjects to be Enrolled: Approximately 2200	
Methodology: This is a Phase 3, single-arm, multicenter OLE study designed to investigate the long-term safety and efficacy of 150 mg risankizumab in the treatment of moderate to severe chronic plaque psoriasis. Approximately 2200 subjects who meet the entry criteria are planned to be enrolled in this study, rolling over from the preceding Phase 2/3 studies. During this study, all subjects will receive risankizumab 150 mg subcutaneously every 12 weeks for 252 weeks (last dose of study drug to be administered at visit Week 252 [EOT]). Study visits will occur every 12 weeks starting from Baseline until the Week 156 visit. From Week 156 until the EOT visit, subject visits will occur every 24 weeks. At Weeks 168, 192, 216 and 240, subjects or caregivers will self-administer risankizumab at home after having been instructed at Week 156 by the site staff on how to self-inject via the pre-filled syringe. Alternatively, subjects may receive the study drug of Weeks 168, 192, 216 and 240 at the study site. All subjects will have an End of Observation Visit (EOO) via phone, approximately 20 weeks after their last administered dose of study drug. Study completion is defined as a subject having completed the EOO visit.	

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subjects with moderate to severe chronic plaque psoriasis who have completed one of the preceding Studies 1311.3, 1311.4, 1311.13, 1311.28, 1311.30, 1311.38 and M16-178.
2. Subjects must be candidates for prolonged open label risankizumab treatment according to investigator judgment

Main Exclusion:

1. Premature discontinuation for any reason in the preceding study.

Investigational Product:	Risankizumab (ABBV-066): 75 mg pre-filled syringe, 90 mg/mL, 0.83 mL dispensed volume, 0.87 mL fill volume
Dose:	Risankizumab (ABBV-066): 150 mg administered every 12 weeks
Mode of Administration:	Subcutaneous injection

Duration of Treatment: The study duration is 252 weeks.

Criteria for Evaluation:

Efficacy:

Key variables to be summarized at all visits:

- Proportion of subjects achieving ≥ 90% reduction in Psoriasis Area and Severity Index (PASI) score (PASI 90)
- Proportion of subjects achieving the Static Physician Global Assessment (sPGA) score of clear or almost clear
- Proportion of subjects achieving ≥ 75% reduction in PASI score (PASI 75)
- Proportion of subjects achieving 100% reduction in PASI score (PASI 100)
- Proportion of subjects achieving the sPGA score of clear

Pharmacokinetics (PK) and Immunogenicity:

Blood samples will be collected for measurement of risankizumab concentration and anti-drug antibody (ADA) and neutralizing antibody (NAb) just prior to dosing at Baseline, Week 48, Week 96, Week 156, Week 204 and End of Treatment (EOT) visit.

Safety:

Adverse events (AE)s, laboratory data and vital signs will be assessed throughout the study.

Statistical Methods:

Efficacy:

For all efficacy analyses (including the assessment of PASI responses), baseline refers to the last non-missing value prior to the first dose of study drug in the preceding studies.

Summary statistics will be provided. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, maximum, 25^{th} and 75^{th} percentile, as well as the 95% confidence intervals (CIs) of mean values. Categorical variables will be summarized by counts and percentages, as well as the 95% CIs of the percentages.

Statistical Methods (Continued):

Pharmacokinetics (PK) and Immunogenicity:

Risankizumab plasma concentrations will be determined. Descriptive statistics will be calculated for each sampling time (study visit). The number and percentage of subjects with ADA will be calculated.

Additional analyses combining pharmacokinetic and ADA data from this study and other studies may be conducted if appropriate. After completion of the study, PK and ADA plasma samples may be used for further methodological investigations, e.g., stability testing.

Safety:

All AEs, serious adverse events (SAE)s, AEs leading to discontinuation, and pre-specified AEs of Special interest and AEs of Safety 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 (either in the preceding study or this study) and within 20 weeks after the last study drug 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 patient-years) of SAEs, deaths, AEs leading to discontinuation from the study, and pre-specified AESIs will be provided as well. Mean change in laboratory and vital signs variables will be summarized. For selected parameters, a listing of all subjects with clinically significant laboratory or vital sign determinations will be provided. Shift tables for changes from baseline according to the normal range will also be provided.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AAC	Anaphylaxis Adjudication Committee
ADA	Anti-Drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
C_{max}	Maximal concentration
COVID-19	Coronavirus Disease - 2019
CRF	Case report form
DLQI	Dermatology Life Quality Index
DMC	Data monitoring committee
DTP	Direct-to-Patient
E12W	Every 12 weeks
E24W	Every 24 weeks
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOO	End Of Observation
EOT	End Of Treatment
EudraCT	European Clinical Trials Database
FU	Follow-up
GCP	Good clinical practice
Hct	Hematocrit
Hb	Hemoglobin
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFU	Instructions for Use
IGRA	Interferon gamma release assay
IL	Interleukin

INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional review board
IRT	Interactive response system
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LDH	Lactic dehydrogenase
LOCF	Last observation carried forward
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular event
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTX	Methotrexate
NAb	Neutralizing antibody
NAPSI	Nail Psoriasis Severity Index
OLE	Open label extension
PASI	Psoriasis Area and Severity Index
PK	Pharmacokinetics
PMN	Polymorphonuclear
PoCC	Proof of clinical concept
POR	Proof of receipt
PPD	Purified protein derivative
PPASI	Palmoplantar Psoriasis Area and Severity Index
PSSI	Psoriasis Scalp Severity Index
RZB	Risankizumab
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
s.c.	Subcutaneous
sPGA	Static Physician Global Assessment
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
ULN	Upper limit of normal

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3.0 Introduction

Psoriasis is a chronic inflammatory disease with raised, well-demarcated erythematous plaques with adherent silvery scales.[1] It is the most prevalent immune mediated skin disease, affecting 2% of the world population.[2] Twenty-five percent of subjects have moderate to severe disease with considerable negative impact on psychosocial and economic status.[3] It is increasingly recognized that psoriasis is more than a superficial disease, with 30% of subjects having joint involvement and a high correlation between psoriasis and obesity, diabetes, depression, metabolic syndrome and cardiovascular risk.[4]

While the majority of psoriasis subjects are managed initially with topical therapies, those with severe and/or refractory disease may require phototherapy and/or systemic therapy. Oral systemic agents provide modest efficacy, but increasingly subjects are treated with biological agents, such as tumor necrosis factor (TNF)-alpha inhibitors (etanercept, adalimumab) and the p40 Interleukin (IL)-12/23 inhibitor (ustekinumab).[5] While the clinical efficacy of ustekinumab indicates a role for both IL-12 and IL-23 in the pathogenesis of psoriasis,[6] more recent data suggest that IL-23 is disproportionately involved in the maintenance of chronic psoriasis,[6] IL-23 is thought to be involved in the pathophysiology of psoriasis via induction and maintenance of Th17 type cells, and other IL-23 responsive cells. This is supported by recent clinical data indicating that monoclonal antibodies (mAb) that block IL-17, the cytokine produced by Th17 cells, have high efficacy in psoriasis.[7]

There is still clinical need for increased efficacy as the most effective anti-TNF and IL12/23 agents provide only 75% improvement in psoriasis in about 60 – 70% of subjects and these responses tend to be lost over time. While the anti-IL-17 agents (i.e., secukinumab) provide better efficacy, they require monthly injections, thus their long-term utility is still undetermined. Risankizumab (ABBV-066) is a humanized mAb with high affinity for the p19 component of human IL-23A that specifically neutralizes IL-23. Proof of clinical concept (PoCC) for risankizumab was demonstrated in a single dose Phase 1 study in 39 subjects with moderate to severe plaque psoriasis where 87% of

subjects achieved at least 75% reduction in Psoriasis Area and Severity Index (PASI) from baseline (PASI 75) with no safety concerns.[8]

Positive results were observed from 4 pivotal Phase 3 clinical trials that evaluated risankizumab compared with ustekinumab, placebo, and adalimumab for the treatment of patients with moderate to severe plaque psoriasis. Results from these pivotal studies demonstrated that risankizumab is highly effective for the treatment of psoriasis, meeting co-primary endpoints of achieving at least a 90% improvement in the Psoriasis Area and Severity Index (PASI 90) and static physician global assessment (sPGA) score of clear or almost clear (0 or 1) versus comparator or placebo at Week 16 across all 4 studies.[9] Risankizumab has been well tolerated in the completed and ongoing studies.

The current study is being performed to establish the long-term safety and efficacy of risankizumab.

Risankizumab is a fully humanized mAb of the IgG1 subclass directed towards IL-23p19. The antibody has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity. Risankizumab binds with high affinity to human IL-23 and inhibits IL-23 stimulated IL-17 production at inhibitory concentration (IC) 50 concentrations below 10 pM, as compared with 167 pM for ustekinumab in the same system. Risankizumab does not affect IL-12 at a maximum tested concentration (33 nM) and it does not inhibit IL-12 stimulated IFN-γ production.

The toxicology data suggest risankizumab can be safely administered to humans, as supported by chronic administration to monkeys for up to 26 weeks. The monkey was identified as the most relevant toxicology species with no observed adverse effect level (NOAEL) of 50 mg/kg/dose, corresponding to an exposure (combined sex) of 677 µg/mL for the maximal concentration (C_{max}) and 86,250 µg•h/mL (3594 µg•day/mL) for area under the curve (AUC) $_{0\text{-}168}$, respectively.

After a single intravenous administration in subjects with psoriasis, risankizumab geometric mean AUC_{0-inf} ranged from 2.93 – 1650 µg•day/mL and C_{max} from 0.311 –

110 µg/mL, with exposure increasing in a dose-proportional manner. Group mean clearance and terminal phase volume of distribution were 0.33 L/day and 10.8 L, respectively. Pharmacokinetic (PK) parameter variability, expressed as the geometric mean of coefficient variation (gCV) (%) was < 50%. After a single subcutaneous (s.c.) administration of risankizumab, maximal exposures were reached between 4 – 10 days and subcutaneous estimated bioavailability was 73%.

