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Clinical Protocol IM011075

An Open-Label, Multi-Center Extension Study to Characterize the Long-Term Safety and Efficacy of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis

Short Title: Long-Term Safety and Efficacy of BMS-986165 in Subjects with Psoriasis

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DOCUMENT HISTORY

Document	Date of Issue	Approver(s)	Summary of Change
Original Protocol	05-Feb-2019	Roland Chen, MD Head, Innovative Clinical Development, IMD Bristol-Myers Squibb Anthony Waclawski, PhD Head of IMD Regulatory and Pharmaceutical Sciences Bristol-Myers Squibb	Not applicable
Global Protocol v2.0, Amendment 1	04-Jun-2019	Roland Chen, MD Head, Innovative Clinical Development, IMD Bristol-Myers Squibb Anthony Waclawski, PhD Head of IMD Regulatory and Pharmaceutical Sciences Bristol-Myers Squibb	This amendment (1) adds yearly fasting lipids testing in order to collect long-term data on lipid profiles in subjects receiving BMS-986165, (2) removes routine urinalysis testing because it is not indicated in subjects receiving BMS-986165, (3) clarifies prohibited and/or restricted concomitant medications, (4) clarifies that efficacy assessments are to be recorded in an electronic device provided by the Sponsor, and (5) clarifies that blood samples will not be collected from subjects for exploratory biomarker assessments where country/local practice does not permit it.
Global Protocol v2.0, Amendment 2 Japan	04-Jul-2019	Roland Chen, MD Head, Innovative Clinical Development, IMD Bristol-Myers Squibb Anthony Waclawski, PhD Head of IMD Regulatory and Pharmaceutical Sciences Bristol-Myers Squibb	Japan-specific Amendment; the key changes were the addition of an HBV DNA test and updates to Appendix 4 Contraception Guidance for Female Subjects of Childbearing Potential

Global Protocol v2.0, Amendment 3 Japan	26-Aug-2019	Roland Chen, MD Head, Innovative Clinical Development, IMD Bristol-Myers Squibb Anthony Waclawski, PhD Head of IMD Regulatory and Pharmaceutical Sciences Bristol-Myers Squibb	Japan-specific revision; the key purpose was to incorporate specific requirements for erythrodermic psoriasis and generalized pustular psoriasis and psoriatic arthritis in subjects who completed Study IM011066.
Global Protocol v2.0, Revised Protocol 4 China	26-Aug-2019	Roland Chen, MD Head, Innovative Clinical Development, IMD Bristol-Myers Squibb Anthony Waclawski, PhD Head of IMD Regulatory and Pharmaceutical Sciences Bristol-Myers Squibb	China-specific revision; the key purpose was to account for differences in local clinical practices between global study sites and study sites in mainland China.
Global Protocol v3.0, Revised Protocol 5 Global	08-Jan-2020	Subhashis Banerjee, MD Clinical Program Lead Bristol-Myers Squibb Anthony Waclawski, PhD Head of IMD Regulatory and Pharmaceutical Sciences Bristol-Myers Squibb	The key purpose of this global revised protocol was to add a safety follow-up visit (30 days after discontinuation); to add a Suicidal and Behavior Ideation Adjudication Committee; to add suicidal ideation as a study treatment discontinuation criterion; and to update contraceptive language.

SUMMARY OF CHANGES

Revised Protocol Rationale:

The purpose of this revised protocol is (1) to incorporate a safety follow-up visit (30 days after discontinuation), as required by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA), (2) to add a Suicidal and Behavior Ideation Adjudication Committee, (3) to add suicidal ideation as a study treatment discontinuation criterion to be consistent with the parent studies, and (4) to update contraceptive language to align with BMS final contraception guidance for BMS-986165 (12-Jun-2019). This revised protocol applies to all subjects enrolled globally.

This revised protocol will be implemented after the investigator receives all appropriate agency and Investigational Review Board/Independent Ethics Committee (IRB/IEC) approvals.

All changes applied to the body were applied to the synopsis, as necessary, and synopsis changes are not included in the list below.

Generally, all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications, as well as reorganizational changes, are not included in this section.

