1.0 Title Page

Clinical Study Protocol M16-178

A Randomized, Controlled, Multicenter, Open Label Study with Blinded Assessment of the Efficacy of the Humanized Anti-IL-23p19 Risankizumab Compared to FUMADERM® in Subjects with Moderate to Severe Plaque Psoriasis Who are Naïve to and Candidates for Systemic Therapy

Incorporating Amendments 1, 2 and 3

AbbVie Investigational Product:	Risankizumab
Date:	28 November 2017
Development Phase:	3
Study Design:	A Randomized, Controlled, Multicenter, Open Label Study with Blinded Assessment of the Efficacy of the Humanized Anti-IL-23p19 Risankizumab Compared to FUMADERM® in Subjects with Moderate to Severe Plaque Psoriasis Who are Naïve to and Candidates for Systemic Therapy
EudraCT Number:	2016-003718-28
Investigator(s):	Multicenter Trial (Investigator information is on file at AbbVie)
Sponsor:	AbbVie Deutschland GmbH & Co KG Knollstrasse 50 67061 Ludwigshafen Germany
Sponsor/Emergency Contact:	[redacted] Phone: [redacted] Fax:

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

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	05 January 2017
Amendment 1	13 March 2017
Amendment 2	05 July 2017

The purpose of this amendment is to implement the following changes:

- Section 1.0, Title Page: to change the Emergency Contact, Therapeutic Area Medical Director´s fax number.

  Rationale: *New fax number.*

- Section 5.2.1, Inclusion Criteria: removal of the following redundancy: "Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing at Study Day 1."

  Rationale: *Editorial change.*

- Section 5.2.3.3, Prohibited Therapy: moving the time point from which phototherapy (e.g., UVA, UVB, any other UV-therapy or balneotherapy) not-associated with systemic UV-sensitizing agents, topical treatment for psoriasis or any other skin condition (e.g., corticosteroids,[c] vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, andanthralin, α-hydroxy acid, fruit acids) are prohibited from 14 days prior to Screening to 14 days prior to Baseline.

  Rationale: *The half-life of those therapies is short and no interaction with study medication is to be expected if they are discontinued 14 weeks before 1st dose of study medication, i.e., 14 days before Baseline (Day 1, Week 0).*

- Section 5.3.1.1, Study Procedures, and Appendix C, Study Activities: FUMADERM® INITIAL and FUMADERM® Subject Diary: Clarification that the subject diary will be dispensed to the subject at every visit, starting at the Week 0/Baseline Visit rather than at the Screening Visit, and that the

subject will be trained on how to complete the diary at the Week 0/Baseline Visit.

Rationale: *Clarification.*

- Section 5.4.1.1, Discontinuation of Subjects on FUMADERM®: Point 8: Restriction of the discontinuation of the subjects on FUMADERM® for rash/flush to those with severe rash/flush.

  Rationale: *In clinical practice only severe persistent rash/flush leads to discontinuation of the patients from FUMADERM®.*

  The FUMADERM® label language does not request discontinuation of FUMADERM® treatment for all adverse events of rash/flush, but says: "... severe forms (of rash/flush) may lead to (FUMADERM®) treatment discontinuation."

- Section 5.5.1, Treatments Administered: the sentence "Additional dosing instructions will be provided separately from this protocol" has been removed.

  Rationale: *Risankizumab will be administered by site personnel only, therefore no additional instructions on how to administer an SC injection is required.*

- Appendix J, NAPPA-CLIN®: Extension of the prohibition of artificial nail and/or nail polish to all subjects instead of subjects with nail psoriasis only.

  Rationale: *Consistency within the protocol. The analysis of the efficacy on nail psoriasis is planned on all subjects regardless of a concomitant nail psoriasis.*

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-178
Name of Study Drug: Risankizumab	**Phase of Development:** 3
Name of Active Ingredient: Risankizumab	**Date of Protocol Synopsis:** 28 November 2017
Protocol Title: A Randomized, Controlled, Multicenter, Open Label Study with Blinded Assessment of the Efficacy of the Humanized Anti-IL-23p19 Risankizumab Compared to FUMADERM® in Subjects with Moderate to Severe Plaque Psoriasis who are Naïve to and Candidates for Systemic Therapy	
Objective: The objective of this study is to compare the efficacy and safety of subcutaneous (SC) risankizumab and oral FUMADERM® provided as study medication in subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy.	
Investigator: Investigator information on file at AbbVie.	
Study Site: Approximately 25 sites in Europe	
Study Population: Adults with moderate to severe plaque psoriasis [Psoriasis Area and Severity Index (PASI > 10), affected body surface area (BSA) > 10% and Dermatology Life Quality Index (DLQI) > 10] who are naïve to and candidates for systemic therapy.	
Number of Subjects to be Enrolled: Approximately 110 [2 × 55]	
Methodology: This study is a randomized, controlled, multicenter, open-label study with blinded assessment of efficacy to demonstrate the efficacy and safety of SC risankizumab in adult subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy compared with oral FUMADERM® provided as study medication. This study will be conducted in approximately 110 subjects. Subjects will be randomized in a 1:1 ratio (stratified by prior phototherapy, with a maximum of 20% of subjects with prior phototherapy) to one of two arms of either risankizumab or oral FUMADERM® provided as study medication. The following are the dosing arms: • Risankizumab 150 mg SC at Week 0/Day 1, Week 4 and Week 16 or, • Oral FUMADERM® provided as study medication daily starting at Week 0/Day 1 and until Week 24 (last intake in the morning on the day of Week 24 visit): FUMADERM® INITIAL provided as study medication starting at Week 0/Day 1 until Week 2 and FUMADERM® provided as study medication starting at Week 3, both at starting dose of 1 tablet per day, followed by an increase in the daily dose of 1 tablet per week, with the intention of achieving PASI 90. The maximum daily dose of FUMADERM® provided as study medication may not exceed 6 tablets per day. After the targeted efficacy on the psoriasis cutaneous lesions has been reached, an attempt should be made to reduce the dose of FUMADERM® provided as study medication to the individual maintenance dose. Efficacy outcomes will be measured at each visit until Week 24 and safety data will be collected throughout the study.	

Methodology (Continued):

At the Week 24 visit, subjects who completed the study will be offered the opportunity to participate in a separate extension study. For subjects that do not elect to enroll into the extension study, a follow-up phone call will be performed at Week 31.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female subject ≥ 18 and < 80 years of age at the time of screening.
2. Have a diagnosis of chronic plaque psoriasis for at least 6 months before the first administration of study drug. Duration since diagnosis may be reported by the patient.
3. Subject has stable moderate to severe plaque psoriasis with or without psoriatic arthritis at Baseline
   - Has an involved BSA > 10% and
   - Has a PASI score > 10 and
   - Has a DLQI > 10.
4. Must be naïve to and candidate for systemic therapy, as assessed by the investigator.
5. Subject has an inadequate response, intolerance or contraindication to topical psoriasis treatment as documented in the patient's medical history or reported by the patient or determined by the investigator at screening.

Main Exclusion:

1. Subjects with
   - Non-plaque forms of psoriasis (including guttate, erythrodermic, or pustular)
   - Drug-induced psoriasis (including an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium)
   - Active ongoing inflammatory diseases other than psoriasis that might confound study evaluations according to investigator's judgment
2. Subject has previously received systemic therapy for psoriasis, whether biologic or non-biologic, or photochemotherapy (e.g., PUVA therapy, any UV-therapy or balneotherapy associated with UV-sensitizing agent).
3. Active systemic infection during the last 2 weeks (exception: common cold) prior to screening.
4. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
5. Subject has any condition or contraindication to FUMADERM® that would preclude the patient's participation in the present study, including, but not limited to:
   - A known hypersensitivity to fumaric acid derivatives or other components of FUMADERM® Initial or FUMADERM®,
   - Any parameter of the complete blood count (CBC), at Screening Visit, outside of normal range according to the central laboratory
   - Severe liver disease (ALT or AST > 2 × ULN according to central laboratory normal range, or total bilirubin > 1.5 × ULN according to central laboratory normal range at Screening visit),
   - Severe kidney disease (serum creatinine above normal value according to central laboratory normal range at Screening visit),

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

Main Exclusion (Continued):

- Severe gastro-intestinal disease, such as a known active gastro-duodenal ulcer,
- Inability to understand the complexity of FUMADERM® dosing regimen,
- Any other exclusionary condition provided in Fumaderm® local label,
- Any of the following risk factors for renal toxicity:
  - peripheral vascular disease
  - diabetes mellitus with microalbuminuria (UACR > 30 mg/g), at Screening Visit,
  - systolic blood pressure measurement of > 140 mmHg or a diastolic blood pressure measurement of > 90 mmHg at the Screening visit, unless there is confirmation from an internist or a cardiologist that no renal or cardiovascular risk is associated with the elevated blood pressure.
  - history of congestive heart failure (NYHA Class III or IV*)

Investigational Product:	Risankizumab
Doses:	150 mg at Weeks 0 and 4, and 16.
Mode of Administration:	Subcutaneous Injection (SC) (pre-filled syringe)
Investigational Product:	FUMADERM® INITIAL and FUMADERM® provided as study medication
Doses:	QD to TID
Mode of Administration:	Oral

Duration of Treatment: The treatment duration will be 16 weeks for risankizumab and 24 weeks for FUMADERM®.

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint is the proportion of subjects with a ≥ 90% improvement in Psoriasis Area and Severity Index (PASI90) at Week 24.

Secondary efficacy variables are:

PASI, Body Surface Area (BSA), static Physician Global Assessment (sPGA), Palmoplantar psoriasis Severity Index (PPASI), Psoriasis Scalp Severity Index (PSSI), Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA-CLIN), Total Score Psoriasis Symptom Scale (PSS), Dermatology Life Quality Index (DLQI), Short Form 36 (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores, Patient Benefit Index (PBI), Hospital Anxiety and Depression Scale (HADS) Patient Global Assessment (PtGA), European quality of life – 5 dimensions 5 Level (EQ-5D-5L)

Pharmacokinetics and Immunogenicity:

Blood samples will be collected for measurement of risankizumab concentration and anti-drug antibody (ADA) between Day 1/Week 0 and Week 24/early termination (ET) visits.

Safety:

Safety and tolerability evaluations include adverse event monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology, chemistry, and urinalysis). Toxicity management guidelines are provided within the study protocol.

Statistical Methods:

Efficacy:

The efficacy analysis will be performed in the Intent to Treat (ITT) set which includes all subjects who are randomized.

The primary efficacy endpoint (PASI90 at Week 24) will be analyzed using a two-sided Cochran-Mantel Haenszel test stratified by prior phototherapy at level of significance 5%. Missing data will be imputed using non-responder imputation, i.e., a subject with missing PASI90 at Week 24 will be considered a non-responder in the primary analysis.

For categorical secondary endpoints, the same statistical test as for the primary endpoint will be used, missing data will be imputed using non-responder imputation. For continuous secondary endpoints, two-sided two-way ANOVA will be used with treatment and prior phototherapy as factors and missing data will be imputed using last observation carried forward (LOCF).

Secondary endpoints will not be used for confirmatory interpretation, thus no adjustment for multiplicity will be done.

Pharmacokinetics (PK) and Immunogenicity:

Risankizumab serum 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.

Safety:

The safety analysis will be performed in the safety set which includes all subjects who received at least one dose of study drug.

Treatment-emergent adverse events will be tabulated by system organ class and preferred term, whereby the most current implemented MedDRA dictionary will be used. Also, summaries by severity and relationship to study drug will be done. Certain adverse events, like serious or severe, leading to discontinuation, will be listed and described in detail. Adverse events of interest for treatment with biologics will be defined in the statistical analysis plan and analyzed separately.

Adverse events will be summarized by frequency and percentage and presented by treatment group, statistical comparisons will be performed using Fisher's exact test.

Other safety variables like laboratory data and vital signs will also be described by descriptive statistics for each treatment group. Treatment comparisons will be performed by one way ANOVA. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used.

* Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADA	Anti-Drug Antibody
AE	Adverse event
AP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATEMS	AbbVie Temperature Excursion Management System
AUC	Area under the curve
BI	Boehringer Ingelheim
BSA	Body surface area
CA	Competent authority
CASPAR	ClASsification criteria for Psoriatic Arthritis
CBC	Complete blood count
CCVT	Cardiovascular, cerebro Vascular and Thrombosis
CDSM	Clinical Drug Supply Management
CK	Creatine kinase
CK-MB	Creatine kinase MB isozyme
C_{max}	Maximal concentration
CRA	Clinical research associate
CRP	C-reactive protein
CYP3A	Cytochrome P450 3A
DILI	Drug induced liver injury
DLQI	Dermatology Life Quality Index
DMC	Data monitoring committee
DMF	Dimethyl fumarate
DNA	Deoxyribonucleic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Edetic acid (ethylenediaminetetraacetic acid)

EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life – 5 Dimensions 5 Level
EP	European Pharmacopoeia
ET	Early termination
EudraCT	European Clinical Trials Database
FDA	US Food and Drug Administration
FSH	Follicle stimulating hormone
G-BA	Gemeinsamen Bundesausschusses
GGT	Gamma-glutamyl transferase
GCP	Good Clinical Practice
GOT	glutamic oxaloacetic transaminase
GPT	glutamate-pyruvate transaminase
gCV	Geometric mean of coefficient vatiation
HADS	Hospital Anxiety & Depression Scale
HAV-IgM	Hepatitis A virus immunoglobulin M
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
IB	Investigator's brochure
IC	Inhibitor concentration
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IGRA	Interferon-gamma release assay
IL	Interleukin
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IVRS/IWRS	Interactive voice response system/Interactive web response system
LOCF	Last observation carried forward
mAB	Monoclonal antibodies

MACE	Major adverse cardiovascular events
MCS	Mental Component Summary
MHF	Methyl hydrogen fumarate
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
NAPPA-CLIN	Nail Assessment in Psoriasis and Psoriatic Arthritis
NDC	National Drug Code
NYHA	New York Heart Association
PASI	Psoriasis Area and Severity Index
PBI	Patient Benefit Index
PCS	Physical Component Summary
PD	Pharmacodynamic
PEE	Primary Efficacy Endpoint
PGA	Physician's Global Assessment
PK	Pharmacokinetic
PMN	Polymorphonuclear
PoCC	Proof of clinical concept
PPASI	Palmoplantar Posoriasis Severity Index
PPD	Purified Protein Derivative
POR	Proof of Receipt
PRO	Patient Reported Outcome
PSSI	Psoriasis scalp severity index
PSS	Psoriasis Symptom Severity
PtGA	Patient Global Assessment
PUVA	Psoralen plus ultraviolet light
QD	One a day
QTc	QT interval corrected for heart rate
RNA	Ribonucleic acid
SAE	Serious adverse event
SC	Subcutaneous
SF-36	Short Form 36
sPGA	Static Physician Global Assessment
SUSAR	Suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director

TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TID	Three times a day
TNF	Tumor necrosis factor
UACR	Urinary Albumin-to-Creatinine Ratio
ULN	Upper limit of normal
US	Ultrasound
USP	United States Pharmacopoeia
UV	Ultra Violet
VAS	Visual Analog Scale
VCAM-1	Vascular cell adhesion molecule 1
WOCBP	Women of childbearing potential

Definition of Terms

Moderate to severe psoriasis defined as:[1] BSA > 10 and PASI > 10 and DLQI > 10

2.0 Table of Contents

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3.0 Introduction

Psoriasis is a chronic inflammatory disease with raised, well-demarcated erythematous plaques with adherent silvery scales.[2] It is the most prevalent immune mediated skin disease, affecting 2% of the world population.[3] Twenty-five percent of patients have moderate to severe disease with considerable negative impact on psychosocial and economic status.[4] It is increasingly recognized that psoriasis is more than a superficial disease, with 30% of patients having joint involvement and a high correlation between psoriasis and obesity, diabetes, depression, metabolic syndrome and cardiovascular risk.[5]

While the majority of psoriasis patients 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 patients are treated with biological agents such as tumor necrosis factor (TNF)-alpha inhibitors (etanercept, adalimumab) and the interleukin (IL)-12/23 inhibitor (ustekinumab).[6] While the clinical efficacy of ustekinumab indicates a role for both IL-12 and IL-23 in the pathogenesis of psoriasis,[7] more recent data suggest that IL-23 is disproportionately involved in the maintenance of chronic psoriasis.[7] IL-23 is thought to be involved in the pathophysiology of psoriasis via induction and maintenance of 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.[8]

There is still clinical need for increased efficacy as the most effective anti-TNF and IL12/23 agents provide approximately 75% improvement in psoriasis in about 60 – 70% of patients and these responses tend to be lost over time. While the anti-IL-17 agents (i.e., secukinumab) may provide better efficacy, they require monthly injections, thus their long term utility is still undetermined.[8]

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 nM 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 that 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 for area under the curve (AUC) 0 – 168, respectively.

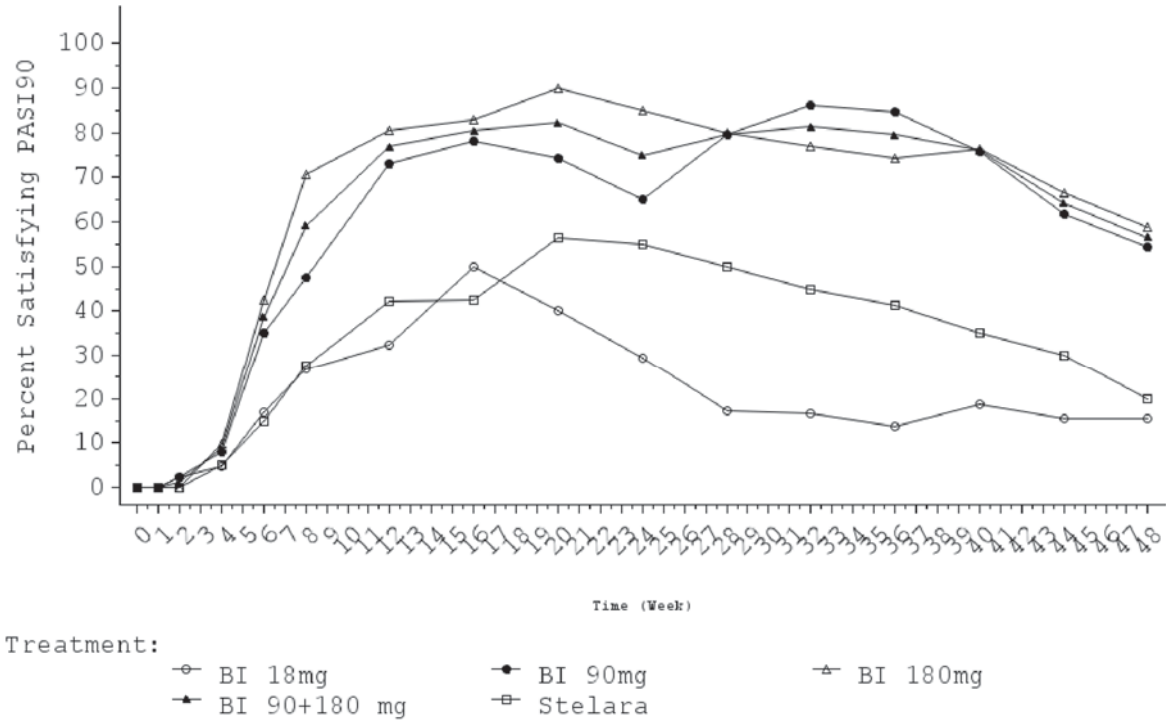
In Phase 1 and Phase 2 risankizumab has been studied in approximately 200 subjects with psoriasis without any unexpected adverse events (AEs) or safety signals. Based on the efficacy and safety findings in the completed and ongoing studies, the risk benefit profile of risankizumab is appropriate for further conduct of Phase 3 studies. In the Boehringer Ingelheim (BI) Study 1311.1,[9] a Phase 1 single rising dose study in 39 subjects with chronic plaque psoriasis, both intravenous (i.v.) and subcutaneous (s.c.) administration of risankizumab was well tolerated. Over the 24 weeks following a single i.v. or s.c. administration of risankizumab, 65% (20/31) of subjects experienced an adverse event (AE) compared with 88% (7/8) of subjects receiving placebo. There was no relationship between the overall frequency of AEs and treatment groups, or between the occurrence of AEs in specific system organ classes, or individual AEs, and treatment groups.
Four serious adverse events (SAE) were reported in subjects receiving risankizumab. All resolved without sequelae and were considered unrelated to study treatment.

After a single i.v. administration, risankizumab geometric mean AUCAUC$_{0\text{-inf}}$ ranged from 2.93 – 1650 day•µg/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. Based on all dose groups, the absolute bioavailability of risankizumab after SC administration was estimated to be 73%.

In a 48 week Phase 2 dose ranging study of risankizumab vs. ustekinumab in 166 subjects, approximately 73% of subjects reported an AE; the most common were nasopharyngitis (32% of 126 subjects in risankizumab arms), headache (9%), back pain (6%) and arthralgia (5%). Overall, there was no difference in the AEs across treatment groups and no evidence of a dose effect for any AE. During the 48-week study, 11 subjects (8.7%) on risankizumab reported at least 1 serious adverse event. One subject administered risankizumab (90 mg) experienced an SAE that was considered related to study treatment (basal cell carcinoma). All other SAEs were considered unrelated to study treatment.

Treatment with 90 or 180 mg risankizumab resulted in a higher percentage of subjects satisfying and maintaining Psoriasis Area and Severity Index (PASI) 90 through Week 48 as compared with ustekinumab and risankizumab 18 mg.[10]

Figure 1. PASI 90 Over Time (Observed) – Full Analysis Set



The 12 week data indicate a 37% greater improvement for risankizumab (90 mg and 180 mg, pooled data) compared to ustekinumab in the proportion of subjects achieving PASI 90.[10]

The current study compares the safety and efficacy of risankizumab versus Fumaderm® provided as study medication in subjects with moderate to severe psoriasis.

For a more detailed description of the drug profile, refer to the latest version of the investigator's brochure (IB).[9]

Fumaric acid esters was approved in Germany as systemic therapy for the treatment of psoriasis in 1995. The commercial product, Fumaderm® contains a mixture of dimethyl fumarate (DMF) and three salts of ethyl hydrogen fumarate. DMF is considered to be the actual active ingredient.[1]

Most of the reports on the clinical effects of Fumaderm® on psoriasis are from open label studies that consistently showed that a significant improvement in the condition of the skin is reached over a period of about 3 months of treatment.[1-16]

Preliminary results of a recent adequate and well controlled clinical study including a Fumaderm® arm indicate that PASI 75 and PGA 0 or 1 responses were achieved at Week 16 in 40.3% and 37.4% of the subjects treated with Fumaderm®, whereas 22.3% of the subjects achieved PASI 90 at Week 16.[17]

Serious adverse events were reported in 2.8% of the subjects and discontinuation due to adverse events occurred in 24% of the subjects receiving FUMADERM®. The most frequently reported treatment-emergent adverse events (TEAEs) were gastrointestinal disorders, including diarrhea (39.9%), upper abdominal pain (22.6%), abdominal pain (15.9%) and nausea (8.5%). Flushing was also commonly reported (16.3%) as well as pruritus (9.9%). Lymphopenia was observed in 10.6% of the subjects and was considered severe in two subjects (0.07%). Erythema, headache and nasopharyngitis were also reported (8.1% each). Proteinuria was reported in 2.1% of the subjects.

3.1 Differences Statement

The present study will only include subjects with moderate to severe plaque psoriasis who are naïve to systemic therapy, whereas the subjects included in the worldwide risankizumab psoriasis development program may have previously been exposed to biologic or non-biologic systemic treatment for psoriasis.

The comparator will be fumaric acid esters, commercialized as FUMADERM® in Germany whereas the ongoing studies of risankizumab use placebo, ustekinumab or adalimumab as comparators.

One further difference between other studies of risankizumab in psoriasis and this study relates to the definition of moderate to severe psoriasis, which, for this study, is defined as PASI > 10, body surface area (BSA) > 10% and dermatology life quality index (DLQI) > 10, this later definition being based on a European consensus decision.[1,18] In other studies of risankizumab, moderate to severe psoriasis is defined as PASI ≥ 12, BSA ≥ 10% and static physician global assessment (sPGA) ≥ 3.

3.2 Benefits and Risks

In Phase 1 and Phase 2 studies of risankizumab in patients with psoriasis, the majority of subjects receiving risankizumab achieved 90% improvement of their disease and risankizumab was well tolerated.

As with many immune modulating agents, 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 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 5.2.1 of this protocol. Interleukin-23 inhibition is not known to increase the risk of TB infection or impair the response to TB infection in animal models.[19,20] Thus, low

risk subjects with positive Quantiferon testing do not need 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.[21]

There is not enough information at this time to rule out a risk of cancer with risankizumab, but this risk is considered small with this type of compound as experience with the anti-Il-12/23 mAb ustekinumab has not suggested significant risk for cancer or serious infection.

Increases in major adverse cardiovascular (MACE) events including myocardial infarction, cerebrovascular accident, and cardiovascular death, reported initially with anti-IL-12/23 agents, such as ustekinumab, have not been observed in longer term studies. Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects' safety.