For a more detailed description of the drug profile refer to the current Investigator's Brochure (IB).[9]

3.1 Differences Statement

Study M15-997 will assess long-term safety and efficacy of risankizumab in subjects with moderate to severe chronic plaque psoriasis. The duration of this study will be 252 weeks.

3.2 Benefits and Risks

Based on data from completed and ongoing studies with risankizumab, patients with moderate to severe plaque psoriasis are expected to benefit from long-term treatment with risankizumab. In the Phase 2 study (Study 1311.2), treatment with 90 mg or 180 mg of risankizumab resulted in a higher percentage of patients achieving and maintaining PASI 90 through Week 48 as compared with ustekinumab, an approved therapy for moderate to severe plaque Psoriasis. Favorable results were also observed from 4 pivotal Phase 3 clinical trials that evaluated risankizumab compared with ustekinumab, placebo, and adalimumab for the treatment of patients with moderate to severe plaque psoriasis. Results from these pivotal studies demonstrated that risankizumab administered 150 mg every 12 weeks is highly effective for the treatment of psoriasis, meeting co-primary endpoints of achieving at least a 90% improvement in the Psoriasis Area and Severity Index (PASI 90) and static physician global assessment (sPGA) score of clear or almost clear (0 or 1) versus comparator or placebo at Week 16 across all 4 studies.

As of 29 March 2019, risankizumab safety data were available for 3236 subjects, including 2673 subjects with plaque psoriasis, 177 in subjects with PsA, 17 subjects with GPP/EP, 115 with CD, 149 with AS, and 105 with asthma.[9] In the Phase 2 psoriasis study (Study 1311.2), 126 subjects received risankizumab and the most commonly occurring AEs were nasopharyngitis (32%), headache (9%), back pain (6%), and arthralgia (5%). There was no relationship between treatment groups or doses and the overall frequency of AEs or the occurrence of AEs in specific organ classes, or any individual AE based on available unblinded safety data.

As with any biologic therapy, hypersensitivity reactions may be possible. There have been no reported instances of drug hypersensitivity to risankizumab. Injection site erythema was reported in 4.8% of subjects who received 180 mg of risankizumab and 3/126 (2.4%) of total subjects receiving risankizumab in Study 1311.2. As an 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 a positive QuantiFERON®-test or a positive purified protein derivative (PPD) skin test for tuberculosis (TB) must fulfill entry criteria as specified in Section 5.2.2.

IL-23 inhibition is not known to increase the risk of TB infection or impair the response to TB infection in animal models.[10,11] Thus, low risk subjects with positive QuantiFERON TB testing are not required to be treated with anti-tuberculosis therapy prior to receiving risankizumab, but should be carefully monitored for any sign of TB reactivation. Absence of TB reactivation, despite not receiving anti-tuberculosis prophylaxis will provide important information in humans as to whether TB testing is required prior to treatment with risankizumab.[12]

There have been post marketing reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving ustekinumab, anti-IL12/23 mAb who had

pre-existing risk factors for developing NMSC.[13] Patients with moderate to severe PsO generally have risk factors for development of NMSC. In the completed studies to date, risankizumab has not been associated with an increased risk of malignancies but the risk with long-term therapy is not known.

Increases in the incidence rate of major adverse cardiovascular events (MACE) including myocardial infarction, cerebrovascular accident, and cardiovascular death, reported in the 12 week controlled portions of the clinical trials with anti-IL-12/23 agents, such as ustekinumab, have not been observed in longer term studies.[14]

In order to recognize any safety signals as early as possible, an independent Data Monitoring Committee (DMC) has been monitoring unblinded data from all studies where subjects are receiving risankizumab. As the sponsor has comprehensive safety monitoring measures in place to enable signal detection in open label studies, monitoring by the independent DMC will no longer be in effect for this open-label study. Routine pharmacovigilance surveillance will continue to be conducted.

An independent adjudication committee will be adjudicating all observed cardio- and cerebro-vascular events including major adverse cardiovascular events (MACE) in a blinded manner.

In conclusion, the benefit-risk profile of risankizumab is considered appropriate for allowing subjects to continue therapy under this long-term extension study.

In view of the coronavirus disease of 2019 (COVID-19) pandemic, the benefit-risk profile of various immunomodulatory therapies on COVID-19 is being evaluated based on real world and clinical trial data. At this time, the effects of risankizumab on the course of COVID-19 are not well defined.

4.0 Study Objective

The primary objective of Study M15-997 is to investigate long-term safety and tolerability of risankizumab in subjects with psoriasis who have completed one of the preceding Phase 2/3 studies.

The secondary objective of Study M15-997 is to investigate the long-term efficacy of risankizumab in the treatment of psoriasis.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, single-arm, multicenter, OLE study designed to investigate the long-term safety and efficacy of risankizumab 150 mg E12W in the treatment of moderate to severe chronic plaque psoriasis. Approximately 2200 subjects who meet the entry criteria are planned to be enrolled in this study, rolling over from the preceding Studies 1311.3, 1311.4, 1311.13, 1311.28, 1311.30, 1311.38 and M16-178 (Phase 2/3, randomized clinical studies in subjects with moderate to severe chronic plaque psoriasis, conducted by Boehringer Ingelheim or AbbVie).

All subjects need to complete one of the preceding Phase 2/3 psoriasis studies. The subject preferably has the Baseline visit of Study M15-997 on the same day of the completion visit of the preceding study; however, the Baseline visit can be delayed up to 8 weeks if needed.

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in Section 5.3.1.1 Study Procedures. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to logistical restrictions or other pandemic-related reasons, follow the updates below on how to proceed.

Baseline Visit

Baseline assessments will include medical history, physical examination, electrocardiogram (ECG) and laboratory results including pregnancy testing, all of which will be reviewed by the study site to confirm selection criteria are met prior to enrolling the subject.

If the Baseline visit occurs on the same day or in the 4 days following the completion visit of the preceding study, only selected activities are required as some activities are common to both studies and are not required twice. See Study Activities Flow Chart in Appendix C. If the Baseline visit occurs > 4 days and ≤ 8 weeks after the completion visit of the preceding study, all procedures specified in Appendix C at the Baseline visit are required.

Subjects will be assigned a unique patient number via interactive response system (IRT).

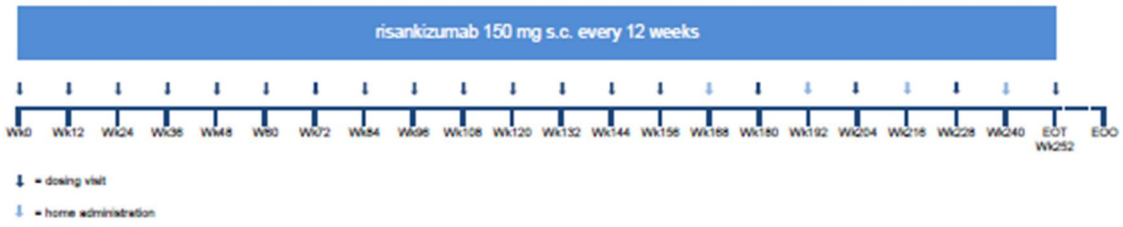
Administration of study medication should be the last activity at the Baseline visit.

All subjects will be administered 150 mg risankizumab s.c. at the Baseline visit.

Treatment Period

From the Baseline visit onwards, risankizumab will be administered subcutaneously E12W during the study.

Figure 1. Study Schematic



Study visits for dosing, efficacy and safety assessments will be performed E12W starting from Baseline until the Week 156 visit. After this visit until the End of Treatment (EOT) visit at Week 252, study visits will be performed E24W. There is a ± 7 days visit window for study visits. Every effort will be made to bring subjects back to their original scheduled visit (calculated from Baseline) if they are out of the visit window.

At Weeks 168, 192, 216 and 240, subjects will self-administer risankizumab at home after proper training to the subject and/or caregiver on the injection technique with the pre-filled syringe at Week 156 by the site staff. Alternatively, subjects may receive the injection of study drug of Weeks 168, 192, 216 and 240 at the study site. Subjects who discontinue study drug treatment early will need to attend an early EOT visit ideally within 2 weeks after the decision and preferably prior to the administration of any new therapies (Section 5.4.1).

End of Observation Visit

All subjects, including those that prematurely discontinued study drug treatment, will have an End of Observation Visit (EOO) via phone, approximately 20 weeks after their last administered dose of study drug. Study completion is defined as a subject having completed the EOO visit.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

1. Subjects with a history of moderate to severe chronic plaque psoriasis, who have completed one of the preceding studies.
2. Subjects must be candidates for prolonged open label risankizumab treatment according to investigator judgment.
3. Females of childbearing potential must have a negative urine pregnancy test result at Baseline.

If female, subject must be either postmenopausal, OR permanently surgically sterile OR for women of childbearing potential practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Baseline through at least 20 weeks after the last dose of study drug.

4. Subjects must have signed and dated a written informed consent in accordance with Good Clinical Practice (GCP) and local legislation prior to admission into the study.

Rationale for the Inclusion Criteria:

1, 2	To select the adequate subject population
3	The impact of risankizumab on pregnancy and reproduction is unknown
4	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

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

1. Premature discontinuation for any reason in the preceding study.
2. Subjects who have developed guttate, erythrodermic, pustular or drug-induced psoriasis as diagnosed by the investigator during the preceding study.
3. Use of any prohibited medication as specified in Section 5.2.3.1 or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator.
4. Known tuberculosis (TB) or evidence of TB infection. Subjects with a positive QuantiFERON® TB test or a positive purified protein derivate (PPD) skin 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 TB.