The summary of key changes are provided in the table below:

Summary of Key Changes to the Revised Protocol

Section Number & Title	Description of Change	Brief Rationale
1.2 Schema 1.3 Schedule of Activities, Table 1 4.1.3 Open-Label Dosing and Assessments, Figure 1 4.3 End of Study Definition 7.1 Discontinuation from Study Treatment 7.2 Discontinuation from the Study	Added safety follow-up visit (30 days after discontinuation) for all subjects	Required as per the UK MHRA.
4.1.4.3 Suicidal Ideation and Behavior Committee 7.1 Discontinuation from Study Treatment Appendix 14 Suicidal Ideation and Behavior Categories and Definitions	Added Suicidal and Behavior Ideation Adjudication Committee and added suicidal ideation as a study treatment discontinuation criterion	To align with the parent studies, as appropriate.
5.1 Inclusion Criteria Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	Updated contraception requirements	To align with BMS final contraception guidance for BMS-986165 (12-Jun-2019), which was generated upon completion of all BMS reproductive toxicology studies. These studies found no demonstrated or suspected human genotoxicity, teratogenicity, or fetotoxicity.

Summary of Key Changes to the Revised Protocol

8.2 Adverse Events 9.5.1 Adverse Events	Updated recording of adverse events (AEs) in Study IM011075 related to parent studies	To clarify collection of AEs in Study IM011075 since this study is an open-label extension study of several parent studies.

Please provide a copy to your Investigational Review Board/Ethics Committee, unless agreed otherwise with BMS.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-Label, Multi-Center Extension Study to Characterize the Long-Term Safety and Efficacy of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis

Short Title: Long-Term Safety and Efficacy of BMS-986165 in Subjects with Psoriasis

Study Phase: 3b

Rationale:

BMS-986165 is being evaluated as a therapeutic option for the treatment of subjects with moderate-to-severe plaque psoriasis based on results of a 12-week, randomized, Phase 2, placebo-controlled, parallel-group study (Study IM011011). In the Phase 2 study, 267 subjects (44 to 45 subjects per treatment arm), with moderate-to-severe plaque psoriasis were randomized, and 5 different BMS-986165 treatment arms were evaluated: 3 mg every other day (QOD); 3 mg once daily (QD); 3 mg twice daily (BID); 6 mg BID; and 12 mg QD. All BMS-986165 treatment groups, except 3 mg QOD, achieved the primary endpoint of superiority compared with placebo in the proportion of subjects experiencing at least a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) after 12 weeks of treatment. Compared with the placebo treatment group, in which 6.7% of subjects achieved PASI 75 response, 38.6% ($P = 0.0003$), 68.9% ($P < 0.0001$), 66.7% ($P < 0.0001$) and 75% ($P < 0.0001$) of subjects treated with 3 mg QD, 3 mg BID, 6 mg BID, and 12 mg QD achieved PASI 75, respectively. The PASI 75 responses plateaued at a dose of 3 mg BID with a slightly higher response rate following 12 mg QD. Although a 6 mg QD dose of BMS-986165 was not tested in the Phase 2 psoriasis study, simulations based on the final population pharmacokinetic (PK) model and exposure-response model indicate that the predicted therapeutic response at 6 mg QD is similar to the 3 mg BID dose studied in Phase 2. Ongoing Phase 3 studies are designed to confirm the efficacy and safety of BMS-986165 6 mg QD. This open-label, long-term extension (LTE) study will provide additional safety, efficacy, and patient-reported outcome (PRO) data of BMS-986165 in subjects who have previously been enrolled in an applicable BMS-986165 parent psoriasis treatment study.

Study Population:

Subjects originally determined to have moderate-to-severe plaque psoriasis who have successfully completed the protocol-required treatment period in an applicable study of BMS-986165 (ie, parent study). Applicable parent studies include, but are not limited to, IM011046, IM011047, IM011065, and IM011066. Only study sites that enrolled subjects from these parent studies will participate in IM011075.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To characterize the safety and tolerability of long-term use of BMS-986165 in subjects with moderate-to-severe plaque psoriasis	• Adverse events and serious adverse events
Secondary and Additional	
• To characterize the maintenance of response to BMS-986165 in the treatment of subjects with moderate-to-severe plaque psoriasis	Secondary • sPGA 0/1 response • PASI 75 response Additional Endpoints • sPGA 0 response • PASI 90 response • PASI 100 response • Change from baseline and percent change from baseline in BSA • Change from baseline in PSSD total score • Change from baseline in PSSD symptom score • Change from baseline in PSSD sign score • PSSD total score of 0 • PSSD symptom score of 0 • PSSD sign score of 0 • Change from baseline in DLQI score • DLQI 0/1 • EQ-5D-3L • Change from baseline in WLQ score • ss-PGA 0/1 response • PGA-F 0/1 response