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

Fumaderm® is a widely prescribed systemic therapy for moderate to severe psoriasis, although registered for this indication in Germany only, a high proportion of patients treated with FUMADERM® experience a significant improvement in their psoriatic skin disease over a period of about 3 months of treatment.[1]

The safety profile of FUMADERM® is well characterized. Gastrointestinal complaints (in up to 60% of subjects especially in the initial weeks of therapy) and flush are the most common side effects of fumaric acid esters. Gastrointestinal tract symptoms include diarrhea, increased frequency of stools, nausea, and abdominal cramps. The symptoms of flush are highly variable and range from a brief feeling of warmth to reddening of the face

lasting for several hours. Leukocytopenia, lymphocytopenia, and eosinophilia are common side effects of fumaric acid esters. The other adverse events reported in association with FUMADERM® remain uncommon to very rare: acute lymphocytic leukemia, increase in liver function tests, Fanconi syndrome, opportunistic infection increases including isolated cases of progressive multifocal encephalopathy.

There is no known association of FUMADERM® with malignancy.[1,22]

There are no studies on the use of fumaric acid esters during pregnancy or in nursing women. Toxicology studies have shown that fumaric acid esters have neither teratogenic nor mutagenic potential.

The well codified dosing schedule for FUMADERM®, based on individual efficacy and safety response and the long experience in clinical practice since its commercialization guarantees an acceptable risk-benefit balance. Pregnancy and breastfeeding as well as severe liver, kidney and gastrointestinal diseases are contraindication to Fumaderm®.

4.0 Study Objective

The objective of this study is to compare the efficacy and safety of SC risankizumab and oral FUMADERM® provided as study medication in subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a randomized, controlled, multicenter, open-label study with blinded assessment of efficacy to demonstrate the efficacy and safety of SC risankizumab in adult subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy as compared with oral FUMADERM® provided as study medication. Eligible male and female subjects with moderate to severe plaque psoriasis will be selected to participate in the study according to the selection criteria.

The study will include a 30-day screening period and a 24 week active-controlled treatment period followed by a follow-up phone call at Week 31 for subjects that do not elect to enroll into the extension study. The maximum study duration is approximately 35 weeks for subjects that do not elect to enroll into the extension study and approximately 28 weeks for subjects that do participate in the extension study. This study was designed to enroll 110 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

After meeting the selection criteria, enrolled subjects will be randomly assigned in a 1:1 ratio to one of two arms as shown below:

- Risankizumab 150 mg SC at Week 0/Day 1, Week 4 and Week 16 or,
- Oral FUMADERM® INITIAL provided as study medication starting at Week 0/Day 1 until Week 2 and FUMADERM® provided as study medication starting at Week 3 until Week 24 (last intake in the morning on the day of Week 24 visit):

Screening Period

Within 30 days prior to the Week 0/Day 1 visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in Appendix C.

Paper diaries for FUMADERM® INITIAL and FUMADERM® (provided as study medication) dosing will be provided to the subjects at the visits outlined in Appendix C.

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

- A repeat of all screening procedures is needed with the possible exceptions noted below.

- If the subject had a complete initial screening evaluation including the assessment of an Interferon-Gamma Release Assay (IGRA; QuantiFERON Tuberculosis [TB] Gold In Tube test) or a purified protein derivative (PPD) test (or equivalent), and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met.

- There is no minimum period of time a subject must wait to re-screen for the study. If there is an exclusionary laboratory result during screening or re-screening within the 30 day screening window, one re-test of that particular value is allowed without repeating all other laboratory tests.
- The subject must meet all inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study.

Treatment Period

This period will begin at the Week 0/Day 1 (Baseline) Visit and will end at the Week 24/Early Termination (ET) Visit. At the Baseline Visit, subjects who meet all the inclusion criteria and none of the exclusion criteria described in Section 5.2 will be enrolled into the study and randomized to open-label treatment. During this period of the study, subjects will visit the site at Week 0 (Day 1/Baseline), Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24/ET. A ± 4 day window is permitted around scheduled study visits. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Visits should take place on the same day of the week as much as possible. At the Week 24 visit, subjects who have completed the study will be offered the opportunity to participate in a separate extension study. For subjects that do not elect to enroll into the extension study, a follow-up phone call will be performed at Week 31.

Safety data will be collected throughout the treatment period and up to 15 weeks after the last dose of risankizumab and/or 7 weeks after the last dose of FUMADERM® provided as study medication in this study. Subjects may discontinue study drug treatment at any time during study participation. Subjects that discontinue the study prior to Week 24 will have an ET visit and complete the procedures outlined in Appendix C within 2 weeks

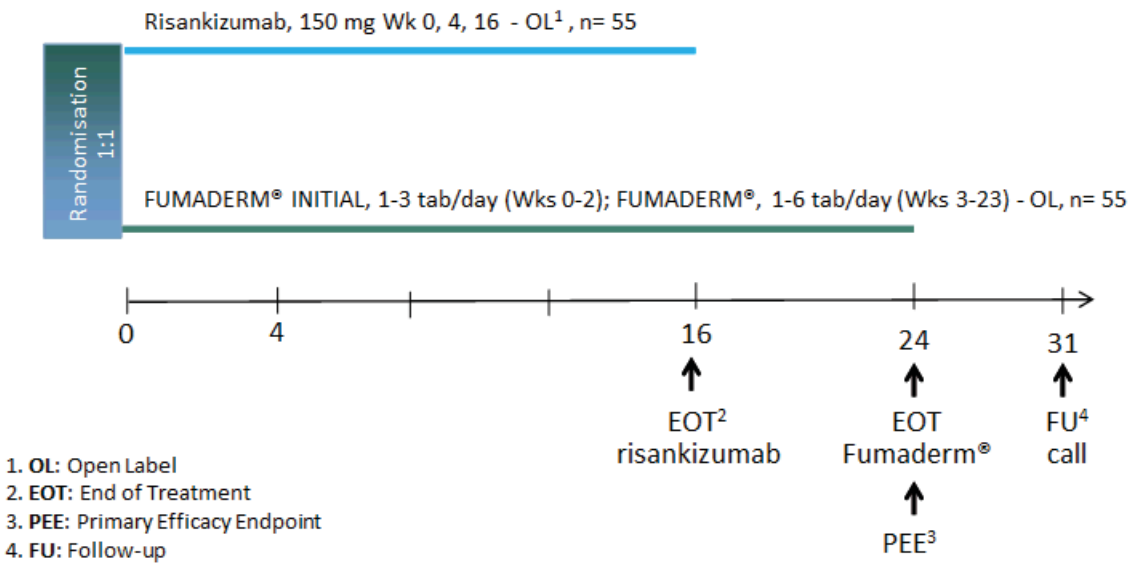
after the decision to discontinue and preferably prior to the administration of any new therapies.

Follow-Up Period

Subjects will have a follow-up phone call at approximately Week 31 (approximately 15 weeks after the last dose of risankizumab and 7 weeks after the last dose of FUMADERM® provided as study medication) with the exception of those subjects that elect to enroll into the extension study. All follow-up phone call procedures are noted in Appendix C.

A schematic of the study design is shown below in Figure 2.

Figure 2. Study Schematic



5.2 Selection of Study Population

It is anticipated that approximately 110 subjects with stable moderate to severe Plaque Psoriasis will be enrolled at approximately 25 sites in Europe. The subject population

will include adults with moderate to severe plaque psoriasis (PASI score of > 10, affected BSA > 10% and DLQI > 10) who are naïve to and candidates for systemic therapy.

A subject may be enrolled in this study provided that he/she has met all of the inclusion criteria and none of the exclusion criteria specified in this protocol.

5.2.1 Inclusion Criteria

1. Male or female subject ≥ 18 and < 80 years of age at the time of screening.
2. Have a diagnosis of chronic plaque psoriasis for at least 6 months before the first administration of study drug. Duration since diagnosis may be reported by the patient.
3. Subject has stable moderate to severe plaque psoriasis with or without psoriatic arthritis at Baseline
   - Has an involved BSA > 10% and
   - Has a PASI score > 10 and
   - Has a DLQI > 10
4. Must be naïve to and candidate for systemic therapy, as assessed by the investigator.
5. Subject has an inadequate response, intolerance or contraindication to topical psoriasis treatment as documented in the patient's medical history or reported by the patient or determined by the investigator at screening.
6. Patient who is a candidate for Fumaderm®, Ciclospirin, Methotrexate or phototherapy as per investigator's discretion.
7. If female, subject must be either postmenopausal OR Women of Childbearing Potential (WOCBP) and practicing at least one protocol specified method of birth control (detailed in Section 5.2.4), starting at Study Day 1 (or earlier) through at least 15 weeks after the last dose of risankizumab or FUMADERM® provided as study medication.

8. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing at Study Day 1.
9. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the study and prior to any study related procedure.

Rationale for the Inclusion Criteria:

1 – 6	To select the adequate subject population
7 – 8	The impact of risankizumab on pregnancy and reproduction is unknown
9	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. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for at least 15 weeks (i.e., 105 days) after the last dose of study drug.
2. Subjects with:
   - Non-plaque forms of psoriasis (including guttate, erythrodermic, or pustular)
   - Drug-induced psoriasis (including an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium)
   - Active ongoing inflammatory diseases other than psoriasis that might confound study evaluations according to investigator's judgment
3. Subject has previously received systemic therapy for psoriasis, whether biologic or non-biologic or photochemotherapy (e.g., PUVA therapy, any UV-therapy or balneotherapy associated with UV-sensitizing agent).

4. Subject cannot avoid excessive sun exposure (e.g., occupational exposure for a gardener or a roofer) or use of tanning booth for at least 4 weeks before baseline and during the study.
5. Participation in another study with an investigational drug or device within 4 weeks or 5 half-lives (whichever is greater) prior to screening.
6. Subjects who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator, (see Section 5.2.3).
7. Plans for administration of live vaccines during the study period or within 6 weeks prior to screening.
8. Major surgery performed within 12 weeks prior to screening or planned within the duration of the study (e.g., hip replacement, aneurysma removal, stomach ligation).
9. Active systemic infection during the last 2 weeks (exception: common cold) prior to screening.
10. Known chronic or relevant acute infections including HIV, viral hepatitis and/ or tuberculosis. Subjects with a positive QuantiFERON® TB/PPD test result may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis.
11. Subjects with a documented history of active TB may not enter the study unless they have completed a full course of anti-TB therapy and have been discussed with the AbbVie Therapeutic Area Medical Director (TA MD).
12. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
13. Evidence of a current or previous disease, medical condition other than psoriasis, surgical procedure (i.e., organ transplant), medical examination finding (including vital signs and ECG), or laboratory value at the screening visit outside the reference range that in the opinion of the investigator is clinically significant and

would make the study participant unreliable to adhere to the protocol or to complete the study, compromise the safety of the patient, or compromise the quality of the data.

14. Subject has any condition or contraindication to FUMADERM® that would preclude the patient's participation in the present study, including, but not limited to:

- A known hypersensitivity to fumaric acid derivatives or other components of FUMADERM® Initial or FUMADERM®
- Any parameter of the CBC outside of normal range according to the central laboratory at Screening visit,
- Severe liver disease (ALT or AST > 2 × ULN according to central lab normal range, or total bilirubin > 1.5 × ULN according to central laboratory normal range at Screening visit),
- Severe kidney disease (serum creatinine above normal value according to central laboratory normal range at Screening visit),
- Severe gastro-intestinal disease, such as a known active gastro-duodenal ulcer,
- Inability to understand the complexity of FUMADERM® dosing regimen,
- Any other exclusionary condition provided in FUMADERM® local label,
- Any of the following risk factors for renal toxicity:
  - peripheral vascular disease
  - diabetes mellitus with microalbuminuria (UACR > 30 mg/g) at Screening visit
  - Systolic blood pressure measurement of > 140 mmHg or a diastolic blood pressure measurement of > 90 mmHg at the Screening visit unless there is confirmation from an internist or a cardiologist that no renal or cardiovascular risk is associated with the elevated blood pressure.
  - History of congestive heart failure (NYHA Class III or IV[23])

15. History of allergy/hypersensitivity to any of the excipients in the risankizumab formulation.

Rationale for Exclusion Criteria:

1	The impact of risankizumab on pregnancy and reproduction is unknown
2 – 6	To select the adequate subject population
7 – 15	To ensure the safety of the subjects throughout the study

5.2.3 Prior and Concomitant Therapy

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prior Therapy

Any prior use of systemic treatment for psoriasis is prohibited.

Complete history of phototherapy will be captured as well as topical psoriasis medicine use for the past 5 years.

5.2.3.2 Concomitant Therapy

Any medication or vaccines (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving 4 weeks prior to screening or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate eCRF.