5. Subjects who have developed active or suspected malignancy during the preceding study, except appropriately treated basal cell or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
6. Subjects who have laboratory evidence of Human Immunodeficiency Virus (HIV), hepatitis B or hepatitis C viral infection from laboratory testing within the preceding clinical trial or any other source.
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 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 study, 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. Previous enrollment in this study.
10. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or within 20 weeks after the last dose of study drug.
11. Time elapsed is > 8 weeks since the completion visit in the preceding study.
12. Subject is considered by the investigator for any reason, to be an unsuitable candidate for the study and not able to comply with the study protocol.

Rationale for Exclusion Criteria:

10	The impact of risankizumab on pregnancy and reproduction is unknown
1, 7, 9, 11	To select the adequate subject population
2, 3, 4, 5, 6, 8, 12	To ensure the safety of the subjects throughout the study

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, or receives during the study, must be recorded 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 electronic case report form (eCRF).

The AbbVie primary Therapeutic Area Medical Director (TA MD) identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

COVID-19 Pandemic-Related Vaccination Guidance

Non-live vaccines may be administered during screening or treatment period, if not contraindicated or medically inappropriate.

The potential impact of risankizumab on SARS-CoV-2 vaccination is unknown. The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject and/or guardian.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF.

5.2.3.1 Prohibited Therapy

Use of the following therapies are prohibited from administration of the first dose of study drug in the preceding study throughout the EOT visit of Study M15-997, including any gap between the preceding study and Study M15-997:

- Investigational devices or products
- anti-IL-12/23, and anti-IL-17 agents, including but not limited to guselkumab, tildrakizumab, ustekinumab, ixekizumab and secukinumab; only comparator drug use in previous study is allowed for ustekinumab

- TNF inhibitors; only comparator drug use in preceding study is allowed for Adalimumab (Humira®)
- Topical treatment for psoriasis or any other skin condition such as retinoids, vitamin D analogues, vitamin A analogs, anthralin and steroids. Exception: Lower potency topical steroids such as alclometasone dipropionate cream, ointment 0.05, desonide cream, gel, foam, ointment 0.05, fluocinolone acetonide cream, solution 0.01, dexamethasone cream 0.1, hydrocortisone cream, lotion, ointment, solution 0.25, 0.5, 1, or hydrocortisone acetate cream, ointment 0.5 - 1 may be used for limited period of time defined as approximately 6 weeks without removing subjects from the study with a restriction of use within 24 hours prior to study visit.
- Systemic immunomodulating medications including methotrexate (MTX), cyclosporine A and corticosteroids except steroids with only a topical effect (e.g., inhalative corticosteroids to treat asthma or drops used in the eye or ear)
- Systemic psoriasis medications including retinoids and fumarates, or any other drugs known to possibly benefit psoriasis
- Photochemotherapy (e.g., PUVA)
- Phototherapy (e.g., UVA, UVB, Ultra Violet A/B)
- Live vaccines (Live vaccines are not permitted up to 20 weeks after the last dose of study drug).

The AbbVie TA MD should be contacted if there are any questions regarding prohibited therapy.

5.2.4 Contraception Recommendations and Pregnancy Testing

Female subjects of childbearing potential must be ready and able to use highly effective methods of birth control per International Conference on Harmonization (ICH) M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. Or subjects must have only vasectomized sexual partner(s) (vasectomy at least 1 year prior to enrolment), or be abstinent throughout the study for at least 20 weeks after the last dose of study drug is given.

Women of childbearing potential are defined as:

- having experienced menarche and are
- not postmenopausal (12 months with no menses without an alternative medical cause) and are
- not permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

The following is a list of accepted contraception methods.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
- 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).

See Pregnancy Testing paragraph in Section 5.3.1.1 for pregnancy testing instructions.

5.3 Efficacy, Pharmacokinetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed

Study procedures will be performed at the study visits as specified in Appendix C. Study visits are scheduled E12W, starting from Baseline (Week 0) until Week 156 and E24W from Week 156 until the EOT visit. Study procedures are discussed in detail in this section, with the exception of drug concentration measurements and antibody measurements (discussed in Section 5.3.2), study drug administration (discussed in Section 5.5.1), and the collection of AE information (discussed in Section 6.1.5). All study data will be recorded in source documents and on the appropriate eCRFs.

5.3.1.1 Study Procedures

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to logistical restrictions or other reasons, the following modifications are allowed:

- If permitted by local regulations, the IRB/IEC and the subject, the visits may be conducted in the subject's home.
- If a subject is unable to go to the site for a study visit, a phone call/virtual visit from the site should be completed as close as possible to the planned date of the study visit. The phone call will query for any AEs and review concomitant medications. If possible, complete DLQI assessment. An on-site study visit to complete the missed study procedures, including study drug administration, should be scheduled as soon as feasible.
- If a subject is unable to come to the site for a study visit, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations and if the subject has been trained for self-injection. For more information, please refer to Section 5.5.4.
- If for any reason laboratory samples cannot be shipped to the central laboratory, a local laboratory may be used for routine assessment. Local

laboratory results should be reviewed by the Investigator as soon as possible. Local labs should be added to the Unscheduled local lab eCRF.

Informed Consent

The subject will sign and date a study specific, Independent Ethics Committee (IEC)/Institutional 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.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

Inclusion/Exclusion Criteria

Subject will be eligible for study enrollment if he/she meets all inclusion criteria and none of the exclusion criteria at Baseline.

Demographics

The subject's demographic data, including date of birth, gender, race, ethnicity, and disease status that has been collected at the screening visit of the preceding study will be used in Study M15-997, so does not need to be collected again.

Medical and Surgical History

Medical history collected in the preceding study will be used in Study M15-997. Only new information and updates will need to be collected at the Study M15-997 Baseline Visit.

Physical Examination

Symptom directed physical examination will be performed at visits as described in Appendix C. Clinically relevant abnormal findings will be reported as medical history or AEs.

Vital Signs Assessment

Vital signs assessments include temperature, pulse rate, sitting blood pressure, and respiratory rate, after subjects have been seated comfortably for at least 5 minutes.

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

Additional vital signs assessments should be made 5 (± 2) minutes post-dose and 60 (± 10) minutes post-dose at Visit 1 and Visit 2.

Body Weight

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

- 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.)

12-Lead Electrocardiogram (ECG)

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

ECGs will be recorded after the subject has 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.

ECGs 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.

Dated and signed printouts will be stored in the subject's medical file.

In the event a scheduled ECG may not be performed due to study modifications related to the COVID-19 pandemic, perform the 12-lead ECG at the next earliest feasible visit or arrange to have an alternative acceptable local facility perform the ECG for the subject.

Psoriasis Area and Severity Index (PASI) Evaluation

The PASI score is an established measure of clinical efficacy for psoriasis medications.[12] If possible, the efficacy assessor from the preceding study should perform the efficacy assessments in this study. If not possible, a qualified and delegated site staff member will perform the PASI assessment at the designated study visits identified in Appendix C. Information and instructions on the calculation of the PASI score are provided in Appendix E.

Static Physician Global Assessment (sPGA)

The sPGA is a 5 point score ranging from 0 to 4, based on the physician's assessment of the average thickness, erythema, and scaling of all psoriatic lesions. If possible, the assessor from the preceding study should perform the efficacy assessments in this study. If not possible, a qualified and delegated site staff member will perform the sPGA assessment at the designated study visits identified in Appendix C. Information and instructions on the calculation of the sPGA score are provided in Appendix F.

Nail Psoriasis Severity Index (NAPSI)

The NAPSI assesses how much of the fingernail is affected with psoriasis. If a subject has nail psoriasis, if possible, the assessor from the preceding study should perform this assessment in this study. If not possible, a qualified and delegated site staff member will assess the nail psoriasis at the designated study visits identified in Appendix C. Use of artificial nails and/or nail polish should be avoided for subjects with nail psoriasis throughout the study in order to ensure accuracy of assessments. Information and instructions on the calculation of the NAPSI score are provided in Appendix G.

Palmoplantar Psoriasis Area and Severity Index (PPASI)

The PPASI provides a numeric scoring for psoriasis affecting the hands and feet. It is a linear combination of percent of surface area of hands and feet that are affected and the severity of erythema, induration, and desquamation.

If a subject has palmoplantar psoriasis, if possible, the assessor from the preceding study should perform this assessment in this study. If not possible, a qualified and delegated site staff member will assess the psoriasis at each protocol defined time point. Information and instructions on the calculation of the PPASI score are provided in Appendix H.

Psoriasis Scalp Severity Index (PSSI)

If a subject has scalp psoriasis, if possible, the assessor from the preceding study should perform this assessment in this study. If not possible, a qualified and delegated site staff member will assess the erythema (redness), induration (hardness), desquamation (shedding of skin) and percent of scalp covered at each protocol defined time point. Information and instructions on the calculation of the PSSI score are provided in Appendix I.

Dermatology Life Quality Index (DLQI)

DLQI is a self-administered, ten-question questionnaire used to assess the effect of different skin diseases on a subject's quality of life, overall health, and disability status. The questionnaire covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment and has a 1 week recall period.[15] The questionnaire should be completed by the subject on his/her own. A schedule of assessments for the DLQI is provided in Appendix C and instructions on the calculation of DLQI score are provided in Appendix J.

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In this situation, sites will read the DLQI questions and response options to the subject and record the subject's responses. The subject's ability to view the DLQI to understand the questions and response options should be preserved. Sites may share the questionnaire by videoconference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of DLQI data collection should be recorded along with who collected the information.

Pregnancy Testing

Urine pregnancy testing for all women of child-bearing potential will be conducted on-site at every study visit and must be negative to further treat the subject. Additional serum pregnancy testing will occur in case of a positive urine test result at any of the visits.

Urine pregnancy self-testing for women of child-bearing potential will be required prior to self-injection of risankizumab at home at Weeks 168, 192, 216 and 240. If the result is positive, the injection should not be performed.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Baseline in Study M15-997 do not require pregnancy testing.

Laboratory Testing

Laboratory sample collection should be the last procedure prior to study drug administration.