BSA = body surface area; DLQI = Dermatology Life Quality Index; EQ-5D-3L = Euro Quality of Life Five Dimensions Questionnaire: 3-Level Version; PASI = Psoriasis Area and Severity Index; PGA-F = Physician's Global Assessment-Fingernail; PSSD = Psoriasis Symptoms and Signs Diary; sPGA = static Physician's Global Assessment; ss-PGA = scalp-specific Physician's Global Assessment; WLQ = Work Limitations Questionnaire

Overall Design:

This is a multi-year, multi-center, open-label study to evaluate the long-term safety and efficacy of BMS-986165 in subjects who have completed an applicable prior Phase 3 psoriasis study of BMS-986165 (ie, parent study). Applicable parent studies include, but are not limited to, IM011046, IM011047, IM011065, and IM011066.

The End of Study Visit for the parent psoriasis studies, and the relevant procedures performed, will serve as the baseline visit for assessments in IM011075. Procedures will not be duplicated between the End of Study Visit of the parent study and the baseline visit of IM011075; however, applicable data will be captured in both databases.

In this longitudinal study, qualified subjects from an applicable parent psoriasis study with BMS-986165 will receive oral open-label BMS-986165 at a dose of 6 mg QD.

All subjects will return to the clinic for assessments at Weeks 4, 8, 16, and 24, then every 12 weeks for the remainder of the study. Investigator- and subject-administered endpoint assessments will be performed at each scheduled clinic visit. Subjects will also return to the clinic for a safety follow-up visit (30 days after discontinuation), which will include a pregnancy test for WOCBP.

Number of Subjects:

The total number of subjects will be based on the number who complete the psoriasis parent studies and continue into IM011075.

Treatment Arms and Duration:

Study Treatment: Subjects will receive investigational product (IP) for at least 96 weeks during treatment. BMS-986165 will be administered orally at a dose of 6 mg QD.

Study Treatment for IM011075		
Medication	**Potency**	**IP/Non-IP**
BMS-986165 tablet	6 mg	IP

IP = investigational product

Statistical Methods

Sample Size and Power Determination:

As the primary purpose of this study is to understand the longer term safety of BMS-986165 in subjects with psoriasis who have completed a prior psoriasis study with BMS-986165, no formal calculations of sample size and power determination will be made. All qualified subjects who complete the final treatment visit from an applicable parent psoriasis study with BMS-986165 will be eligible to participate.