5.2.3.3 Prohibited Therapy

Table 1. Prohibited Psoriasis Medications

Medication or Class of Medications	Restriction Duration (Through 15 Weeks After the Last Dose of Risankizumab and Through 1 Week after Last Dose of FUMADERM®[a] Provided as Study Medication)
All systemic biologics (including investigational products) to treat psoriasis, including guselkumab, tildrakizumab, briakinumab, efalizumab (Raptiva®), secukinumab (Cosentyx®), ustekinumab (Stelara®), brodalumab, ixekizumab, adalimumab (Humira®), infliximab (Remicade®), etanercept (Enbrel®), alefacept (Amevive®)	Not allowed before or during study participation
All systemic non biologic to treat psoriasis (including investigational products), including Fumaderm®, except if provided as study medication, methotrexate, cyclosporine A, cyclophosphamide, mycophenolate mofetyl, retinoids, corticosteroids,[b] tofacitinib, apremilast, and any other drug known to possibly benefit psoriasis	Not allowed before or during study participation
Any investigational device or product (excludes psoriasis products)	30 days prior to screening or during study participation
Photochemotherapy (e.g., PUVA therapy, UV-therapy or balneotherapy associated with UV-sensitizing agent).	Not allowed before or during study participation
Phototherapy (e.g., UVA, UVB, any other UV-therapy or balneotherpy) not- associated with UV-sensitizing agents, topical treatment for psoriasis or any other skin condition (e.g., corticosteroids,[c] vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, andanthralin, α-hydroxy acid, fruit acids)	14 days prior to Baseline (Week 0/Day 1) or during study participation

a. Except if a psoriasis flare requires urgent therapy.

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

c. Exception: Topical corticosteroids of US class 7 (mild, such as desonide) or German class 1 (least potent, such as hydrocortisone 0.5 to 2.5%) for use on the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to study visit in which PASI is assessed.

The following therapies are prohibited in both groups.

- Live virus vaccines, from 6 weeks prior to Screening through 15 weeks after the last dose of risankizumab and 1 week after the last dose of FUMADERM® provided as study medication.
- Nephrotoxic drugs, from 2 weeks prior to Screening through 15 weeks after the last dose of risankizumab and 1 week after the last dose of FUMADERM® provided as study medication. Namely:
  - retinoids, psoralens, methotrexate, cyclosporine, immunosuppressants, cytostatics
  - aminoglycosides, amphotericin B, foscarnet, indinavir, tacrolimus, cisplatin, gold therapy, lithium, radiocontrast dyes

Rationale for the prohibited therapies:

Psoriasis medications (Table 1): prevent an interaction with efficacy outcome and protect patient's safety.

Live vaccine and nephrotoxic drugs: protect patient's safety. The investigator should review the FUMADERM® label for a current list of excluded or cautionary medications.

5.2.4 Contraception Recommendations and Pregnancy Testing

If female, subject must be either postmenopausal defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L OR
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Women of child bearing potential should practice at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 15 weeks after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) 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.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the WOCBP study participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

5.3 Efficacy and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed

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

5.3.1.1 Study Procedures

Study procedures will be performed at the study visits as specified in Appendix C. Study visits are scheduled at Week 0/Day 1, Weeks 4, 8, 12, 16, 20 and 24/ET. 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 6.1.1.1). All study data will be recorded in source documents and on the appropriate eCRFs.

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.

Inclusion/Exclusion Criteria

Subjects will be evaluated to ensure they meet all inclusion criteria and have none of the exclusion criteria at the Week 0/Day 1 visit.

Medical and Surgical History

A complete medical history, including history of tobacco, nicotine-containing products and alcohol use and ClASsification criteria for Psoriatic Arthritis (CASPAR)[24] classification will be taken from each subject during the Screening Visit. An updated medical history will be obtained prior to study drug administration and updated as necessary. Phototherapy and topical psoriasis medication history prior to Baseline visit, other medication (prescription or over-the-counter, including vitamins and/or herbal supplements) use at the time of enrollment and through the end of the study will also be recorded.

Demographics

The subject's demographic data, including year of birth, gender, race, and ethnicity will be collected.

Physical Examination

A complete or targeted physical examination will be performed at the designated study visits as specified in Appendix C. A complete physical examination will include vital sign assessment and general appearance as well as evaluation of all organ systems. Targeted physical examination will include vital sign assessment and evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities. Clinically relevant abnormal findings will be reported as baseline conditions or AEs.

All physical examination findings whether related to an AE or part of a subject's medical history will be recorded on the appropriate eCRF page.

Vital Signs

Vital signs evaluations will be performed at visits as shown in Appendix C.

This includes temperature, pulse rate, systolic/diastolic blood pressure and respiratory rate. Respiratory rate, pulse rate, and blood pressure will be measured after subjects have been sitting comfortably for at least 5 minutes. In the case of an elevated blood pressure (systolic blood pressure > 140 mmHg or a diastolic blood pressure > 90 mmHg) at initial measurement, the recommendations in Appendix D[40] should be followed in order to screen the subjects that will require further explorations. Measurement of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements.

12-Lead Electrocardiogram (ECG)

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

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

ECGs may be repeated for quality reasons and the repeat used for analysis. Additional ECGs may be collected for safety reasons at the Investigator's discretion. Clinically relevant, abnormal findings will be reported as AEs.

The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the subject's medical file.

Pregnancy Testing

A serum pregnancy test will be performed for all female subjects at the Screening Visit and at any other visit if the urine pregnancy test is positive. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test at screening is positive in a female of child bearing potential, the subject is considered a screen failure. If the serum pregnancy test at screening is borderline, it should be repeated to determine eligibility. If the repeat test is not negative, the subject must be excluded/discontinued.

A urine pregnancy test will be performed for all female subjects of child-bearing potential, by the site at the Baseline Visit prior to the first dose of study drug and at all subsequent visits. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements.

- If the urine pregnancy test performed at the site is negative, then dosing with study drug may begin/continue.
- If the urine pregnancy test performed at the site is positive, dosing must not be started/must be withheld and a serum pregnancy test is required. For the serum pregnancy test, follow the steps above.

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study.

HIV Testing

Subjects with a known history of HIV infection are excluded from study participation. HIV testing will be conducted as part of the infection screening at the screening visit. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.

Tuberculosis Screening

All subjects will be tested for TB by either the QuantiFERON-TB Gold Test (or equivalent) or a TB Skin Test (Purified Protein Derivative, PPD) at Screening visit as specified in Appendix C. If the TB screening test [either, PPD 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.

- 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 tuberculosis.
- If the subject is diagnosed with active tuberculosis, 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 tuberculosis is established treatment should be initiated and maintained according to local country guidelines. If latent tuberculosis occurs during the study, it is also necessary to report it as an adverse event in the source documents and eCRFs.
- If subject had a positive QuantiFERON®-TB Gold or PPD test at Screening, the test should not be repeated
- 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 tuberculosis-related adverse event, a TB supplemental form that provides additional information will be completed by the investigator or designee.

Blinded Efficacy Assessor

At all treatment visits, the subjects will be assessed for efficacy by a blinded efficacy assessor.

Prior to all examinations by the efficacy assessor, a bandage of the previous risankizumab injection site(s) in the subjects randomized to risankizumab will be applied.

To maintain the efficacy assessor's blind to treatment, site personnel (except the blinded efficacy assessor) will put a bandage over a viable injection site location in those subjects who are receiving FUMADERM®.

A qualified physician (may be a non-dermatologist) or designee (may be a non-physician) from the site will be responsible for performing the efficacy assessments, including PASI, BSA, static physician global assessment (sPGA), palmoplantar psoriasis severity index (PPASI), psoriasis scalp severity index (PSSI) and nail assessment in psoriasis and psoriatic arthritis (NAPPA-CLIN), at all appropriate study visits. The site will make every attempt to have the same qualified physician or designee perform these assessments throughout the study for each subject. The efficacy assessor must remain blinded to patient's treatment, clinical laboratory results and all subject safety data during the course of the study. The efficacy assessor will not view or discuss any subject specific safety data with the investigators or any other site personnel, with the exception of the dermatologic safety findings requiring urgent medical attention. The efficacy assessor therefore cannot be the Principal Investigator.

The efficacy assessor will not access patient's eCRF and will document the dermatologic assessments and potential dermatologic safety findings on paper worksheets that will be filed as source in the patient's record.

It is recommended that each study site has a designated back-up for the efficacy assessor.

The tasks of the blinded efficacy assessor are described in Table 2.

Table 2. Tasks of the Efficacy Assessor[a] and Investigator

Activities	Responsible Party
Assesses PASI, BSA, sPGA, PPASI, PSSI and NAPPA-CLIN	Efficacy Assessor
Looks for any potential dermatologic safety finding	Efficacy Assessor[b]
Documents the efficacy assessments and any potential safety findings on worksheets	Efficacy Assessor
Assesses safety	Investigator
Knows treatment allocation	Investigator
Inquires about treatment compliance, whether relating to psoriasis or not	Investigator
Reviews laboratory data	Investigator
Conduct the complete and targeted physical examinations[b]	Investigator
Completes the CRF and PROs	Investigator
Adjust FUMADERM® dosage according to protocol	Investigator
Documents findings in the e-CRF	Investigator
Reports information about safety findings[c]	Investigator

a. The efficacy assessor is a physician or a designee that is blinded to all aspects of the study other than the efficacy assessments.

b. The investigator will also look for potential dermatologic safety findings.

c. If the efficacy assessor identifies a safety issue this will be transmitted to the investigator over the worksheet. Dermatologic safety findings requiring urgent medical attention will be the only safety issues that the efficacy assessor may discuss with the investigator.

Clinical Laboratory Tests

Blood samples will be obtained for the laboratory tests listed ("complete lab") in Table 3 at Screening, Week 0, 8, 16 and 24 visits. At Week 4, 12, 20 visits only "targeted lab," i.e., CBC with differential count (hematology), ALT, AST, gamma-GT, alkaline phosphatase (AP) and serum creatinine, will be obtained. Blood draws should be performed after all clinical assessments and patient reported outcomes, ECGs, and vital sign determinations are obtained before study drug administration during a visit.

Urine samples will be obtained for urinalysis testing at all visits as listed in Table 3. The central laboratory will be responsible for performing a macroscopic urinalysis (urine

dipstick) on the collected urine specimens. Specified abnormal macroscopic urinalyses will be followed up with a microscopic analysis at the central laboratory.

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution. Laboratory abnormalities are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be an adverse event.

Instructions regarding the collection, processing and shipping of these samples will be provided by the central laboratory chosen for this study.

Table 3. Clinical Laboratory Tests

Category	Test Name
Hematology	Hematocrit (Hct) Hemoglobin (Hb) Red Blood Cell Count/Erythrocytes White Blood Cells/Leukocytes Platelet Count/Thrombocytes
Diff. Automatic	Neutrophils (absolute count) Eosinophils (absolute count) Basophils (absolute count) Monocytes (absolute count) Lymphocytes (absolute count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Enzymes	AST(GOT) ALT(GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-glutamyl gransferase (GGT/γ-GT)
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN Creatinine Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Albumin C-Reactive Protein (CRP) (high sensitivity) Cholesterol, total[a] Triglycerides[a] LDL-Cholesterol[a] HDL-Cholesterol[a] FSH[b]

Table 3. Clinical Laboratory Tests (Continued)

Category	Test Name
Urine Pregnancy test (only for female subjects of childbearing potential)[c]	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (in all female subjects at screening or if urine pregnancy test is positive in female subjects of child bearing potential)	Human Serum Chorionic Gonadotropin
Autoantibodies (only at screening)	Rheumatoid Factor
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/Erythrocytes Urine WBC/Leukocytes Urine pH Urine creatinine
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC/Erythrocytes Urine Sediment WBC/Leucocytes
Urine	UACR
Infection screening	Hepatitis B Surface Antigen (qualitative)[d,e] Hepatitis B Surface Antibody (qualitative)[d,e] Hepatitis B Core Antibodies total (qualitative)[d,e] Hepatitis B Virus DNA (quantitative)[d,e] Hepatitis C Antibodies (qualitative)[d,e] Hepatitis C Virus RNA (quantitative)[d,e] HIV-1, and HIV-2 Antibody (qualitative)[d,e] QuantiFERON®-TB (if applicable)

a. To be done at screening only.

b. (FSH) To be done at Screening in all women aged ≤ 55 years with no menses for 12 or more months without an alternative medical cause.

c. Urine pregnancy test performed at every visit except Screening.

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

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

Clinically relevant abnormal findings will be reported as baseline conditions or AEs. A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed and should be repeated until normalization or stabilization or until an alternative explanation has been found.

Clinical Assessments and Patient Reported Outcomes

Clinical and patient reported efficacy endpoints will be assessed over the course of the study at the time points defined in Appendix C. Patient reported outcomes (PROs) should be completed by the patient on his/her own in a pre-specified order in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the study team. Details of the following clinical and efficacy assessments are listed in the appendices. Details of the patient reported outcomes are listed below.