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. Instructions regarding sample collection, sample handling/processing and sample shipping are provided in the Laboratory Manual. Laboratory sampling will be done at each study visit as outlined in Appendix C. The following clinical laboratory tests only need to be done at the Visit 5, Visit 10, Visit 14, Visit 16 and the EOT visit: Electrolytes, C-reactive protein, cholesterol, urinalysis, urine sediment and urine. During these visits, the subject should be fasting for at least 8 hours prior to the blood sample being taken. 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.

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.

Table 1. Clinical Laboratory Tests

Category	Test Name
Hematology	Hematocrit (Hct) Hemoglobin (Hb) Red blood cell count/Erythrocytes Reticulocyte count White blood cells/Leukocytes Platelet count/Thrombocytes
Differential test automatic	Neutrophils (relative count) Eosinophils (relative count) Basophils (relative count) Monocytes (relative count) Lymphocytes (relative count)
Differential test manual (if differential test automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	International Normalized Ratio (INR)[a]
Enzymes	AST (GOT) ALT (GPT) Alkaline phosphatase (AP) Creatine kinase (CK) CK-MB, **only if CK is elevated** Gamma-glutamyl transferase (GGT/γ-GT) Lactic dehydrogenase (LDH) Amylase Lipase
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate

Table 1. Clinical Laboratory Tests (Continued)

Category	Test Name
Substrates	Glucose BUN (blood urea nitrogen) Uric acid Creatinine eGFR (estimated by CKD-EPI formula; for Japan) Bilirubin total Bilirubin direct **(if total is elevated)** Bilirubin indirect **(if total is elevated)** Troponin I **(Reflex when CK is elevated)** Albumin C-reactive protein (high sensitive) Cholesterol, total Triglycerides LDL-cholesterol (calculated by Friedewald formula) HDL-cholesterol
Urine pregnancy test (only for female subjects of childbearing potential)	Human chorionic gonadotropin in urine Dipstick not performed at central laboratory
Serum pregnancy test (only for female subjects of childbearing potential if urine pregnancy test is positive)	Human serum chorionic gonadotropin (quantitative)
Urinalysis (dipstick)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine RBC/Erythrocytes Urine WBC/Leukocytes Urine pH
Urine sediment (microscopic examination, only if urine analysis abnormal)	Urine sediment bacteria Urine cast in sediment Urine squamous epithelial cells Urine sediment crystals, unspecified Urine sediment RBC/Erythrocytes Urine sediment WBC/Leucocytes
Urine	Urine albumin/creatinine ratio Albumin (quantitative) Urine creatinine (quantitative)

a. INR test only performed if ALT or AST > 3 × ULN (upper limit of normal).

Clinically relevant abnormal findings will be reported as AEs. 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.

If logistical restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible.

Tuberculosis Testing

All subjects that had a negative TB test during the last testing in the preceding study or Study M15-997 will be tested for TB by either the QuantiFERON®-TB Gold Test (or equivalent) or a TB Skin Test (PPD) at the Visit 5, Visit 10, Visit 14, Visit 16 and EOT visit as specified in Appendix C. If PPD and/or the QuantiFERON®-TB Gold test (or Interferon gamma release assay (IGRA) equivalent) is positive, or if there is a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) upon retesting, subjects may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then tuberculosis prophylaxis should be pursued according to clinical judgment of investigator and local

country guidelines. It is also necessary to report a positive TB test as an adverse event in the source documents and eCRFs (AE and TB supplemental forms).

Monitoring Adverse Events

New AEs or unresolved AEs from the preceding study will be assessed at every study visit from the first dose of study drug at Baseline through the EOO visit. Refer to Section 6.1.1.1 for additional information.

Prior and Concomitant Therapy Assessment

Any medication that the subject is receiving at the time of Baseline or receives during the study must be recorded on the source documents as well as the appropriate eCRF. See Section 5.2.3 for full details regarding documentation of prior and concomitant therapy.

Local Tolerability Assessment

Local tolerability at the administration site of the previous s.c. injection will be assessed by the investigator or representative according to "swelling," "induration," "heat," "redness," "pain," or "other findings" at all dosing visits. This assessment should be done pre-dose. Any abnormal findings at the injection site will be reported as AEs.

Study Drug Administration

Until the Week 156 visit, and at visits Week 180, 204, 228, study medication will be administered at the study site in accordance with the protocol by authorized study personnel (e.g., study nurse) or optionally subjects can self-administer at the study site following successful completion of training and demonstration of adequate injection technique.

At Weeks 168, 192, 216 and 240, subjects will self-administer study medication at home. Alternatively, subjects may receive the injection of study drug of Weeks 168, 192, 216 and 240 at the study site. Injections will be given in an open label fashion with each subject receiving s.c. injections of risankizumab as two 75 mg (150 mg total) prefilled

syringes at each dosing visit (every 12 weeks). Syringes will be administered as assigned by IRT.

Risankizumab will be administered as a s.c. injection in the abdomen, thigh or arm. The two injections done subsequently 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.

Training on Self-Administration

At Visit Week 156, a site staff member will provide training to the subject and/or caregiver on how to administer the study drug using the PFS. During this training, the subject and/or caregiver will be provided the IFU and proceed with self-injection under supervision of the observer.

Training will consist of the site staff member using a PFS for injection. The site staff member will use the IFU to walk through all steps of injection with the subject. The subject or caregiver will then repeat the steps using the same PFS to complete a self-injection.

The subjects will be provided a dosing diary to record the date and time of the home-injections.

Monitoring for Hypersensitivity Reactions

Subjects should be closely monitored for signs and symptoms of hypersensitivity for approximately 2 hours after administration of the first dose (Baseline visit) and approximately 1 hour after dose administration for all study visits thereafter.

While no concerns with systemic hypersensitivity have been identified with the use of risankizumab, the sponsor has established an independent, blinded, expert committee to adjudicate events of anaphylaxis based on pre-specified definition. This independent

external Anaphylaxis Adjudication Committee (AAC) will be adjudicating observed suspected anaphylactic reactions and will remain blinded to treatment allocation. The events that are adjudicated and the adjudication process will be detailed in the Anaphylaxis Adjudication Committee Charter. A supplemental Hypersensitivity/Anaphylactic reactions eCRF will be used to collect information pertinent to the events. In addition, the site may be contacted for additional source documentation for relevant events.

In the event of a suspected systemic post-dose hypersensitivity reaction, a PK, ADA, and NAb sample should be collected once within 24 hours of the reaction. In addition to PK, ADA and NAb assays, blood tests to be conducted in the event of a systemic hypersensitivity reaction are:

- Serum tryptase: Optimally, measurement needs to be obtained from 15 minutes to 3 hours of symptom onset, and no later than 6 hours (as tryptase may remain elevated for 6 or more hours after the onset and therefore may still be informative if obtained after 3 hours); it is also requested to collect a follow-up tryptase level a minimum of 2 weeks after the recorded event or at the next study visit
- Plasma histamine: optimally, within 5 to 15 minutes of the onset of symptoms, and no later than 1 hour

Subjects will be given instructions regarding management of signs and symptoms of anaphylaxis to be followed during home dosing at Weeks 168, 192, 216 and 240.

Hypersensitivity reactions should be treated according to medical standards. Any events of hypersensitivity should be reported as an adverse event on the AE eCRF and additionally the supplemental hypersensitivity reaction eCRF should be completed. Pre-medications for further injections might be considered and will be agreed on between investigator and the AbbVie TA MD.

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 by venipuncture into appropriately labeled collection tubes at the time points specified in Appendix C. 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 and PK and anti-drug antibody (ADA) sampling will be recorded in the source documents.

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

Blood samples, approximately 3 mL, for risankizumab ADA assay will be collected 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 and PK and ADA sampling will be recorded in the source documents.

The PK and ADA samples collected under previous protocol amendments may not be analyzed for PK and ADA per protocol Amendment 4 and 5.

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 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. The ADA samples collected under previous protocol amendments may not be analyzed for NAb per protocol Amendment 4. All immunogenicity samples drawn at the visits specified in Appendix C will be analyzed.

5.3.3 Efficacy Variables

5.3.3.1 Key Variables

Key variables to be summarized at all visits:

- Proportion of subjects achieving PASI 90
- Proportion of subjects achieving the sPGA score of clear or almost clear
- Proportion of subjects achieving PASI 75
- Proportion of subjects achieving PASI 100
- Proportion of subjects achieving the sPGA score of clear

5.3.3.2 Additional Variables

- Additional variables include proportion of subjects achieving ≥ 50% reduction in PASI score (PASI 50), absolute PASI of < 3, DLQI score of 0, DLQI score of 0 or 1, a reduction of at least 5 points in DLQI, as well as change and percent change from baseline in PASI, DLQI, NAPSI, PPASI, and PSSI. Summaries will be provided at all visits that the corresponding variables are evaluated.

5.3.4 Safety Variables

Safety will be assessed descriptively based on AEs, physical examination, vital signs, local tolerability and laboratory data during the entire study.