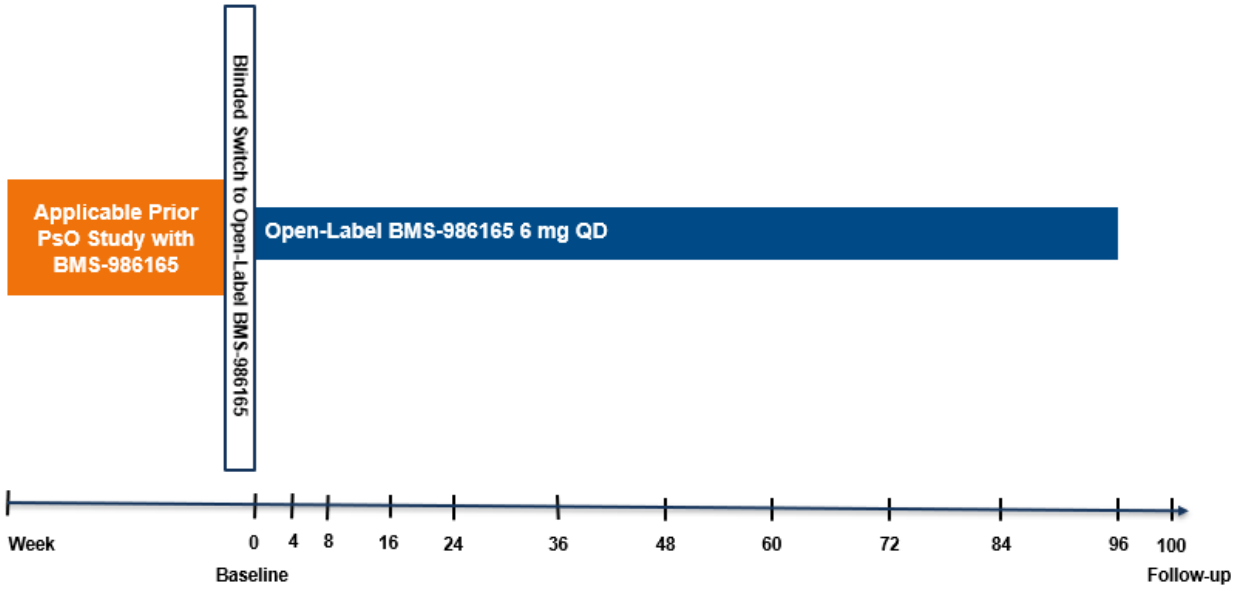
General Methodology

The 'As-treated' population will be used to summarize subject data. The 'As-treated' population will include all subjects enrolled in IM011075 who took at least one dose of study treatment during IM011075.

Data will be summarized descriptively at each timepoint. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

Missing data will not be imputed.

1.2 Schema



PsO = psoriasis; QD = once daily; WOCBP = women of childbearing potential
Safety follow-up visit includes a pregnancy test for WOCBP.

1.3 Schedule of Activities (SOA)

The schedules of assessments and procedures are documented in Table 1.

Table 1: On Treatment Procedural Outline (IM011075): Week 0 through Week 96

Procedure	Week 0 Baseline V1[a]	Week 4 (±7d) V2	Week 8 (±7d) V3	Week 16 (±7d) V4	Week 24 (±14d) V5	Week 36 (±14d) V6	Week 48 (±14d) V7	Week 60 (±14d) V8	Week 72 (±14d) V9	Week 84 (±14d) V10	Week 96 (or early DC) (±14d) V11[b]	Safety Follow-Up (Week 100 [±3d] or early DC+30d) V12	Notes
Eligibility	X												
Informed consent	X												
Safety Assessments													
Complete Physical Examination							X				X	X	General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, psychiatric, skin, musculoskeletal
Targeted Physical Examination		X	X	X	X	X		X	X	X			See Section 8.4.1
Body Weight							X				X	X	
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	Includes body temperature (ear or oral), respiratory rate, seated blood pressure, and heart rate.

Table 1: On Treatment Procedural Outline (IM011075): Week 0 through Week 96

Procedure	Week 0 Baseline V1[a]	Week 4 (±7d) V2	Week 8 (±7d) V3	Week 16 (±7d) V4	Week 24 (±14d) V5	Week 36 (±14d) V6	Week 48 (±14d) V7	Week 60 (±14d) V8	Week 72 (±14d) V9	Week 84 (±14d) V10	Week 96 (or early DC) (±14d) V11[b]	Safety Follow-Up (Week 100 [±3d] or early DC+30d) V12	Notes
													Blood pressure and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
ECG							X				X		
AE Assessment		X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication Use		X	X	X	X	X	X	X	X	X	X	X	
Laboratory Tests													
Hematology		X	X	X	X	X	X	X	X	X	X	X	
Chemistry Panel		X	X	X	X	X	X	X	X	X	X	X	Include CK
Fasting Lipid Panel							X				X		Subjects are required to fast for at least 10 hours prior to collection
TB Questionnaire	X						X				X		IGRA for high-risk subjects (Refer to Section

Table 1: On Treatment Procedural Outline (IM011075): Week 0 through Week 96

Procedure	Week 0 Baseline V1[a]	Week 4 (±7d) V2	Week 8 (±7d) V3	Week 16 (±7d) V4	Week 24 (±14d) V5	Week 36 (±14d) V6	Week 48 (±14d) V7	Week 60 (±14d) V8	Week 72 (±14d) V9	Week 84 (±14d) V10	Week 96 (or early DC) (±14d) V11[b]	Safety Follow-Up (Week 100 [±3d] or early DC+30d) V12	Notes
													8.4.3 and APPENDIX 13
Pregnancy Test (Urine)		X	X	X	X	X	X	X	X	X	X	X	WOCBP only
Biomarker Assessments													
Plasma for Inflammation and CV Markers		X			X		X		X		X		
Serum for Inflammation and CV Markers		X			X		X		X		X		
Blood RNA		X			X		X		X		X		
Pharmacokinetic Assessments													
Blood samples for PK assessments		X			X		X		X		X		Predose
Clinical Efficacy/Health Outcomes													
sPGA		X	X	X	X	X	X	X	X	X	X		
PASI		X	X	X	X	X	X	X	X	X	X		