Clinical Assessments

- PASI
- BSA
- sPGA
- PPASI
- PSSI
- NAPPA-CLIN

Patient Reported Outcomes

The order of completion should be as follows, applicable for each PRO as specified in Appendix C.

- PSS
- DLQI
- SF36
- PBI

- HADS
- PtGA
- EQ-5D-5L

Psoriasis Symptom Scale (PSS)

The PSS is a four-item PRO instrument that assesses the severity of psoriasis symptoms in patients with moderate to severe psoriasis. The symptoms included are: pain, redness, itching and burning from psoriasis. Current symptom severity is assessed as a daily diary, using a 5-point Likert-type scale ranging from 0 (none) to 4 (very severe).

Dermatology Life Quality Index (DLQI)[26,27]

The DLQI has been extensively used in clinical studies and has a large evidence base supporting reliability and validity. 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. The questionnaire covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment and has a one week recall period.[26,27] 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").

Medical Outcome Short Form Health Survey (SF-36) Version 2 (Acute Form)[28,29]

The SF-36 is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed. The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different

treatments, and in screening individual subjects. The purpose of the SF-36 in this study is to assess the Health Related Quality of Life (HRQoL) of subjects. Given the acute nature of this disease, version 2, with a 1-week recall period, will be used in this study.

Patient Benefit Index (PBI)[30,31]

The PBI is a 25 item PRO instrument that assesses the benefit of psoriasis treatment. Patient relevant treatment needs and benefits are assessed through these 5 subscales: Reducing social impairment, reducing psychosocial impairments, reducing impairments due to therapy, reducing physical impairments, having confidence in healing. Treatment benefit is assessed using the PBI score ranging from 0 ("no benefit") to 4 ("maximal benefit").

Hospital Anxiety & Depression Scale (HADS)[32,33,34]

The HADS is a self-assessment scale which detects the presence and severity of anxiety and depression in the general population. It contains 14 items and is comprised of anxiety (7 items) and depression (7 items) subscales, which are scored separately and summed to give a total score. Item scores range from 0 (best) to 3 (worst) and total scores are categorized as normal (0 – 7), borderline abnormal (8 – 10) and abnormal (11 – 21). The HADS has been widely used in clinical trials in a variety of disease areas and has extensive evidence to support its acceptability, reliability and validity.

Patient's Global Assessment (PtGA)[35,36]

The PtGA is a PRO instrument to assess the patient's assessment of disease severity. This self-reported measure is used to assess disease activity using a 4-point scale where a higher score indicates higher level of disease activity. Disease activity is assessed from 0 ("complete disease control") to 3 ("uncontrolled disease").

European Quality of Life 5 Dimensions (EQ-5D)[37]

The EQ-5D is a standardized non-disease specific instrument for describing and valuing health-related quality of life.[1] The EQ-5D consists of 5 dimensions: mobility, self-care,

usual activity, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problem, slight problem, moderate problem, severe problem or unable to perform activity/extreme problem. It also contains a Visual Analogue Scale (VAS). Subjects are asked to indicate the level that describes their current level of function or experience for each dimension. As a measure of health status, it provides a descriptive profile and can be used to generate a single index value for health status, where full health is equal to 1 and death is equal to 0. The VAS records the subject's assessment of his/her own health along a vertical 20 cm line, which has health state scores between 0 and 100.

FUMADERM® INITIAL and FUMADERM® Subject Diary

Subjects will be dispensed a paper diary at every visit, starting at the Week 0/Baseline visit and will be trained on how to complete the diary for FUMADERM® INITIAL and FUMADERM® (provided as study medication) dosing by site staff during the Week 0/Baseline visit. All subjects should complete their subject diary on a daily basis throughout the entire study. The diary will be reviewed by site personnel with the subject at each visit and collected at the Week 24/ET Visit.

The dosing records will be reviewed and verified for compliance at each visit by the site personnel at the study center and reinforced if necessary. All relevant dosing information will be captured into the eCRF by site personnel.

Study Drug Administration

Refer to Section 5.5.1.

Monitoring for Hypersensitivity Reactions

A hypersensitivity reaction is a clinical sign or symptom, or constellation of signs or symptoms, caused by an inappropriate and excessive immunologic reaction to study drug administration. A systemic hypersensitivity reaction is a hypersensitivity reaction that does not occur at the local site of study drug administration (e.g., not an injection site reaction). A serious systemic hypersensitivity reaction is a systemic hypersensitivity reaction that fulfills criteria for a serious adverse event.

Subjects should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose administration (Week 0/Day 1) and 1 hour after all other doses of study drug (visits after Week 0/Day 1) in the patients randomized to risankizumab. Hypersensitivity reactions should be treated according to medical standards.

In the event of a suspected hypersensitivity reaction or other systemic post-dose reaction, a (PK/ADA) blood and urine sample will be collected once within 24 hours of the reaction.

In the event of a suspected systemic hypersensitivity reaction, a supplemental form that provides additional information is be completed by the investigator or designee.

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. The timing of blood collection will take priority over all other scheduled study activities except for PROs, ECG and vital signs. Blood samples for the PK assay should be collected as closely as possible relative to the time of dosing and within 30 minutes prior to dosing. Date and exact time (to the nearest minute) of drug administration will be recorded on eCRFs. The time that each blood sample is collected will be recorded to the nearest minute in the source document.

A total of three samples will be collected per subject for pharmacokinetic analysis during the treatment and follow-up periods.

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

Blood samples, approximately 3 mL, for risankizumab ADA assay will be collected at the 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 30 minutes prior to dosing. Date and exact time (to the nearest minute) of drug administration will be recorded on eCRFs. The time that each blood sample is collected will be recorded to the nearest minute in the source document.

A total of four samples will be collected per subject for ADA analysis during the treatment and follow-up periods.

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

5.3.2.4 Measurement Methods

Serum 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. Serum samples collected for risankizumab and risankizumab ADA analysis may be used for future assay development or validation activities.

The presence of ADA to risankizumab will be assessed via a tiered approach using a validated electrochemiluminescence assay (screening, confirmatory, and titration analysis

as appropriate). Samples that are confirmed positive may be further characterized in a validated neutralizing antibody (NAb) assay.

5.3.3 Efficacy Variables

5.3.3.1 Primary Variable

The primary efficacy endpoint is the proportion of subjects with a ≥ 90% improvement in Psoriasis Area and Severity Index (PASI 90)[30] at Week 24.

5.3.3.2 Secondary Variables

1. Proportion of subjects with a PASI 50/75/90/100 response at Weeks 4, 8, 12, 16, 20 and 24.
2. Change from baseline in PASI at Weeks 4, 8, 12, 16, 20 and 24.
3. Change from baseline in BSA affected by psoriasis at Weeks 4, 8, 12, 16, 20 and 24.
4. Proportion of subjects with a sPGA[24] of 0 or 1 at Weeks 4, 8, 12, 16, 20 and 24.
5. Proportion of subjects with sPGA of 0 at Weeks 4, 8, 12, 16, 20 and 24.
6. Change from Baseline in PPASI Total Score at Weeks 16 and 24.
7. Change from Baseline in PSSI Total Score at Weeks 16 and 24.
8. Change from Baseline on the NAPPA-CLIN Total Score at Weeks 16 and 24.
9. Change from Baseline in Psoriasis Symptom Scale (PSS) total score at Weeks 16 and 24.
10. Proportion of subjects achieving PSS (0) at Weeks 16 and 24.
11. Change from Baseline in DLQI total score at Weeks 16 and 24.
12. Proportion of subject achieving DLQI (0, 1) at Weeks 16 and 24.
13. Change from Baseline in SF-36 PCS and MCS Scores at Weeks 16 and 24.
14. Change from Baseline in PBI at Weeks 16 and 24.

15. Change from Baseline on HADS at Weeks 16 and 24.
16. Change from Baseline on PtGA at Weeks 16 and 24.
17. Change from Baseline in EQ-5D-5L Index, EQ-5D Utility Index and VAS at Weeks 16 and 24.

The order of the secondary endpoints does not reflect a ranking.

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

Risankizumab serum 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 for Either Risankizumab or FUMADERM®

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns or failure to comply with the protocol.

Whether randomized to risankizumab or to FUMADERM®, subjects will be withdrawn from the study immediately if any of the following occur:

1. Clinically significant abnormal laboratory results or adverse events, which rule out continuation of study drug, as determined by the Investigator and the AbbVie TA MD.
2. The Investigator believes it is in the best interest of the subject.
3. The subject requests withdrawal from the study.
4. Deviation from inclusion and exclusion criteria was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
5. Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
6. Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
7. The subject becomes pregnant while on study drug.
8. Subject has known malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
9. Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the study in consultation with the AbbVie TA MD.
10. Occurrence of following hepatic test abnormalities considered by the investigator to be related to study drug:
    - Confirmed ALT or AST > 8 × Upper Limit of Normal (ULN)
    - Confirmed ALT or AST > 5 × ULN for more than 2 weeks
    - Confirmed ALT or AST > 3 × ULN and (total bilirubin > 2 × ULN)
    - Confirmed 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, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the Early Termination Visit must be completed within 2 weeks after the decision to discontinue, 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. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

A final telephone call will occur for all subjects who do not roll over into the extension study, approximately 15 weeks after the last dose of risankizumab and 7 weeks after the last dose of FUMADERM®, provided as study medication, to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

All attempts must be made to determine the date of the last study drug dose and the primary reason for early termination. 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.

Subjects who discontinue the study prematurely will not be replaced.

Subjects are considered study completers if they have completed the Week 24 visit.

5.4.1.1 Discontinuation of Subjects on FUMADERM®

Subjects that are randomized to FUMADERM® INITIAL or FUMADERM® should be discontinued if any of the following occur:

1. A pronounced decrease in WBC count of > 50% between 2 visits or an absolute WBC count below 3,000/µl.

2. A lymphocyte count below 500/µl.
3. A lymphocyte count below 700/µl that persists 4 weeks after having reduced the dose of FUMADERM® INITIAL or FUMADERM® by half.
4. A Platelet count < 100 000/µl.
5. A diagnosis of progressive multifocal leukoencephalopathy.
6. An opportunistic infection, including but not limited to visceral herpes simplex, disseminated candidiasis, aspergillus colonization, acute pneumocystis carinii pneumonia or visceral CMV infection.
7. An increase in creatinine level above normal according to central laboratory normal range.
8. Severe rash/flush that does not resolve with continued treatment.
9. Major gastro-intestinal complaints that do not resolve with continued treatment in spite of dose reduction.

5.4.2 Discontinuation of Entire Study

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

5.5 Treatments

5.5.1 Treatments Administered

Subjects randomized to risankizumab will receive SC injections of risankizumab in the form of [redacted] mg (150 mg total) pre-filled syringes at Weeks 0, 4 and 16.

Risankizumab will be administered as a SC injection in the abdomen, thighs, gluteal regions, or upper arms (contra-lateral to that used for pharmacokinetic (PK)/pharmacodynamics (PD) samples). 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.

Subjects randomized to FUMADERM® will receive doses as noted in Table 5.

FUMADERM® dose is increased with the intention of achieving PASI 90, if tolerability allows. The decision of a slow increase in FUMADERM® INITIAL or FUMADERM® dose or of a return to FUMADERM® INITIAL after initiation of FUMADERM® will be made by the investigator and the justifications for all deviations from the pre-specified dosing schedule of FUMADERM® will be documented in the eCRF. The maximum daily dose of FUMADERM® may not exceed 6 tablets per day. After the targeted efficacy on the psoriasis cutaneous lesions has been reached, an attempt should be made to reduce the dose of FUMADERM® to the individual maintenance dose. FUMADERM® INITIAL and FUMADERM® tablets must be swallowed without chewing with plenty of liquid during and immediately after meals. In general, care must be taken to ensure subjects drink sufficient liquids (i.e., 1½ to 2 liters) daily.

The dose of FUMADERM® INITIAL or FUMADERM® should be reduced if any of the following occur:

1. A drop in lymphocyte count below 700/µl.
2. A platelet count < 150 000/µl and ≥ 100 000/µl.

3. WBC count < 3 500/µl and ≥ 3 000/µl.
4. Gastrointestinal disorders, nausea, abdominal cramps, diarrhea.
5. Nervous system disorders (i.e., tiredness, dizziness or headache).

After dose reduction of FUMADERM®, the blood count should be monitored until it returns to normal.

5.5.2 Identity of Investigational Product(s)

5.5.2.1 Identity of Risankizumab Investigational Product

Information about the risankizumab formulation to be used in this study is presented in Table 4.

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

- Risankizumab (ABBV-066) [redacted] mg/[redacted] mL Solution for Injection Pre-filled Syringe

Risankizumab is presented in a 1 mL pre-filled syringe with [redacted] mL of solution for injection. Dispensed volume is [redacted] mL. The solution in the risankizumab syringes has a concentration of 90 mg/mL, to deliver [redacted] mg per syringe. [redacted] syringes will be used to achieve the 150 mg dose.