5.3.5 Pharmacokinetic Variables

Risankizumab plasma concentrations will be determined. Descriptive statistics will be calculated for each sampling time (study visit). The number and percentage of subjects with ADA will be calculated. Additional analyses combining pharmacokinetic and ADA data from this study and other studies may be conducted if appropriate.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may voluntarily withdraw from the study drug and/or study at any time. Subjects must be withdrawn from the study drug and/or study for reasons including, but not limited to, the following:

- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix

- The investigator believes it is in the best interest of the subject.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie Therapeutic Area Medical Director.
- Post-Baseline occurrence of one or more of the following hepatic test abnormalities (confirmed on a second separate sample at least 48 hours apart):
  - ALT or AST > 8 × ULN
  - ALT or AST > 5 × ULN for more than 2 weeks
  - ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5)
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- If prohibited medication is used during the study for any indication, the subject must discontinue the use of the prohibited medication if he/she wants to continue on study drug. In case of undue safety risk for the subject, the subject should discontinue study drug at the discretion of the investigator.
- If the subject received a live virus vaccination during the study, the subject must discontinue study drug.
- If the subject develops laboratory evidence of or is known to be infected with HIV, hepatitis B or hepatitis C, the subject must be discontinued from the study drug and undergo early EOT Visit activities. Additionally, all subjects who develop laboratory evidence of infection with HIV, hepatitis B or hepatitis C must be referred to an appropriate clinician for management of their viral infection according to medical standards.
- Subject develops active TB at any time during the study.
- If the subject experiences an intolerable increase of psoriasis during the course of the study the subject will be discontinued from the study drug to receive rescue treatment as deemed appropriate by the investigator.
- If the subject experiences a serious infection, the study drug should be held until the infection is resolved or stabilized. The study drug dosing visit could

be postponed such that the study drug of the following visit will not be administered within 14 days. If the subject has not received study drug due to this serious infection for at least 24 weeks, the subject will be permanently withdrawn from study drug.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the subject has the option to continue in the study and complete the remaining visits as scheduled. If remaining visits will be completed, an early EOT visit is not required. If the subject does not continue in the study, the procedures outlined for the early EOT visit must be completed, ideally within 2 weeks of the decision and preferably prior to the initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. For subjects that prematurely discontinue, study drug will not be given at the early EOT visit and subjects should have the telephonic EOO visit, 20 weeks after their last administered dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

All attempts must be made to determine the primary reason for premature discontinuation. The information will be recorded on the appropriate eCRF page.

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

Interruption/Discontinuation of Study Drug Due to COVID-19

For subjects with documented COVID-19, the timing of next administration of study drug or possibility of premature discontinuation from study drug should be discussed with the AbbVie Medical Contact.

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

All subjects will receive s.c. injections of risankizumab as two 75 mg (150 mg total) pre-filled syringes every 12 weeks.

5.5.2 Identity of Investigational Product (IP)

Information about the risankizumab formulation to be used in this study is presented in Table 2.

Risankizumab supplies will be provided by Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany.

- Risankizumab (ABBV-066) 75 mg/0.83 mL Solution for Injection Pre-filled Syringe

Risankizumab is presented in a 1 mL pre-filled syringe with 0.87 mL of solution for injection. Dispensed volume is 0.83 mL. The solution in the risankizumab syringes has a concentration of 90 mg/mL, to deliver 75 mg per syringe. Two (2) syringes will be used to achieve the 150 mg dose.

Table 2. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Risankizumab (ABBV-066)	Solution for injection in pre-filled syringe	75 mg/0.83 mL	Subcutaneous injection	Boehringer Ingelheim Pharma GmbH & Co. KG

5.5.2.1 Packaging and Labeling

Study drug packaged in 75 mg pre-filled syringes will be provided in open-label fashion and packaged in cartons containing one (1) syringe per carton. Each kit will be labeled as required per local requirements. The number identifying the kits dispensed will be managed by the IRT.

All labels must remain affixed to the study drug at all times and should never be removed for any reason.

5.5.2.2 Storage and Disposition of Study Drug

Risankizumab kits will be kept protected from light in their original packaging, in a refrigerator between 2°C to 8°C (36°F to 46°F), and within a secure limited access storage area, and in accordance with the recommended storage conditions on the label. Study drug must not be frozen at any time. A temperature log must be maintained for documentation.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

Upon receipt of study drugs, the site will acknowledge receipt within the IRT system.

At Visits Week 156, 180, 204 and 228, subjects will be provided with a cooler bag and ice pack to maintain adequate storage temperature of the study drug kits during transport from the clinical site to their home. Subjects will need to store study kits in the refrigerator between 2°C to 8°C (36°F to 46°F). Subjects will also receive a tote and sharps container

at Visit Weeks 156, 180, 204 and 228 to safely transport the used PFS back to the study site at Visits Week 180, 204, 228 and EOT. Biohazard bags will also be provided in case of a product complaint.

5.5.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study. The treatment is the same for all subjects so there is no assignment of subjects to treatment groups.

5.5.4 Selection and Timing of Dose for Each Subject

An IRT will be used to allocate study drug to subjects. At visits where study drug is to be administered, study sites will be required to complete the study drug resupply module in the IRT to receive assigned study drug/kit numbers. Details regarding the use of the IRT are described in the site-user manual.

Study drug will be administered at the study site by authorized study personnel (e.g., study nurse). Optionally subjects are allowed to self-administer the study drug at the study site following completion of training and successful demonstration of self-injection.

Once subjects and/or caregivers are trained to self-administer study drug at the investigative site at the visit Week 156, risankizumab will be self-administered by the subject or caregiver at home starting at the visit Week 168, and thereafter according to the schedule as outlined in Appendix C.

Alternatively, subjects may receive the injection of study drug of Weeks 168, 192, 216 and 240 at the study site. Dose modifications or adjustments are not permitted. In exceptional cases of missed or delayed visits, study drug of the following visit should not be administered within 14 days of the prior dose. There should be at least 14 days between two consecutive study drug administrations.

If a subject is unable to come to the study site for a study visit due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if

allowed by local regulations and if the subject has been trained for self-injection. AbbVie will submit any required notifications to the regulatory authority as applicable.

Study drug may be shipped from the study site directly to the subject's home if all the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee
- Study drug can be administered by the subject (or subject's caregiver) at home
- Subject agrees to have the study drug shipped directly to their home
    - Shipments may also include other study supplies (e.g., home pregnancy test, drug dosing diaries, paper copies of DLQI). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
    - AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

5.5.5 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer 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.

In order to document compliance with the treatment regimen, the injection dates and times of the administrations done at site should be documented on the source documents. The injection dates and times of the home-administrations should be documented in the dosing diary. Female subjects of child-bearing potential are asked to also report the outcome of the urine pregnancy tests prior to home-administration on the dosing diary.

5.5.6 Drug Accountability

The investigator or representative will verify that study drug supplies are received intact at the appropriate temperature (temperature recording devices [e.g., TempTales] are provided in the shipments), and in the correct amounts from the drug depot.

This will be documented by signing and dating the Proof of Receipt (POR) or similar document included with each drug shipment, and via direct reporting in the IRT. The original POR note or similar document will be kept in the site files as a record of what was received.

IRT will be used to keep an accurate running inventory of study drug, and will include the kit number, lot number, subject number, the number of pre-filled syringes dispensed and the date study drug was assigned to each subject.

All empty Investigational Product (IP) boxes and used pre-filled syringes will be inventoried by the site. Each site will be given their own sharps disposal container to store used pre-filled syringes.

At Visits Week 180, 204, 228 and EOT, site personnel will review the dosing diary, review returned used PFS in the provided sharps container, and empty study drug packaging to verify compliance of the study drug administration of the Weeks 168, 192, 216 and 240 visit at home.

An overall accountability of the study drug will be performed by the site and verified by an AbbVie monitor throughout the study and at the site close-out visit. Used syringes must be destroyed at the site according to local regulations governing biohazardous waste.

Destruction of used study supplies must be documented. All unused supplies must be inventoried, accounted for and destroyed on site according to local procedures or regulation or returned to a destruction facility by the AbbVie Monitor. A copy of the Drug Accountability Form, in accordance with instructions provided by the AbbVie Monitor, will be included in the return shipments.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The primary objective of Study M15-997 is to investigate long-term safety and tolerability of risankizumab 150 mg E12W in subjects with psoriasis who have completed one of the preceding Phase 2/3 studies.

The secondary objective of Study M15-997 is to investigate the long-term efficacy of risankizumab in the treatment of psoriasis.

Safety and efficacy measurements will be collected at each visit. Study design is consistent with current standards investigating long-term safety and maintenance of efficacy of novel treatment in psoriasis.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. The main clinical efficacy measurements used in this study (PASI and sPGA) have been used in multiple pivotal clinical studies in assessing disease activity in subjects with psoriasis. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Subjects with moderately to severely chronic plaque psoriasis who have completed one of the preceding Studies 1311.3, 1311.4, 1311.13, 1311.28, 1311.30, 1311.38 and M16-178, who meet all inclusion criteria and none of the exclusion criteria are eligible for this study.

This study will provide an opportunity for subjects that completed any of the preceding studies to have extended access to an active therapy until risankizumab is approved and available on the market in the subject's country.

5.6.4 Selection of Doses in the Study

Risankizumab is currently in Phase 3 development for treatment of subjects with moderate to severe chronic plaque psoriasis. Four Phase 3 studies are currently ongoing, planning to enroll approximately 2100 subjects, and evaluating risankizumab dose of 150 mg administered at Week 0, 4 and thereafter E12W. Subjects from these ongoing Phase 3 studies will enter in the current study. Hence, the 150 mg dose administered E12W is selected for this study, so the subjects will continue to receive the same dose as in preceding Phase 3 studies to establish the long-term safety and efficacy of risankizumab. In Japanese Phase 2/3 Protocol 1311.38 some subjects (N = 56) will be treated with risankizumab 75 mg E12W dose. As risankizumab has been well tolerated in the completed and ongoing studies, and based on preliminary PK results indicating no clinically meaningful difference in exposure between Japanese and Caucasian subjects, (approximately 30% higher exposure in Japanese subjects compared to Caucasian subjects) AbbVie considers it appropriate to investigate 150 mg E12W dosing paradigm in these Japanese subjects.

Subjects currently enrolled in BI clinical Trial 1311.13 will also be offered the opportunity to continue receiving treatment for chronic plaque psoriasis with risankizumab in Study M15-997. One-hundred and ten subjects were enrolled in this trial and were treated with risankizumab 90 mg SC E12W with the option to increase the dose to 180 mg if there was evidence of lack of response.

Preliminary results from the pivotal Phase 3 studies support the clinical benefit of the 150 mg dose of risankizumab in subjects with moderate to severe plaque psoriasis. Approximately 1300 subjects received treatment with risankizumab 150 mg SC and all four pivotal trials achieved their co-primary endpoints which were defined as achievement

of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16 and achievement of a sPGA score of clear or almost clear at Week 16.