Table 1: On Treatment Procedural Outline (IM011075): Week 0 through Week 96

Procedure	Week 0 Baseline V1[a]	Week 4 (±7d) V2	Week 8 (±7d) V3	Week 16 (±7d) V4	Week 24 (±14d) V5	Week 36 (±14d) V6	Week 48 (±14d) V7	Week 60 (±14d) V8	Week 72 (±14d) V9	Week 84 (±14d) V10	Week 96 (or early DC) (±14d) V11[b]	Safety Follow-Up (Week 100 [±3d] or early DC+30d) V12	Notes
BSA		X	X	X	X	X	X	X	X	X	X		
PSSD-7d				X	X		X		X		X		Complete at site before other procedures
DLQI				X	X		X		X		X		Complete at site before other procedures
EQ-5D-3L		X			X		X	X	X	X	X		
WLQ	X[f]			X	X		X		X		X		
ss-PGA[c]				X	X		X		X		X		
PGA-F[d]				X	X		X		X		X		
Study Treatment													
Dispense Study Treatment	X	X	X	X	X	X	X	X	X	X	X[e]		
Study Treatment Accountability		X	X	X	X	X	X	X	X	X	X		

AE = adverse event; BSA = body surface area; CK = creatine kinase; CV = cardiovascular; d = day(s); DC = discontinuation; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; EQ-5D-3L = Euro QoL Five Dimensions Questionnaire- 3 Level; IGRA = Interferon Gamma Release Assay; PASI = Psoriasis Area and Severity Index; PGA-F = Physician Global Assessment-Fingernails; PK = pharmacokinetic; PsO = psoriasis; PSSD-7d = Psoriasis Symptoms and Signs Diary 7-day Recall; RNA = ribonucleic acid; sPGA = static Physician Global Assessment; ss-PGA = scalp-specific Physician's Global Assessment; TB = tuberculosis; V = visit; WLQ = Work Limitations Questionnaire; WOCBP = women of childbearing potential

[a] This is the same visit as the end of treatment visit in the parent PsO study. Assessments (denoted by a shaded box in the V1 column) that overlap between IM011075 and parent study will not be repeated; however, the data will be captured in both databases.
[b] For subjects who discontinue from the study prior to Week 96, all Week 96 visit and safety follow-up visit assessments are to be performed.
[c] In subjects with scalp psoriasis at baseline of the parent study
[d] In subjects with nail psoriasis at baseline of the parent study
[e] Only if study continues beyond 96 weeks
[f] Only for subjects where WLQ was not provided in the parent study

STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Bristol-Myers Squibb Company (BMS). Any supplemental information that may be added to this document is also confidential and proprietary to BMS and must be kept in confidence in the same manner as the contents of this protocol.

I have read the original protocol/revised protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make a reasonable effort to complete the study within the time designated.

I will provide copies of the protocol and access to all information furnished by BMS to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I will provide protocol information to my Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s]. I understand that original protocol/revised protocols must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary health authorities before implementation unless to eliminate an immediate hazard to subjects.

I agree that the contents of the protocol may not be disclosed to any other person or entity or used for any other purpose without the prior written consent of BMS. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to BMS of any such disclosure.

I agree that the study data derived from this protocol may only be used and disclosed in furtherance of the protocol, for the medical treatment of a study subject or for publication of study results in accordance with the terms of the clinical trial agreement or as otherwise permitted by the terms of the clinical trial agreement.

I agree not to collect or use samples (eg, tissue, blood, serum, urine) or collect data (other than for diagnostic or treatment purposes) from the study subjects while enrolled in the study, except as expressly permitted by the protocol or the terms of the clinical trial agreement.