Table 4. Identity of Risankizumab Investigational Product

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

5.5.2.2 Identity of FUMADERM® INITIAL and FUMADERM® Investigational Product

The two formulations of Fumaderm are used in this study are FUMADERM® INITIAL and FUMADERM® gastro-resistant tablets, FUMADERM® INITIAL being the low dose formulation to be taken in the first weeks of treatment before moving to FUMADERM®.

Table 5. FUMADERM® INITIAL and FUMADERM® Pre-Specifed Dosing Schedule (in the Absence of an Adjustment to the Efficacy and/or Safety Response):

	Dosage (n of Tablets/Day)		
Week	**Morning**	**Noon**	**Evening**
		FUMADERM® INITIAL	
0	-	-	1
1	1	-	1
2	1	1	1
		FUMADERM®	
3	-	-	1
4	1	-	1
5	1	1	1
6	1	1	2
7	2	1	2
8 – 24*	2	2	2

* Last intake of FUMDERM® in the morning on the day of Week 24 visit.

5.5.2.3 Packaging and Labeling

Risankizumab packaged in [redacted] mg pre-filed 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 of kits dispensed will be managed by the Interactive Response System (IRT).

FUMADERM® is packaged as follows:

- FUMADERM® INITIAL is packaged as a blister pack of 30 mg tablets.
- FUMADERM® is packaged as a blister pack of 120 mg tablets.

FUMADERM® INITIAL and FUMADERM® will be provided in an open-label fashion and packaged in cartons containing blister packs. Each kit will be labeled as required per local requirements. The number of kits dispensed will be managed by the IRT (Interactive Response System). All labels for risankizumab, FUMADERM® INITIAL and FUMADERM® must remain affixed to the study drug at all times, and should never be removed for any reason.

5.5.2.4 Storage and Disposition of Study Drug(s)

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. Risankizumab must not be frozen at any time.

A temperature log must be maintained for documentation of risankizumab storage.

The refrigerator temperature must be recorded each business day. Malfunctions or any temperature excursion must be reported to AbbVie immediately. Risankizumab should be quarantined and not dispensed until AbbVie or the AbbVie Temperature Excursion Management System (ATEMS) deems the drug as acceptable.

FUMADERM® INITIAL and FUMADERM® must be stored at 15°C to 25°C (59°F to 77°F).

A temperature log must be maintained for documentation of FUMADERM® INITIAL and FUMADERM®.

Any temperature excursion for FUMADERM® INITIAL and FUMADERM® must be reported to AbbVie immediately. FUMADERM® INITIAL and FUMADERM® should

be quarantined and not dispensed until AbbVie or the AbbVie Temperature Excursion Management System (ATEMS) deems the drug as acceptable.

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

Investigational products (IP) are for investigational use only and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be centrally randomized using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number/call-in directions and web based information for the IVRS/IWRS will be provided to each site.

All subjects will be assigned a unique identification number by the IVRS/IWRS at the Screening Visit. Subjects who meet the inclusion and exclusion criteria defined in Section 5.2.1 and Section 5.2.2 respectively will be centrally randomized in a 1:1 ratio to one of two dosing arms at Week 0/Day 1 (Baseline). The IVRS/IWRS will assign a randomization number according to the randomization schedule generated by the Statistics Department at AbbVie.

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/dispensed, study sites will be required to complete the study drug resupply module in the IRT to receive assigned study drug/kit numbers.

Risankizumab will be administered at the study site by authorized site personnel (e.g., study nurse) after all study procedures have been completed.

For subjects randomized to risankizumab, injections will be given in an open label fashion with each subject receiving [redacted] injections of risankizumab ([redacted] mg) at each dosing visit.

In exceptional cases of missed or delayed visits, risankizumab should not be administered within 14 days of the prior dose. There should be at least 14 days between two consecutive risankizumab administrations.

For subjects randomized to FUMADERM® INITIAL and FUMADERM®, drug will be provided to subjects for dosing at home as specified in Section 5.5.1.

Dose modifications or adjustments are not permitted for risankizumab. The dose modifications or adjustments for FUMADERM® INITIAL and FUMADERM® will be according to the investigator's instructions.

If one or several doses of FUMADERM® are missed, the patient should re-initiate the treatment with FUMADERM® according to the individualized dosing schedule. The subject should contact the site personnel or the investigator to confirm their dosing schedule. Any further adjustment of FUMADERM® dosing based on patient's individual efficacy and safety response is at the discretion of the investigator.

5.5.5 Blinding

This is an open-label study; however, the efficacy assessor will be blinded to the patient's study treatment as noted in Section 5.3.1.1.

5.5.6 Treatment Compliance

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

Subjects randomized to the FUMADERM® INITIAL and FUMADERM® arm will record all subject dosing information on a subject dosing diary and will return the dosing diary at each visit. Subjects will be instructed to return all drug cartons (even if empty) to the study site personnel at each Study Visit. The study site personnel will document compliance for risankizumab and FUMADERM® INITIAL and FUMADERM®.

5.5.7 Drug Accountability

The investigator and/or named sub-investigators must agree not to supply study drug to any persons not enrolled in the study.

The Investigator or designee 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 by registering the arrival of drug through the IRT. The original POR note or similar document and the IRT confirmation sheet will be kept in the site files as a record of what was received.

An accurate (running) inventory of study drug will be kept by the site, and will include the kit number, lot number, subject number, Proof of Receipt number(s), the number of pre-filled syringes or FUMADERM® blisters dispensed, initials of person who dispensed/administered the drug, and the date study drug was administered for each subject.

All empty/used study drug packaging and used pre-filled syringes will be inventoried by the site and verified by the site monitor. Each site will use their own sharps disposal container designated to store used pre-filled syringes for this study. Empty/used study drug packaging and sharps containers will be retained (unless prohibited by local law or site policy/procedure) by the site for accountability and compliance purposes. Study drug accountability will be completed via IRT, source documents, subject dosing diaries, and by visually inspecting the packaging and syringes in the sharps container whenever possible. Used sharps containers should never be opened.

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. After verification of drug accountability, 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 CRA. 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

This is a parallel group, two arm, open-label study comparing risankizumab with Fumaderm® with a blinded assessment of efficacy.

Although a double-blind study would have been preferable to potentially reduce bias, the logistical difficulties associated with blinding Fumaderm® led to a compromise on an open label-study with a blinded assessment of efficacy.

5.6.1 Discussion of Study Design and Choice of Control Groups

Fumaderm® is widely used for the treatment of psoriasis and is registered as 1st line treatment for moderate to severe psoriasis in Germany where it has a market share > 50%. Fumaderm® will be familiar to the participating investigators, particularly in Germany where the study will be initiated. Alignment on the protocol Fumaderm® dosing adjustment, which are based on the labelled dosing instructions, is expected to be easy to achieve.

In spite of requesting dosing adjustment, Fumaderm® is suitable for a clinical study, since the labelled dosing recommendations are straightforward based on the routine assessment of efficacy and safety.

5.6.2 Appropriateness of Measurements

The primary efficacy endpoint will be PASI 90 at Week 24, which is in line with the Gemeinsamen Bundesausschusses (G-BA) strong requirement for "long-term" data and for a stringent endpoint reflecting a PASI response of at least 75% compared to Baseline. Although PASI 75 has been the primary efficacy variable recommended by the EMA for

clinical trials in psoriasis subjects, the recent breakthroughs in this therapeutic field have led to using a more stringent criterion.

The secondary efficacy endpoints will evaluate the impact of study treatment on the different facets of the cutaneous disease as well as on multiple aspects of quality of life, which will also address a request from the G-BA.

5.6.3 Suitability of Subject Population

The subject enrolled are adults with moderate to severe plaque psoriasis PASI score of > 10, affected BSA > 10% and DLQI > 10 who are naïve to and candidates for systemic therapy.

Risankizumab will be positioned as first line systemic therapy for moderate to severe psoriasis and the study population corresponds to this target population. The definition of moderate to severe psoriasis is derived from the European guideline[1] and differs from that used in risankizumab pivotal studies [PASI ≥ 12, BSA ≥ 10% and sPGA ≥ 3].

The selection criteria relating to safety guarantee that the subjects enrolled can safely be treated with both study drugs, risankizumab and Fumaderm®, based on the current knowledge on those drugs.

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, which have enrolled approximately 2100 subjects, and evaluating risankizumab dose of 150 mg administered at Week 0, 4 and thereafter every 12 weeks. The risankizumab dosing regimen selected for the current study is the same as used in the ongoing risankizumab Phase 3 studies.

The Fumaderm® dosing recommendations are taken from the Fumaderm® label, with the caveat that the dose will be increased until PASI 90 is achieved, if tolerance allows.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

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

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1.1 through 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide another cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

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

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

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

6.1.1.2 Serious Adverse Events

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

Death of Subject An event that results in the death of a subject.

Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

6.1.1.3 Area of Safety Interest

Additional information may be collected for the following events:

Hepatic Adverse Events

In the case of any of the following AEs, a Hepatic Adverse Event eCRF should be completed:

- Discontinuation or interruption of study drug due to a hepatic related AE
- A hepatic related SAE
- A subject experiencing an ALT/AST > 8 × ULN
- A subject experiencing an ALT/AST > 3 × ULN in conjunction with a total bilirubin > 2 × ULN.

Systemic Hypersensitivity/Anaphylactic Reactions

- A Hypersensitivity Reaction Signs and Symptoms Supplemental eCRF should be used for the reporting of systemic hypersensitivity/anaphylactic reactions.

Major Adverse Cardiovascular Events [MACE] Events

In the case of any of the following reported events, appropriate supplemental MACE eCRF/s should be completed:

- Cardiovascular (Cardiac) Adverse Event;
- Myocardial Infarction or Unstable Angina Adverse Event;
- Heart Failure Adverse Event;
- Cerebral Vascular Accident and Transient Ischemic Attack Adverse Event;
- Combination Thrombotic Event
- Arrhythmias
- Non serious AE's Supplemental Laboratory
- Cardiovascular procedures

Tuberculosis [TB]

Infections, especially opportunistic infections, are a theoretical risk with immunomodulators. Subjects will be screened for tuberculosis and those with active

tuberculosis will be excluded from participation in the study. The screening procedures are outlined in Appendix C. A Tuberculosis Supplemental eCRF should be used for the reporting of tuberculosis.

6.1.1.4 CCVT Adjudication Committee

An independent adjudication committee will be adjudicating all observed cardiovascular, cerebro-vascular and thrombotic events (CCVT) including MACE and will remain blinded to treatment allocation. The events that are adjudicated and the adjudication process will be detailed in the CCVT Adjudication Committee Charter. Dedicated CRFs will be used for:

- Cardiovascular (Cardiac) Adverse Event;
- Myocardial Infarction or Unstable Angina Adverse Event;
- Heart Failure Adverse Event;
- Cerebral Vascular Accident and Transient Ischemic Attack Adverse Event;
- Combination Thrombotic Event
- Arrhythmias
- Non serious AE's Supplemental Laboratory
- Death
- Cardiovascular procedures

In addition, the site may be contacted for additional source documentation for relevant events.

6.1.2 Adverse Event Severity

Intensity of AEs

The investigator will use the following definitions to rate the severity of each adverse event:

Mild The adverse event is transient and easily tolerated by the subject.

Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 Relationship to Study Drug

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

Reasonable Possibility	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 serious adverse event.

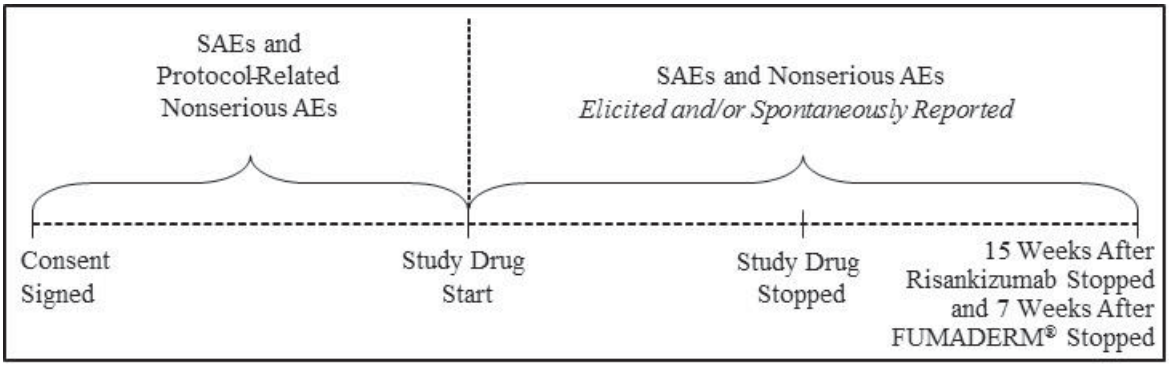
6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 15 weeks following discontinuation of risankizumab and 7 weeks following discontinuation of FUMADERM® (provided as study medication) administration have elapsed will be

collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related non-serious adverse events will be collected from the time the subject signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events 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-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email:	[redacted]
FAX to	

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
USA

Office: [redacted]
Email:

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

Primary AbbVie Therapeutic Area Medical Director:

[redacted]

Telephone Contact Information:
Office:
Mobile: [redacted]
Email:

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

24-hour AbbVie Medical Escalation Phone Hotline: [redacted]

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 Investigator's Brochure for risankizumab and the Summary of Product Characteristics for FUMADERM® INITIAL and FUMADERM®.