Subjects treated with risankizumab experienced substantial skin clearance and clinical improvement in the extent and severity of plaque. Across the four pivotal studies, the proportion of subjects with PASI 90, sPGA score of clear or almost clear, and PASI 100 at Week 16 ranged from 72 – 75%, 84 – 88%, and 36 – 51%, respectively.

In these studies, risankizumab was superior to placebo, ustekinumab, and adalimumab as demonstrated by statistically significant differences between groups in favor of risankizumab in the proportions of subjects who achieved PASI 90 and sPGA clear or almost clear at Week 16. Risankizumab's superiority to ustekinumab was maintained up to 52 weeks. Risankizumab was well tolerated and had a similar safety profile to placebo, ustekinumab, and adalimumab.

Treatment with the risankizumab regimen of 150 mg SC 150 mg E12W is thus supported by pharmacokinetic/pharmacodynamic modeling of Phase 1 and Phase 2 data which indicate near-maximal efficacy would be attained and maintained with the 150 mg risankizumab dose and the robust Phase 3 clinical data in approximate 1300 subjects demonstrating clinical efficacy and safety of risankizumab compared to placebo and existing therapies.

Therefore subjects who have been receiving treatment with risankizumab 150 mg SC as well as those subjects receiving other doses of risankizumab are expected to receive clinical benefit from either continuing or switching to a dosing regimen of risankizumab 150 mg SC E12W.

In this study the 150 mg dose will be administered as two prefilled syringes of 75 mg active drug each, as the 150 mg/mL formulation of risankizumab is still being developed.

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 study contains both:

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

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For AEs, 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 AEs on a routine basis throughout the study. The investigator will assess and record any AE in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE 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 AEs to be considered intermittent, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

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

Such an event can result from use of the drug as stipulated in 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 AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

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

Prior to use, every attempt should be made to contact the AbbVie TA MD for direction on re-introduction of study drug therapy after prohibited medication administration.

6.1.1.2 Serious Adverse Events

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

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 AESI relates to any specific AE that has been identified at the compound level as being of particular interest for prospective safety monitoring and safety assessment within this study, 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 AST and/or ALT > 3-fold 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 ≥ 8-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 adverse event and supplemental hepatic eCRFs.

The supplemental hepatic eCRFs will also need to be completed for any hepatic related AE leading to discontinuation or interruption of study drug or any hepatic related SAE, not meeting the hepatic injury definition.

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 analyzed, 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 patient's clinical presentation.

6.1.2 Adverse Event Severity

Intensity of Adverse Events

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by OMERACT.[14] Refer to the Investigator Site File (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 AE to the use of study drug:

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

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.

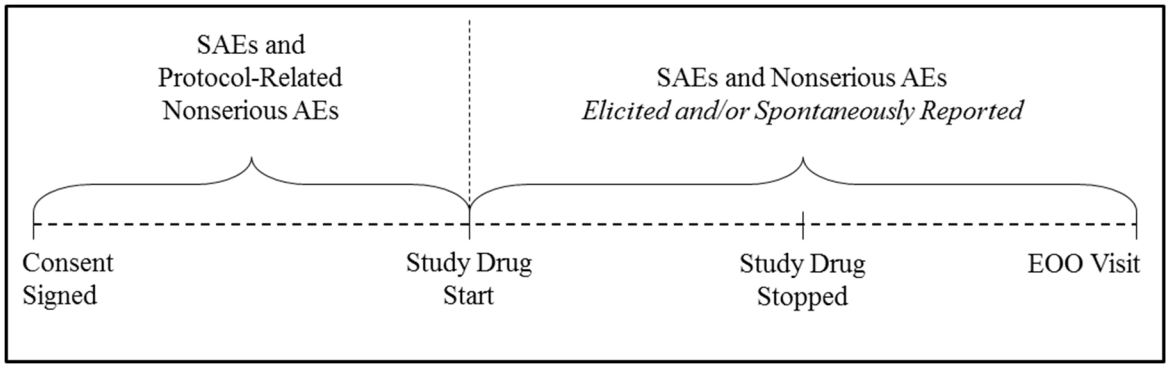
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an 'Other' cause of event must be provided by the investigator for the SAE.

6.1.4 Adverse Event Collection Period

All AEs reported from the time of study drug administration until the End of Observation (EOO) visit will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related non-serious AEs will be collected from the time the subject signed the study-specific informed consent.

AE information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of an SAE, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE event by entering the SAE 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 Form (CRF) and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Immunology Safety Team at:

Immunology Clinical Trial Patient Safety Management
AbbVie Inc.
1 North Waukegan Road
Bldg. AP51-3
North Chicago, IL 60064-3537
USA

Contact Information:

Fax: +1 (847) 785-8227
Safety Hotline: +1 (847) 938-8737
Email: GPRD_SafetyManagement_Immunology@Abbvie.com

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

Primary Therapeutic Area Medical Director:

[redacted]
AbbVie
Immunology Clinical Development
1 North Waukegan Road
[redacted]
North Chicago, IL 60064 USA

Office: [redacted]
Mobile:
Email:

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 TA MD:

Phone: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (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 IB.

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

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor/emergency medical contact listed above before reintroducing study drug.

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as adverse events. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All adverse events associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 24 hours 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 AE. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

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.

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 AE in the proximity of the device, an AE 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 one business day 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 AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

For product complaints occurring during home-administration subjects will be requested to contact the study site.

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, including those that may be due to the COVID-19 pandemic) after a subject has been enrolled, the principal investigator is responsible for notifying IEC/IRB and regulatory authorities (as applicable), and the following AbbVie clinical monitor(s):

Primary Contact:

[redacted]
Study Project Manager II
Wegalaan 9
2132JD Hoofddorp
The Netherlands

Office: [redacted]
Mobile:
Email:

Alternate Contact:

[redacted]
Program Lead I
1 North Waukegan Road
North Chicago, IL 60064
USA

Office: [redacted]
Mobile:
Email:

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.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Safety and efficacy analysis will be performed on all subjects who received at least one dose of study drug in the OLE. Key objective of the analysis is to investigate long-term safety and efficacy of risankizumab. Additional objectives include but are not limited to investigating the safety and efficacy of risankizumab in subjects treated with ustekinumab, adalimumab, or participated in the randomized withdrawal/retreatment phase in the preceding Phase 2/3 studies.

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 study database lock.

8.1.1 Analysis Populations

Subjects are required to have at least one dose of study drug in Study M15-997 to be included in the following populations.

The following populations are to be used for efficacy analyses:

- RZB Population: consists of subjects who were randomized to risankizumab in Studies 1311.3, 1311.30, 1311.28, 1311.38 (150 mg arm only), and M16-178. This population will be used to evaluate the long-term efficacy of risankizumab with loading dose. For subjects from Japan, data after the first dose of RZB from the preceding studies and prior to the start of 75 mg dose will be used for the analyses.
- RZB_NL Population: consists of subjects who were randomized to placebo in the initial study and continued to risankizumab (without loading dose) in Studies 1311.3, 1311.4, 1311.28, and 1311.38 (150 mg arm only). This population will be used to evaluate the long-term efficacy of risankizumab without initial loading dose. For subjects from Japan, data after the first dose of RZB from the preceding studies and prior to the start of 75 mg dose will be used for the analyses.
- Retreatment Population: consists of subjects who were re-randomized to placebo in Part B of Study 1311.4. This population will be used to evaluate the efficacy of re-treatment after temporary withdrawal. For subjects from Japan, data after the re-treatment and prior to the start of 75 mg dose will be used for the analyses.
- UST_RZB Population: consists of subjects who were randomized to ustekinumab in Studies 1311.3 and 1311.28. This population will be used to assess the efficacy of risankizumab when subjects switch from ustekinumab to risankizumab. For subjects from Japan, data prior to the start of 75 mg dose will be used for the analyses.
- ADA_RZB Population: consists of subjects who were randomized to adalimumab in Study 1311.30. This population will be used to assess the efficacy of risankizumab when subjects switch from adalimumab to risankizumab.
- FUM_RZB Population: consists of subjects who were randomized to FUMADERM in Study M16-178. This population will be used to assess the safety and efficacy of risankizumab when subjects switch from FUMADERM® to risankizumab.

- RZB Japan Population: consists of subjects from Japan. This population will be used to assess safety and efficacy during the OLE period, regardless of dosing changes in subjects.

Additional analysis populations may be defined when deemed appropriate.

To assess the benefit-risk profile, safety summaries will be provided for each of the above analysis populations as well. In addition, an All Risankizumab Treated Population, defined as all subjects who received at least one dose of risankizumab in this study, will be used to provide a comprehensive summary of safety.

8.1.2 Planned Methods of Statistical Analysis

Since this is an open-label continuation study, no statistical test will be conducted. Summary statistics will be provided. Data from preceding studies will be integrated with data from this study in the summaries.

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

8.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for each population. Baseline will be defined as the last non-missing measurement prior to the first dose of study drug in the preceding studies.

8.1.4 Statistical Analysis of Efficacy

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, maximum 25th and 75th percentiles, as well as the 95% confidence intervals (CIs) of the mean values. Categorical variables will be summarized by counts and percentages, as well as the 95% CIs of the percentages.

The efficacy summary will be conducted in the populations defined in Section 8.1.1.

Visit windows and the data-handling convention for summarizing efficacy results will be defined in the SAP. Unless otherwise specified, the "baseline" for efficacy variables is the baseline assessment in the preceding studies.

Missing data will be imputed using the following methods for the efficacy analysis:

- Last Observation Carried Forward (LOCF): The LOCF analyses will use the completed evaluation from the previous visit to impute missing data at later visits.
- As-observed: The as observed analysis will not impute values for missing evaluations, and thus a subject who did not have an evaluation on a scheduled visit will be excluded from the as observed analysis for that visit.