I understand that I may terminate or suspend enrollment of the study at any time if it becomes necessary to protect the best interests of the study subjects. Unless otherwise provided in the clinical trial agreement, the study may be terminated at any time by BMS, with or without cause.

Original Protocol ☐ Revised Protocol ☒

Protocol Number: IM011075 Site Number: _____

Date of Protocol or Revised Protocol: 08-Jan-2020

IND Number: 131,993 EUDRACT Number: 2019-000612-29

Investigator _____ Date_____
(signature)

_____
(printed name*)

2 INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder, characterized primarily by erythematous scaly plaques. In the US, the prevalence of psoriasis among adults is 3.2%.[1] Men and women are equally affected and the condition can present at any age.[2,3] Several studies have observed a bimodal distribution of psoriasis onset with the first peak ranging from 15 to 22 years of age, and the second peak ranging from 55 to 60 years of age.[4,5,6] The most common form of psoriasis (58% to 97% of cases) is plaque psoriasis (psoriasis vulgaris), with less common forms being guttate, pustular, inverse (flexural), and erythrodermic psoriasis. The disease can have a fluctuating relapsing course, with flares that may be induced by factors such as infections, trauma, smoking, and stress.[4] Psoriasis can involve skin in any part of the body; particularly disabling is the involvement of specific anatomic regions, such as hands and feet (palmoplantar), face, scalp, and nails. Disease severity can be classified by body surface area (BSA) involvement with mild defined as ≤ 10% BSA, and moderate-to-severe as > 10% BSA.[7] Psoriasis has a profound impact on quality of life and can lead to psychological, social, and economic consequences, especially in moderate-to-severe disease. This condition is also associated with an increased risk of depression, occurrence of sleep disturbances, social stigma, and decreased work productivity.[8,9] Commonly associated comorbidities found in patients with psoriasis include diabetes mellitus and metabolic syndrome. In patients with more severe forms of the disease, life expectancy is decreased due to an increase of cardiovascular (CV) risk.[10]

Treatments for psoriasis include topical preparations, eg, corticosteroids, vitamin D analogs, calcineurin inhibitors, and salicylic acid; phototherapy modalities, including PUVA (psoralens with UVA) and narrow band UVB; and systemic therapies. In moderate-to-severe disease, systemic treatments are usually needed and may include oral agents (retinoids, methotrexate, cyclosporine, and apremilast) or injectables (eg, biologics such as tumor necrosis factor (TNF) inhibitors etanercept, infliximab, and adalimumab), anti-interleukin (IL)-12/IL-23p40 antibody (ustekinumab), IL-17 antagonists (secukinumab, ixekizumab, and brodalumab), and anti-IL-23p19 antibody (guselkumab). Many of these treatments are associated with increased risk of adverse events (AEs) such as hepatotoxicity and neutropenia (methotrexate);[11] nephrotoxicity (cyclosporine);[12] depression and weight loss (apremilast);[13] serious infections (cytokine inhibitors);[14,15,16,17] candidiasis and Crohn's disease (IL-17 antagonists).[17,18,19]

Although these effective therapeutic options are available, under-treatment or nontreatment of psoriasis has been reported in up to half of surveyed patients (based on absence of treatment and/or dissatisfaction with treatment).[20] Many patients with severe disease are still being managed with only topical medication,[5,9] and many patients consider their psoriasis treatment to be inadequate. Accordingly, there remains a need for more effective oral options, when compared with currently available agents, that would improve efficacy responses and increase adherence to treatment.

2.1 Study Rationale

This open-label, long-term extension (LTE) study will provide additional safety, efficacy, and patient-reported outcome (PRO) data of BMS-986165 6 mg QD in subjects who have previously been enrolled in an applicable BMS-986165 parent psoriasis treatment study.

2.2 Background

Tyrosine kinase 2 (TYK2) is a nonreceptor tyrosine kinase associated with receptors for the p40-containing cytokines IL-12 and IL-23, as well as the Type I interferon (IFN) receptor, and is required for the activation of their downstream signaling pathways. TYK2 catalyzes the phosphorylation of the intracellular receptor domains and signal transducer and activator of transcription (STAT) proteins resulting in the activation of STAT-dependent transcription and functional responses specific for these cytokines.[21,22,23] Because TYK2-dependent cytokines (eg, Type I IFNs, IL-12, IL-23) are distinct from those dependent on closely related Janus kinase (JAK) family members JAK1/JAK3 (eg, IL-2, IL-15, IL-7) or JAK2 (eg, erythropoietin, thrombopoietin, GM-CSF), a selective TYK2 inhibitor would be expected to have a highly differentiated profile from inhibitors of other JAK family kinases. TYK2-dependent pathways and the cytokine networks they modulate (eg, IL-23/IL-17, IFNα) have been implicated in the pathophysiology of multiple immune-mediated diseases, including psoriasis, lupus, spondyloarthritides, and Crohn's disease.