6.1.6 Pregnancy

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

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

Pregnancy in a study subject is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a serious adverse event 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(s).

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

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

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

6.2.2 Reporting

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

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

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

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified)

after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact:	Alternate Contact:
[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.

8.0 Statistical Methods and Determination of Sample Size

The specification described here is that envisaged at the time of planning the trial. Should new evidence come to light as a result of running other trials before this trial is analyzed, or should new methods of analysis become available in the statistical literature, or should the trial be affected by unforeseen circumstances, it may be necessary to modify the analysis strategy.

The analysis strategy described below will be supplemented by a detailed statistical analysis plan (SAP), which will be completed prior to database lock.

8.1 Statistical and Analytical Plans

8.1.1 Analysis Populations

The intent-to-treat (ITT) population consists of all subjects who were randomized. The safety population consists of all subjects who were randomized and received at least one dose of study drug.

In order to evaluate the impact of major protocol deviations on the results of the trial, additional sensitivity analyses may be performed on the per-protocol population, which excludes subjects with major protocol deviations from the ITT population. If it is decided that this analysis should be performed, the criteria for exclusion of subjects from the protocol analysis will be fully defined and documented in the final SAP and before the database lock.

8.1.2 Planned Methods of Statistical Analysis

All statistical tests will be two-tailed. The statistical tests for the primary endpoint will be performed at the significance level 0.05. All *P* values will be rounded to 3 decimal places. Descriptive statistics will be provided. These include the number of observations, mean, standard deviation, minimum, median, quartiles and maximum for continuous variables, and counts and percentages for discrete variables. The analyses will be performed using SAS® (SAS Institute Inc., Cary, NC, USA).

8.1.3 Demographic and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized for each treatment arm using descriptive statistics. Statistical tests will be performed to assess the comparability of the treatment arms. Continuous variables will be analyzed using one-way analysis of variance (ANOVA), and discrete variables will be analyzed using Chi squared test or Fisher's exact test as appropriate.

8.1.4 Analysis of Efficacy

All efficacy analyses will be performed in the ITT population.

The primary efficacy endpoint (PASI90 at Week 24) will be analyzed using a two-sided Cochran-Mantel Haenszel test stratified by prior phototherapy at level of significance 5%. Missing data will be imputed using non-responder imputation, i.e., a subject with missing PASI90 at Week 24 will be considered a non-responder in the primary analysis. Further sensitivity analyses for the primary endpoint may be specified in the SAP prior to database lock.

For the analysis of categorical secondary endpoints, the same statistical test as for the primary endpoint will be performed, missing data will be imputed using non-responder imputation. For the analysis of continuous secondary endpoints, two-sided two-way ANOVA with treatment and prior phototherapy as factors will be imputed using last observation carried forward (LOCF).

The order of the secondary endpoints does not reflect a ranking and secondary endpoints will not be used for confirmatory interpretation, thus no adjustment for multiplicity will be done.

Further details regarding the statistical analysis will be specified in the SAP.

8.1.5 Analysis of Safety

All safety analyses will be performed in the safety population.

Treatment-emergent adverse events are defined as events with an onset date on or after the first dose of study drug until 15 weeks (105 days) following the last dose of risankizumab or 1 week (7 days) after the last dose of FUMADERM® provided as study medication or until rollover into the extension study. In a sensitivity analysis, adverse events with an onset date until 7 weeks (49 days) after the last dose of FUMADERM® provided as study medication or until rollover into the extension study will be included.

SAEs and protocol-related non-serious AEs with onset after informed consent but before the first study drug administration will be considered as pretreatment events and reported separately.

Adverse events will be tabulated by system organ class and preferred term, whereby the most current implemented MedDRA dictionary will be used. Also, summaries by severity and relationship to study drug will be done. Certain adverse events, like serious or severe, leading to discontinuation, will be listed and described in detail. Adverse events of interest for treatment with biologics will be defined in the statistical analysis plan and analyzed separately.

Adverse events will be summarized by frequency and percentage and presented by treatment group, statistical comparisons will be performed using Fisher's exact test.

Other safety variables like laboratory data and vital signs will also be described by descriptive statistics for each treatment group. Treatment comparisons will be performed by one way ANOVA. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used.

8.1.6 Interim Analysis

No interim analysis will be done for this study.

8.1.7 Pharmacokinetic and Exposure-Response Analysis

Individual risankizumab serum 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 with 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 clinical study report for this study.

8.2 Determination of Sample Size

Using a two-sided Chi squared test at level of significance 5%, the sample size of 110 (2 × 55) subjects will provide 94% power assuming response rates of the primary endpoint (PASI90 at Week 24) of 70% for risankizumab and 35% for FUMADERM®.

These assumptions are in line with what has been observed in recent studies for Risankizumab (63/83 (75.9%) at Week 24)[9] and FUMADERM® 61/273 (22.3%) of the subjects achieved PASI 90 at Week 16 in the FUMADERM® arm in the BRIDGE trial.[15]

8.3 Randomization Methods

An IVR/IWR system will be used to determine the randomization of subjects. Detailed instructions for using the IVR/IWR system will be provided to the site personnel.

The randomization schedule will be prepared by the statistics department of AbbVie. Subjects who are eligible based on inclusion and exclusion criteria and have had all pre-randomization procedures performed will be randomized in a 1:1 ratio to receive risankizumab or FUMADERM® stratified by prior phototherapy, with a maximum of 20% of subjects with prior phototherapy. Randomization will not be stratified by center due to the limited number of subjects per center. Randomization will be done using an adequate block size.

9.0 Ethics

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

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB). The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the

protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

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

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

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

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

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

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

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 Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

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

10.2 Case Report Forms

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

through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

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

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

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

Patient Reported Outcome (PRO) data must be completed for each subject screened/enrolled in this study. These data are being collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO system is available through the vendor, CRF Health, while the user acceptance testing of the study-specific PRO design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health.

Internet access to the ePRO data will be provided by CRF Health for the duration of the study. This access will be available for the duration of the study to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO 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 ePRO data. It will be possible for the investigator to make paper print-outs from that media.

The ePRO data will be collected by the following methods:

Tablet Based

- The instruments/scales will be collected electronically via a Tablet/Laptop device into which the patient will directly enter the required pieces of information. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for subjects to complete more than one of the same assessment at any one visit. All data entered on the device will be immediately stored to the device itself and automatically uploaded to a central server administrated by CRF Health. The Investigator and delegated staff will be able to access all uploaded patient entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

11.0 Data Quality Assurance

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

Prior to the initiation of the study, a meeting will be held with AbbVie personnel, the investigators and appropriate site personnel. This meeting will include a detailed

discussion of the protocol, performance of study procedures, eCRF, Subject Questionnaires, and Subject Diary completion, and specimen collection methods. The AbbVie monitors will monitor each site throughout the study.

All data hand entered in the database will be verified at AbbVie. Any discrepancies will be reviewed. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates. Any necessary corrections will be made to the eCRF.

The data from the central laboratory analyses will be electronically transferred from the central laboratory to the study database.

12.0 Use of Information

All information concerning specify study drug 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 specify study drug. 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.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the 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 forward a copy of this 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 must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory 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 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, Week 24/Early Termination Visit, see Appendix C.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for risankizumab and the product labeling for FUMADERM INITIAL® and FUMADERM®.
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 Randomized, Controlled, Multicenter, Open Label Study with Blinded Assessment of the Efficacy of the Humanized Anti-IL-23p19 Risankizumab Compared to FUMADERM® in Subjects with Moderate to Severe Plaque Psoriasis Who are Naïve to and Candidates for Systemic Therapy
Protocol Date:	28 November 2017

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

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.
11. Not disclosing the treatment codes or any patient information to the blinded efficacy assessor.

Appendix B. List of Protocol Signatories

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

Appendix C. Study Activities

Activity	Screening –30 to –1	Week 0/ Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/ET[a]	Week 31 Follow-Up Call[b]
Day	**–30 to –1**	**Day 1**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**	**Day 218**
Informed Consent	X								
Medical/Surgical History	X	X[c]							
Alcohol and Nicotine Use	X	X							
Pregnancy Tests[d] u = urine, s = serum	X(s)	X(u)	X(u)	X(u)	X(u)	X(u)	X(u)	X(u)	
Physical Exam c = complete, t = targeted	X(c)	X(c)	X(t)	X(t)	X(t)	X(c)	X(t)	X(c)	
Vital Signs[e]	X	X	X	X	X	X	X	X	
Safety Laboratory Testing[f] c = complete, t = targeted	X(c)	X(c)	X(t)	X(c)	X(t)	X(c)	X(t)	X(c)	
Urinalysis	X	X	X	X	X	X	X	X	
CASPAR Assessment	X								
FSH[g]	X								
PASI/% BSA Involvement	X	X	X	X	X	X	X	X	
Assess Concomitant Medications	X	X	X	X	X	X	X	X	X
12 Lead ECG	X							X	
Infection Screening[h]	X								
Dispense Subject Diary[i]		X	X	X	X	X	X		

Activity	Screening –30 to –1	Week 0/ Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/ET[a]	Week 31 Follow-Up Call[b]
Day	–30 to –1	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 218
DLQI[j]	X	X				X		X	
Randomization		X							
Risankizumab Administration[k]		X	X			X			
FUMADERM® Dispensation[l]		X	X	X	X	X	X		
Blood Sampling for PK[m]			X			X		X	
Blood Sampling for ADA Assay[m]		X	X			X		X	
Subject Diary Review		X	X	X	X	X	X	X	
Monitor Adverse Events		X	X	X	X	X	X	X	X
PPASI/PSSI/NAPPA-CLIN[j]		X				X		X	
sPGA		X	X	X	X	X	X	X	
PSS[j]		X				X		X	
Monitor Compliance[i]		X	X	X	X	X	X	X	
Short Form SF-36[j]		X				X		X	
Patient Benefit Index (PBI)[j]		X				X		X	
HADS[j]		X				X		X	
PtGA[j]		X				X		X	
EQ-5D-5L[j]		X				X		X	

a. Subjects that discontinue the study prior to the end of the study will have an Early Termination visit within 2 weeks after the decision to discontinue.

b. Subjects that discontinue the study prior to the end of the study will have a follow-up phone call within 15 weeks after the last dose of risankizumab and 7 weeks after the last dose of FUMADERM® provided as study medication for collection of safety data. Subjects that elect to enroll into a separate extension study will not require the Week 31 Follow-Up phone call as part of this trial.

c. Update history.

d. Serum pregnancy test in all women at screening and if the urine pregnancy test is positive at any other visit. Urine pregnancy tests are to be performed in all women of child bearing potential prior to administration of study drug at all dosing visits.

e. Height and weight will be measured at the Screening Visit only (with shoes off).

f. Targeted laboratory samples should be limited to CBC with differential count (hematology), serum creatinine (substrates) and ALT, AST, gamma-GT and AP (enzymes).

g. (FSH) To be done at Screening in all women aged ≤ 55 years with no menses for 12 or more months without an alternative medical cause.

h. Infection screening consists of Hepatitis B Surface Antigen (qualitative), Hepatitis B Surface Antibody (qualitative), Total Hepatitis B Core Antibodies (qualitative), Hepatitis B Virus DNA (quantitative) reflex, Hepatitis C Antibodies (qualitative), Hepatitis C Virus RNA (quantitative) reflex, HIV-1 and HIV-2 Antibody (qualitative), PPD/QuantiFERON-TB.

i. For FUMADERM® INITIAL and FUMADERM® provided as study medication only.

j. Prior to other procedures.

k. SC risankizumab 150 mg at Week 0/Day 1, Week 4 and Week 16. Risankizumab will be administered at the study site by authorized site personnel (e.g., study nurse) after all study procedures have been completed.

l. Oral FUMADERM® daily starting at Week 0/Day 1 and until Week 24 (the last dose will be in the morning of the day of Week 24 visit). FUMADERM® INITIAL starting at Week 0/Day 1 until Week 2 and FUMADERM® starting at Week 3, both at starting dose of 1 tablet per day, followed by a dose increase of one tablet per week, depending on efficacy response and tolerability. The maximum dose of FUMADERM® of 6 tablets per day should not be exceeded.

m. PK and ADA samples are collected only from the subjects receiving risankizumab.