8.1.5 Safety Analysis

All AEs, SAEs, AEs leading to discontinuation, and pre-specified AESIs 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 a risankizumab (either in a preceding Phase 2/3 psoriasis study or this study) and within 20 weeks (140 days) after the last study drug 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 patient-years) of SAEs, deaths, AEs leading to discontinuation from the study, and pre-specified AESIs will be provided as well. Mean change in laboratory and vital signs variables will be summarized. For selected parameters, a listing of all subjects with clinically significant laboratory or vital sign values will be provided. Shift tables for changes from baseline according to the normal range will also be provided.

8.1.6 Interim Analysis

An interim analysis will be conducted in the fourth quarter of 2017. The interim analysis will include all available patient data up to the interim analysis data cut-off date. Additional interim analyses may be performed based on regulatory or other requirements.

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.

Additional analyses combining pharmacokinetic and ADA data from this study and other studies may be conducted if appropriate, this may include exploratory analyses of the effect of ADA on risankizumab pharmacokinetics and efficacy as well as the relationships between exposure and clinical observations (efficacy or safety variables of interest). Such analyses, if conducted, may be summarized in a separate report rather than in the CSR for this study.

8.1.8 Data Monitoring Committee

As no new safety signals have been identified to date, the independent Data Monitoring Committee (DMC) that initially reviewed data from this study is no longer in effect. Routine pharmacovigilance surveillance will continue to be conducted.

8.1.9 Cardio- and Cerebro-Vascular Event Adjudication Committee

An independent adjudication committee will be adjudicating all observed cardio- and cerebro-vascular events including MACE, in a blinded manner. The events that are adjudicated and the adjudication process will be detailed in the Adjudication Committee Charter. Supplemental eCRF will be used to collect information pertinent to the events. The Investigator might be contacted for additional information on relevant events.

8.2 Determination of Sample Size

The sample size is determined by the completion of preceding studies and the consenting for the extension.

Multiple clinical studies will be rolling into this OLE study. Eligible subjects from Studies 1311.3, 1311.4, 1311.13, 1311.28, 1311.30, 1311.38 and M16-178 will be offered participation in this OLE study at their respective or referring sites. The check for subject eligibility will be based upon a successful completion of the preceding study, signing the informed consent for this study, and the other inclusion and exclusion criteria.

A 10 to 15% dropout rate from preceding studies is expected, leaving approximately 2200 subjects to be entered in this study.

9.0 Ethics

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

Good clinical practice (GCP) requires that the clinical protocol, any protocol amendments, the IB, 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 the International Conference on Harmonization (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, 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

Prior to the performance of any study specific procedures, including discontinuation of any protocol prohibited medications, the investigator or representative will explain the nature of study procedures and the study to the subject and if applicable per local requirements the subject's legal representative, and all questions regarding the study will be answered. The informed consent form will be reviewed and consent to participate

documented by dated signature of the representative and the person administering the informed consent.

See Appendix D for Japan specific requirements.

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)s 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 EDC system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific 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 or representative 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.

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

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.

During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

Medidata will provide access to the EDC system for the duration of the study 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.

Patient reported data must be completed for each subject enrolled in this study. This data is collected directly onto paper CRFs by the subjects. The completion of these forms is verified by the site staff. The site will enter the forms into the EDC system.

11.0 Data Quality Assurance

To ensure data integrity and subject safety, a study monitor will continuously, throughout the study, verify that all subjects signed the informed consent prior to any study specific procedures being conducted, that the investigator is complying with the protocol, GCP and applicable regulations, and that the information provided in the eCRF is complete, accurate, and supported by information in source documents.

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

All information concerning risankizumab and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of risankizumab. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for trial-related monitoring, audits, IEC/IRB review and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie. 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.

13.0 Completion of the Study

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

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, 20 weeks after the final dose of study drug, see Appendix C.

See Appendix D for Japan specific requirements.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for Risankizumab/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 multicenter, open **L**abel study to assess the safety and efficacy of r**I**sankizu**M**ab for **M**a**I**n**T**enance in moderate to severe p**L**aqu**E** type p**S**oria**S**is (LIMMITLESS)
Protocol Date:	18 October 2021

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the 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 making 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]		Clinical Development, Immunology
		Clinical Development, Immunology
		Data and Statistical Sciences
		Data and Statistical Sciences
		Data and Statistical Sciences
		Clinical Pharmacology & Pharmacometrics
		Clinical Development Operations

Appendix C. Study Activities Flow Chart

Activity	Visit 1/Baseline[a]	Visit 2/Week 12	Visit 3/Week 24	Visit 4/Week 36	Visit 5/Week 48	Visit 6/Week 60	Visit 7/Week 72	Visit 8/Week 84	Visit 9/Week 96	Visit 10/Week 108	Visit 11/Week 120	Visit 12/Week 132	Visit 13/Week 144	Visit 14/Week 156	Week 168	Visit 15/Week 180	Week 192	Visit 16/Week 204	Week 216	Visit 17/Week 228	Week 240	EOT Visit[b]	EOO Visit
Informed Consent[c]	X																						
Inclusion/exclusion criteria	X																						
Demographics[d]	X																						
Medical/Surgical History[e]	X																						
Prior and Concomitant Therapy Assessment	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X
Adverse Event Assessment[g]	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	X
Physical Exam[h]	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	
Electrocardiogram (ECG)	X[f]				X					X				X				X				X	
Vital Signs[i]	X[f,i]	X[i]	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	
Body Weight	X				X					X				X				X				X	
TB Testing[j]					X					X				X				X				X	
Pregnancy Testing[k,q]	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Local Tolerability Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	

Activity	Visit 1/Baseline[a]	Visit 2/Week 12	Visit 3/Week 24	Visit 4/Week 36	Visit 5/Week 48	Visit 6/Week 60	Visit 7/Week 72	Visit 8/Week 84	Visit 9/Week 96	Visit 10/Week 108	Visit 11/Week 120	Visit 12/Week 132	Visit 13/Week 144	Visit 14/Week 156	Week 168	Visit 15/Week 180	Week 192	Visit 16/Week 204	Week 216	Visit 17/Week 228	Week 240	EOT Visit[b]	EOO Visit
Clinical Laboratory Tests (Chemistry, Hematology, Urinalysis)[l]	X[f]	X	X	X	X[l]	X	X	X	X	X[l]	X	X	X	X[l]		X		X[l]		X		X[l]	
Blood Sampling for PK	X[f]				X				X					X				X				X	
Blood Sampling for ADA Assay	X[f]				X				X					X				X				X	
PASI, sPGA	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	
NAPSI, PPASI, PSSI	X[f]		X		X		X		X		X		X	X		X		X		X		X	
Dermatology Life Quality Index (DLQI)[m]	X[f]		X		X		X		X		X		X	X		X		X		X		X	
Study Drug Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[r]	X	X[r]	X	X[r]	X	X[r]	X[o]	
Study Drug Dispensation for Self-Administration[p]														X		X		X		X			
Training subject on self-administration and product complaints														X									
Monitoring for Hypersensitivity Reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	

a. The Baseline visit date will serve as reference for all subsequent visits. A ± 7-day window is permitted around all study visits after Baseline.

b. Premature discontinuation: For subjects who prematurely discontinue the study before study end (for any reason) an early EOT visit is required.

If the decision to discontinue study participation is made at a regular study visit, the visit should be turned into an EOT visit, i.e., an EOT visit is to be performed instead of the scheduled visit.

If the decision to discontinue study participation is made in between study visits, an EOT visit is to be scheduled at the earliest convenience or at the latest the next upcoming visit according to the Flow Chart. This early EOT visit will include the same procedures as the normal EOT visit and the subject will subsequently enter a follow up period of 20 weeks, until a final EOO visit is performed.

c. Informed consent must not be signed before the date of the last visit in the preceding study, but needs to be completed prior to initiation of any Study M15-997 study procedures.

d. The subject's demographic data has been collected at the screening visit of the preceding study, so does not need to be collected again.

e. Medical history collected in the preceding study will be used in Study M15-997. Only new information and updates will need to be collected at the Study M15-997 Baseline visit.

f. For subjects rolling over from the preceding study with ≤ 4 day delay from the last visit per protocol in the preceding study, these procedures do not need to be repeated if already performed at this last visit of the preceding study. Results assessed at this last visit will serve as Baseline visit results for Study M15-997. Subjects initiating the OLE with a delay of > 4 days from completion of the last visit per protocol in the preceding study will need to complete all activities for Baseline.

g. New Adverse Events or unresolved Adverse Events from the preceding study to be followed up in this study.

h. Symptom directed physical exam.

i. Vital Signs must precede blood sampling and must be assessed pre-dose at all dosing visits. Additional vital signs assessments should be made 5 (± 2) minutes post-dose and 60 (± 10) minutes post-dose at Visit 1 and Visit 2.

j. Only subjects that had a negative TB test during the last testing in the preceding study or Study M15-997 will be tested for TB.

k. Urine pregnancy testing at every dosing visit. Additional serum pregnancy testing will occur in case of a positive urine test result at any visit.

l. The following clinical laboratory tests only need to be done at the Visit 5, Visit 10, Visit 14, Visit 16 and the EOT visit: Electrolytes, C-reactive protein, cholesterol, urinalysis, urine sediment and urine. During these visits, the subject should be fasting for at least 8 hours prior to the blood sample being taken.

m. Self-administered patient questionnaire DLQI assessments to be done on paper by the subject and should be completed before any other visit assessments or treatments and, if possible, before any interaction with the investigator or other members of the study team.

n. Study drug must be administered after all laboratory procedures have been completed.

o. Not to be performed for subjects who prematurely discontinue the study drug.

p. Study drug for self-administration will be dispensed to subject at Visit 14, Visit 15, Visit 16 and Visit 17 for self-injection at Week 168, Week 192, Week 216 and Week 240.

q. Urine pregnancy self-testing for females of child-bearing potential will be required prior to self-injection at home at Week 168, Week 192, Week 216 and Week 240. Subjects receiving the injection at the study site at these visits will have an urine pregnancy test at the study site. Negative urine pregnancy test results must be confirmed prior to study drug dosing.

r. Subjects preferring not to self-administer study drug at home at Weeks 168, 192, 216 and 240 may receive the injection at the study site.