BMS-986165 is an orally administered selective TYK2 inhibitor. A comprehensive in vitro and in vivo characterization of BMS-986165 has been established and supports the development of this compound in humans. Inhibition of TYK2 is expected to provide therapeutic benefit for subjects with psoriasis for multiple reasons: 1) Many of the pathways in the TYK2 signaling cascade (IL-23 and the downstream mediators IL-17 and IL-22; IFNα) have been implicated in pathogenesis of psoriasis.[9] 2) Biologic agents targeting the IL-17, IL-23p19, and IL-12/IL-23 p40 pathways have been approved for and are highly efficacious in the treatment of psoriasis.

2.2.1 Early Clinical Development

The clinical data available to date supporting the safety, pharmacokinetics (PK), and pharmacodynamics of BMS-986165 are from 7 completed Phase 1 studies in healthy subjects (IM011002, IM011015, IM011016, IM011025, IM011031, IM011039, and IM011045) and 1 completed Phase 2 study in adult subjects with moderate-to-severe plaque psoriasis (IM011011).

Overall, BMS-986165 has been generally well-tolerated across all studies, and no safety issues have been identified to limit the investigation of the dose of BMS-986165 up to 12 mg QD in further clinical studies. A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986165 is provided in the current Investigator Brochure (IB).

2.3 Benefit/Risk Assessment

Ongoing Phase 3 studies of BMS-986165 6 mg once daily (QD) in subjects with moderate-to-severe plaque psoriasis are based on the efficacy and safety results from a Phase 2, placebo-controlled, dose-ranging study of this compound (Study IM011011).[24] In the Phase 2 study, 267 subjects (44 to 45 subjects per treatment arm), with moderate-to-severe plaque psoriasis were randomized, and 5 different BMS-986165 treatment arms were evaluated: 3 mg every other day (QOD); 3 mg QD; 3 mg twice daily (BID); 6 mg BID; and 12 mg QD. All BMS-986165 treatment groups, except 3 mg QOD, achieved the primary endpoint of superiority compared with placebo in the proportion of subjects achieving at least a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) after 12 weeks of treatment. Compared with the placebo treatment

group, in which 6.7% of the subjects achieved PASI 75 response, 38.6% (P = 0.0003), 68.9% (P < 0.0001), 66.7% (P < 0.0001) and 75% (P < 0.0001) of subjects treated with 3 mg QD, 3 mg BID, 6 mg BID, and 12 mg QD achieved PASI 75, respectively. The PASI 75 responses plateaued at a dose of 3 mg BID, with a higher response rate following 12 mg QD.

In addition, a clinically significant proportion of subjects treated with BMS-986165 achieved a static Physician's Global Assessment (sPGA) score of 0 or 1 compared with placebo at Week 12. Compared with the placebo treatment group in which 6.7% of the subjects achieved an sPGA score of 0 or 1, 41.5%, 75.6%, 65.9%, and 75% of the subjects treated with 3 mg QD, 3 mg BID, 6 mg BID, and 12 mg QD achieved an sPGA score of 0 or 1, respectively, with responses again plateauing at a dose of 3 mg BID.