Appendix D. Recommendations on the Technique of Blood Pressure Measurement

Proper techniques to measure blood pressure are important to ensure consistent and reliable measurements. The purpose of the recommendations below is to screen in routine practice the patients that will require explorations in a specialized department.[40]

1. If anatomical conditions, deformity or surgical history interfering with proper access or blood flow to the upper arm, use the opposite arm for the blood pressure measurement
2. Use a high quality and well calibrated equipment
3. Prepare the patient
    - The examination room should be quiet, with a comfortable ambient temperature.
    - Ideally, blood pressure should not be measured if the patient has engaged in recent physical activity, used tobacco, ingested caffeine, or eaten within the past 30 minutes
    - Correct positioning of the patient is essential.
        - The patient's back and legs should be supported, with the legs uncrossed and the feet resting on a firm surface.
        - The arm in which blood pressure will be measured should be bare to the shoulder, and the garment sleeve, if raised, should be loose, so that it does not interfere with blood flow or with proper positioning of the blood-pressure cuff.
        - The arm should be supported and level with the heart. The manometer should be positioned at the health care practitioner's eye level.
4. Make sure that you are using the properly fitted cuff (undersized cuffs will result in overestimation of blood pressure)
    - Selection of an appropriately sized cuff requires assessment of the patient's arm circumference at the midpoint of the upper arm.

5. Place the cuff on a bare arm, approximately 2 cm above the elbow crease, with the midline of the bladder (usually indicated by the manufacturer) directly over the brachial artery. It should fit snugly but should still allow for two fingers to slide under the cuff.
6. Estimate the systolic blood pressure by first measuring pulse-obliteration pressure
7. For blood pressure measurement, proceed as follows:
    - Place the bell of the stethoscope over the brachial artery, using sufficient pressure to provide good sound transmission without over-compressing the artery. To avoid extraneous noise during cuff deflation, ensure that the stethoscope is not in contact with the patient's clothing or with the blood-pressure cuff.
    - Initiate the auscultatory blood pressure measurement by rapidly inflating the cuff to a level 20 to 30 mmHg above the pulse-obliteration pressure.
    - Then deflate the cuff at a rate of 2 mmHg per second while listening for the Korotkoff sounds. As the cuff is deflated, turbulent blood flow through the brachial artery generates a series of sounds. Classically, these have been described according to five phases.
        - Phase 1 is characterized by a clear, repetitive tapping sound, coinciding with reappearance of a palpable pulse. The initial appearance of Phase 1 sounds is equal to the systolic blood pressure.
        - During Phase 2, audible murmurs in the tapping sounds are heard.
        - In Phases 3 and 4, muted changes in the tapping sounds occur (usually within 10 mmHg of the true diastolic pressure) as the pressure measurement approaches the diastolic pressure.
        - Phase 5 is not really a sound; it indicates the disappearance of sounds and equates to the diastolic blood pressure. To ensure that diastole has been reached, continue to deflate the cuff pressure for an additional 10 mmHg beyond the fifth Korotkoff sound.

Obtain a minimum of two blood-pressure measurements at intervals of at least 1 minute and record the average of the measurements as the blood pressure.

Cross reference: Williams JS et al 2009[40]

Appendix E. CASPAR Classification Criteria

CASPAR Classification Criteria	To meet the CASPAR (**C**l**AS**sification criteria for **P**soriatic **AR**thritis) criteria,* a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥ 3 points from the following 5 categories: 1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis. Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.† A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified healthcare provider. A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report. 2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination. 3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immuosorbent assay or nephelometry, according to the local laboratory reference range. 4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist. 5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

* The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%.

† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

Taylor W, Gladman D, Helliwell P, et al; CASPAR Study Group. Classification criteria for psoriatic arthritis. Arthritis Rheum. 2006;54(8):2665-73.

Appendix F. PASI SCORE Definitions and Use Psoriasis Area and Severity Index (PASI)

The PASI score is an established measure of clinical efficacy for psoriasis medications.[24]

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

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

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

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

- 0 = no involvement
- 1 = < 10%
- 2 = 10% to 29%
- 3 = 30% to 49%
- 4 = 50% to 69%
- 5 = 70% to 89%
- 6 = 90% to 100%

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

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

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

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

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

Assignments for the following body regions are as follows:

- Neck: include with the head
- Buttocks: include with the lower extremities
- Axillae: include with the trunk
- Genitals: include with the trunk
- The inguinal canal separates the trunk and legs anteriorly

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

The PASI score is calculated according to the following formula:

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

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.

* Fredriksson T[38]

Appendix G. Static Physician Global Assessment (sPGA)

This 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.[39]

The assessment is considered "static" which refers to the patients disease state at the time of the assessments, without comparison to any of the patient'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.

The efficacy assessor (or qualified site personnel) scores the erythema, induration and scaling of all psoriatic lesions from 0 – 4 based on the following descriptors:

Erythema

0	Normal (post-inflammatory hyper/hypopigmentation may be present)
1	Faint, diffuse pink or slight red coloration
2	Mild (light red coloration)
3	Definite red coloration (Dull to bright red)
4	Bright to Deep red coloration of lesions

Induration (Plaque Elevation)

0	None
1	Just detectable (possible slight elevation above normal skin)
2	Mild thickening (slight but definite elevation, typically edges are indistinct or sloped)
3	Clearly distinguishable to moderate thickening (marked definite elevation with rough or sloped edges)
4	Severe thickening with hard edges (marked elevation typically with hard or sharp edges)

Scaling

0	No scaling
1	Minimal focal scaling (surface dryness with some desquamation)
2	Predominately fine scaling (fine scale partially or mostly covering lesions)
3	Moderate scaling (coarser scale covering most or all of the lesions)
4	Severe/coarse scaling covering almost all or all lesions (coarse, non-tenacious scale predominates)

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. Just detectable (possible slight elevation above normal skin). No to minimal focal scaling.
2	mild	Pink to light red coloration. Mild thickening (slight but definite elevation, typically edges are indistinct or sloped). 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 H. Palmoplantar Psoriasis 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.

* Fredriksson T[38]

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.

* Fredriksson T[38]

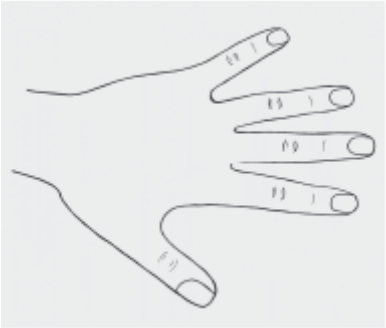
Appendix J. NAPPA-CLIN

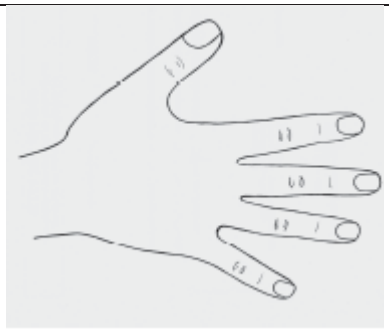
Clinical Severity of Nail Psoriasis (Nappa-Clin)

Please indicate how many quadrants (0 – 4) of the nail are affected by a nail matrix psoriasis (leukonychia, red spots, dots, nail plate crumbling) and how many quadrants are affected by psoriasis of the nail bed (oil drop, splinter haemorrhage, subungual hyperkeratosis, onycholysis). Use of artificial nails and/or nail polish should be avoided throughout the study in order to ensure accuracy of assessments.

4 quadrants

Please record the severity of nail psoriasis for **all fingers:**

left hand		**Number of affected quadrants:**	**matrix**	**bed**
		little finger	|__|	|__|
		ring finger	|__|	|__|
		middle finger	|__|	|__|
		index finger	|__|	|__|
		thumb	|__|	|__|

right hand		**Number of affected quadrants:**	**matrix**	**bed**
		little finger	|__|	|__|
		ring finger	|__|	|__|
		middle finger	|__|	|__|
		index finger	|__|	|__|
		thumb	|__|	|__|

Please record the severity of nail psoriasis for **all toes:**

left foot		**Number of affected quadrants:**	**matrix**	**bed**
		little toe (D. minimus)	|__|	|__|
		Digitus IV	|__|	|__|
		Digitus III	|__|	|__|
		Digitus II	|__|	|__|
		big toe (hallux)	|__|	|__|

right foot		**Number of affected quadrants:**	**matrix**	**bed**
		little toe (D. minimus)	|__|	|__|
		Digitus IV	|__|	|__|
		Digitus III	|__|	|__|
		Digitus II	|__|	|__|
		big toe (hallux)	|__|	|__|

* Fredriksson T[38]

Appendix K. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

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

[redacted]

Has been changed to read:

[redacted]

Section 5.2.1 Inclusion Criteria
Criterion 8
Delete: last paragraph

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing at Study Day 1.

Table 1. Prohibited Psoriasis Medications
Last row previously read:

Medication or Class of Medications	Restriction Duration (Through 15 Weeks After the Last Dose of Risankizumab and Through 1 Week after Last Dose of FUMADERM®[a] Provided as Study Medication)
Phototherapy (e.g., UVA, UVB, any other UV-therapy or balneotherpy) not- associated with UV-sensitizing agents, topical treatment for psoriasis or any other skin condition (e.g., corticosteroids,[c] vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, andanthralin, α-hydroxy acid, fruit acids)	14 days prior to screening or during study participation

Has been changed to read:

Medication or Class of Medications	Restriction Duration (Through 15 Weeks After the Last Dose of Risankizumab and Through 1 Week after Last Dose of FUMADERM®[a] Provided as Study Medication)
Phototherapy (e.g., UVA, UVB, any other UV-therapy or balneotherpy) not- associated with UV-sensitizing agents, topical treatment for psoriasis or any other skin condition (e.g., corticosteroids,[c] vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, andanthralin, α-hydroxy acid, fruit acids)	14 days prior to Baseline (Week 0/Day 1) or during study participation

Section 5.3.1.1 Study Procedures
Subsection FUMADERM® INITIAL and FUMADERM® Subject Diary
First paragraph, first sentence previously read:

Subjects will be dispensed a paper diary at every visit Screening and will be trained on how to complete the diary for FUMADERM® INITIAL and FUMADERM® (provided as study medication) dosing by site staff during the Screening Visit.

Has been changed to read:

Subjects will be dispensed a paper diary at every visit, starting at the Week 0/Baseline visit and will be trained on how to complete the diary for FUMADERM® INITIAL and FUMADERM® (provided as study medication) dosing by site staff during the Week 0/Baseline visit.

Section 5.4.1.1 Discontinuation of Subjects on FUMADERM®
Item 8 previously read:

Rash/flush that does not resolve with continued treatment.

Has been changed to read:

Severe rash/flush that does not resolve with continued treatment.

Section 5.5.1 Treatments Administered
Second paragraph
Delete: last sentence

Additional dosing instructions will be provided separately from this protocol.

Appendix B. List of Protocol Signatories
Previously read:

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

Has been changed to read:

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

Appendix C. Study Activities
Activity "Dispense Subject Diary[i]" previously read:

Activity	Screening –30 to –1	Week 0/ Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/ET[a]	Week 31 Follow-Up Call[b]
Day	**–30 to –1**	**Day 1**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**	**Day 218**
Dispense Subject Diary[i]	X	X	X	X	X	X	X		

Has been changed to read:

Activity	Screening –30 to –1	Week 0/ Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/ET[a]	Week 31 Follow-Up Call[b]
Day	**–30 to –1**	**Day 1**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**	**Day 218**
Dispense Subject Diary[i]		X	X	X	X	X	X		

Appendix J. NAPPA-CLIN
Subsection Clinical Severity of Nail Psoriasis (Nappa-Clin)
First paragraph, last sentence previously read:

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.

Has been changed to read:

Use of artificial nails and/or nail polish should be avoided throughout the study in order to ensure accuracy of assessments.

Document Approval

Study M16178 - A Randomized, Controlled, Multicenter, Open Label Study with Blinded Assessment of the Efficacy of the Humanized Anti-IL-23p19 Risankizumab Compared to FUMADERM in Subjects with Moderate to Severe Plaque Psoriasis Who are Naïve to and Candidates for Systemic Therapy - Amendment 3 - EudraCT 2016-003718-28 - 28Nov2017

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Signed by:	Date:	Meaning Of Signature:
[redacted]	28-Nov-2017 09:39:55 PM	Approver
	29-Nov-2017 09:15:59 AM	Approver
	29-Nov-2017 11:13:43 AM	Approver
	29-Nov-2017 03:36:48 P	Approver
	02-Dec-2017 02:27:59 PM	Approver