Appendix D. Local Requirements – Japan

5.3.1.1 Study Procedures

Clinical Laboratory Tests

eGFR (estimated by CKD-EPI Japan formula)

Tuberculosis Screening

All subjects will be tested for TB by either the QuantiFERON®-TB Gold Test (or equivalent) or a TB skin test or equivalent, most commonly the PPD, at Visit 5, Visit 10 and EOT visit.

A TB skin test or equivalent should be utilized only when a QuantiFERON®-TB Gold Test is not possible for any reason (unless both tests are required per local guidelines).

- QuantiFERON®-TB Gold Test will be analyzed by the central laboratory (QuantiFERON test is preferred over TB skin test).
- If the QuantiFERON®-TB Gold Test is NOT possible (or if both the QuantiFERON®-TB Gold Test and the PPD skin test are required per local guidelines) the PPD skin test will be performed according to standard clinical practice.
- The PPD skin test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test.
- The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative."
- If PPD and/or the QuantiFERON®-TB Gold test (or IGRA equivalent) is positive, or if there is a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) upon retesting, subjects may continue in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active TB.

- If the subject is diagnosed with active TB, the subject should not receive any further study drug and follow the premature treatment discontinuation procedure (Early EOT visit) in Section 5.4.1.
- **If presence of latent TB is established treatment should be initiated and maintained according to local country guidelines.** It is also necessary to report it as an AE in the source documents and eCRFs.
- If subject is known to have a positive QuantiFERON®-TB Gold or PPD test in the preceding study, do not repeat in this study.
- Subjects who have had an ulcerating reaction to the TB skin test in the past should not be re-exposed and should not be tested by a PPD skin test.

In the case of a TB-related AE, a supplemental TB case report form that provides additional information is be completed by the investigator or designee.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from this 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 IEC/IRB and regulatory authorities (as applicable), and the following AbbVie clinical monitor(s):

Primary Contact:

[redacted]
Study Project Manager II
Wegalaan 9
2132JD Hoofddorp
The Netherlands

Office:
Mobile:
Email: [redacted]

Alternate Contact:

[redacted]
Program Lead I
1 North Waukegan Road
North Chicago, IL 60064
USA

Office:
Mobile:
Email: [redacted]

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.

9.3.1 Informed Consent Form and Explanatory Material

Prior to the performance of any study specific procedures, including discontinuation of any protocol prohibited medications, the investigator or representative will explain the nature of study procedures and the study to the subject and if applicable per local requirements the subject's legal representative, and all questions regarding the study will be answered. The informed consent form will be reviewed and consent to participate documented by dated signature of the representative and the person administering the informed consent.

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 IEC/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 IEC/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.

13.0 Completion of the Study

The investigator will conduct the study in compliance with this protocol and complete the study within the timeframe specified in the contract between the investigator (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 investigator (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 investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the investigator 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 this protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

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

Appendix E. Psoriasis Area and Severity Index (PASI)

To calculate the Psoriasis Area and Severity Index (PASI)[16,17] score, the four main body areas are assessed: head (h), trunk (t), upper extremities (u) and lower extremities (l).

The area affected by psoriasis within 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), 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:

$$PASI = 0.1(E_h + I_h + D_h)A_h + 0.2(E_u + I_u + D_u)A_u + 0.3(E_t + I_t + D_t)A_t + 0.4(E_l + I_l + D_l)A_l$$

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. Static Physician Global Assessment (sPGA)

The sPGA is a 5 point score ranging from 0 to 4, based on the physician's or representative's assessment of the average thickness, erythema, and scaling of all psoriatic lesions. The assessment is considered "static" which refers to the subject's disease state at the time of the assessments, without comparison to any of the subject's previous disease states, whether at baseline or at a previous visit.

A lower score indicates less body coverage, with 0 being clear and 1 being almost clear.

Erythema
(0) Normal (Post-inflammatory hyperpigmentation may be present)
(1) Pink coloration of lesions
(2) Light red coloration of lesions
(3) Dull to bright red coloration of lesions
(4) Bright to Deep red coloration of lesions

Induration
(0) None
(1) Just detectable
(2) Mild thickening
(3) Clearly distinguishable to moderate thickening
(4) Severe thickening with hard edges

Scaling
(0) No scaling
(1) Minimal focal scaling
(2) Predominately fine scaling
(3) Moderate scaling
(4) Severe/coarse scaling covering almost all or all lesions

Scoring: a composite score is generated from the above data and the final sPGA is determined from this composite score as follows:

Clear	0 = 0 for all three
Almost clear	1 = mean > 0, < 1.5
Mild	2 = mean >= 1.5, < 2.5
Moderate	3 = mean >= 2.5, < 3.5
Severe	4 = mean >= 3.5

sPGA Rating Scale for Overall Psoriatic Disease

Score	Short Description	Detailed Description
0	**clear**	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present
1	**Almost clear**	Normal to pink coloration; No thickening No to minimal focal scaling
2	**mild**	Pink to light red coloration Just detectable to mild thickening Predominantly fine scaling
3	**moderate**	Dull to bright red coloration Clearly distinguishable to moderate thickening Moderate scaling
4	**severe**	Bright to deep dark red coloration; Severe thickening with hard edges Severe coarse scaling covering almost all or all lesions

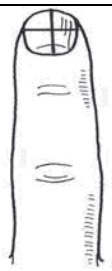
Appendix G. Nail Psoriasis Severity Index (NAPSI)

The nails will be graded for nail matrix psoriasis and nail bed psoriasis. The sum of the two scores is the total score for that nail.[18]

Nail Matrix Psoriasis

The Nail Matrix Psoriasis consists of any of the following: pitting, leukonychia, red spots in the lunula, and nail plate crumbling.

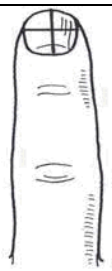
Score for Matrix Psoriasis

	0 = none 1 = present in 1 quadrant of nail 2 = present in 2 quadrants of nail 3 = present in 3 quadrants of nail 4 = present in 4 quadrants of nail

Nail Bed Psoriasis

The Nail Bed Psoriasis is the presence or absence of any of the following: onycholysis, splinter hemorrhages, oil drop (salmon patch) discoloration, and nail bed hyperkeratosis.

Score for Nail Bed Psoriasis

	0 = none 1 = present in 1 quadrant of nail 2 = present in 2 quadrants of nail 3 = present in 3 quadrants of nail 4 = present in 4 quadrants of nail

The sum of the scores will be added resulting a range of 0 to 80. If an individual finger assessment is missing (not done), the average of the remaining measured digits will be imputed and added to the sum. If < 50% of the finger assessments are missing the imputation will be performed. If more than 50% of the assessments are missing then the sum of the scores will be left as missing.

Appendix H. Palmoplantar Psoriasis Area and Severity Index (PPASI)

The PPASI provides a numeric scoring for psoriasis affecting the hands and feet with scores ranging from 0 to 72. It is a linear combination of percent of surface area of hands and feet that are affected and the severity of erythema, induration, and desquamation.

If a subject has palmoplantar psoriasis, the physician will assess the psoriasis at each protocol defined time point. Both palms and soles on each hand and foot will be individually assessed for erythema, induration, desquamation and percentage of area affected as follows:

- Erythema, Induration and Desquamation:
  0 = None
  1 = Slight
  2 = Moderate
  3 = Severe
  4 = Very Severe

- Percent of Palm and Sole Area Covered:
  0 = Clear
  1 = < 10%
  2 = 10 – 29%
  3 = 30 – 49%
  4 = 50 – 69%
  5 = 70 – 89%
  6 = 90 – 100%

The PPASI is a composite score and will be computed for each palm and sole, left and right and is derived from the sum of the scores for erythema (E), induration (I) and desquamation (D) multiplied by the score recorded for the extent of palm and sole area involved. PPASI is calculated as follows: (sum of scored for E+I+D)*Area

*0.2(location: right palm) + (sum of scored for E+I+D)*Area *0.2(location: left palm) + (sum of scored for E+I+D)*Area *0.3(location: right sole) +(sum of scores for E+I+D)*Area *0.3(location: left sole). The range is 0 to 72.

Appendix I. Psoriasis Scalp Severity Index (PSSI)

If a subject has scalp psoriasis, the physician will assess the erythema (redness), induration (hardness), desquamation (shedding of skin) and percent of scalp covered at each protocol defined time point.

Erythema, Induration and Desquamation:

0 = None
1 = Slight
2 = Moderate
3 = Severe
4 = Very Severe

Percent of Scalp Covered:

1 = < 10%
2 = 10 – 29%
3 = 30 – 49%
4 = 50 – 69%
5 = 70 – 89%
6 = 90 – 100%

The PSSI is a composite score derived from the sum of the scores for erythema, induration and desquamation multiplied by the score recorded for the extent of scalp area involved. The range is 0 to 72.

Appendix J. Dermatology Life Quality Index (DLQI)

The DLQI has been extensively used in clinical studies and has a large evidence base supporting reliability and validity.[19] The DLQI is a self-administered, ten-question questionnaire used to assess the effect of different skin diseases on a subject's quality of life, overall health, and disability status.[20] The questionnaire covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment and has a 1-week recall period.[15]

Each item is scored on a 4 point scale where a 0 score indicates "not relevant/not at all," and scores from 1 to 3 range from "a little," to "very much." Question 7 is a "yes"/"no"question where "yes" is scored as 3. If Question 7 is answered "no," scores range from 0 ("not at all") to 2 ("a lot").[21]

The 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 4-point change from baseline is considered a clinically important difference.[20]

The DLQI will be analyzed under six headings as follows:[17]

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 relationship	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3