In Study IM011011, BMS-986165 was generally safe and well-tolerated. There is a theoretical risk for increased frequency and/or severity of infections based on the mechanism of action of BMS-986165. The most common AEs reported by subjects were nasopharyngitis, upper respiratory tract infection, headache, diarrhea, and nausea. Most of the AEs reported in the study were mild or moderate in intensity. There were 8 reversible events of mild to moderate nature of acne that were dose related (4 at 12 mg QD, 2 at 6 mg BID, 1 at 3 mg BID, and 1 at 3 mg QOD). There were 7 events of localized oral or nasal herpes simplex lesions that appeared to be dose-related (4 at 12 mg QD, 2 at 6 mg BID, and 1 at 3 mg BID). No reports of herpes zoster were noted in this study. A total of 6 subjects had creatine kinase (CK) elevations of Grade 3 or higher (3 subjects at 3 mg QOD, and 3 subjects at 12 mg QD) with the CK elevations temporally associated with increased physical activity by the subjects. These CK elevations are considered unlikely to be drug related. No drug-related changes were observed in lymphocyte subsets, neutrophils, red blood cells, or cholesterol, which are markers of off-target activity on JAK family members JAK1-3, thus supporting the selectivity of BMS-986165.

At the maximum concentrations expected in this study (in portal vein or systemic circulation, as appropriate), the potential for drug-drug interactions (DDIs) involving CYP450 enzymes and most transporters is low. BMS-986165 has low turnover in in vitro metabolism studies, and a number of enzymes are involved in the metabolism of the fraction metabolized. Additionally, BMS-986165 is not an inhibitor or inducer of CYP450 enzymes at the expected clinical concentrations. Therefore, the potential for DDIs resulting from CYP450 inhibition or induction is low. BMS-986165 is a breast cancer resistance protein (BCRP) inhibitor with an in vitro IC50 = 0.31 μM. However, due to overlapping substrate specificity between BCRP and other transporters not affected by BMS-986165 at the expected concentrations, the impact of BMS-986165 on the exposures of potential comedications that are BCRP substrates, such as rosuvastatin, was also expected to be low. This was confirmed in the IM011015 DDI study where co-administration of BMS-986165 12 mg QD and rosuvastatin 10 mg had no impact on the exposure of rosuvastatin, a BCRP and OATP substrate.

Taken together, the nonclinical data, as well as the clinical data in healthy subjects, and in those with psoriasis, combined with the design of this Phase 3 LTE study, indicate an overall risk/benefit assessment that is appropriate for long-term investigation of BMS-986165 6 mg QD as an oral treatment for patients with moderate-to-severe plaque psoriasis. Detailed information about the

known and expected benefits and risks and reasonably anticipated AEs of BMS-986165 is provided in the current IB.

3 OBJECTIVES AND ENDPOINTS

Table 2: Objectives and Endpoints

Objective	Endpoint
Primary	
• To characterize the safety and tolerability of long-term use of BMS-986165 in subjects with moderate-to-severe plaque psoriasis	• Adverse events and serious adverse events
Secondary and Additional	
• To characterize the maintenance of response to BMS-986165 in the treatment of subjects with moderate-to-severe plaque psoriasis	Secondary • sPGA 0/1 response • PASI 75 response Additional Endpoints • sPGA 0 response • PASI 90 response • PASI 100 response • Change from baseline and percent change from baseline in BSA • Change from baseline in PSSD total score • Change from baseline in PSSD symptom score • Change from baseline in PSSD sign score • PSSD total score of 0 • PSSD symptom score of 0 • PSSD sign score of 0 • Change from baseline in DLQI score • DLQI 0/1 • EQ-5D-3L • Change from baseline in WLQ score • ss-PGA 0/1 response • PGA-F 0/1 response

BSA = body surface area; DLQI = Dermatology Life Quality Index; EQ-5D-3L = Euro Quality of Life Five Dimensions Questionnaire: 3-Level Version; PASI = Psoriasis Area and Severity Index; PGA-F = Physician's Global Assessment-Fingernail; PSSD = Psoriasis Symptoms and Signs Diary; sPGA = static Physician's Global Assessment; ss-PGA = scalp-specific Physician's Global Assessment; WLQ = Work Limitation Questionnaire

4 STUDY DESIGN

4.1 Overall Design

This is a multi-year, multi-center, open-label, Phase 3b study to evaluate the long-term safety,

tolerability, and efficacy of BMS-986165 in the treatment of psoriasis. This LTE study will provide additional data on the use of BMS-986165 in subjects who have previously been enrolled in an applicable prior Phase 3 psoriasis study of BMS-986165 (ie, parent study). Applicable parent studies include, but are not limited to, IM011046, IM011047, IM011065, and IM011066.

Investigator- and subject-administered endpoint assessments will be performed at each scheduled clinic visit (Table 1).

The study design schematic is presented in Figure 1.

4.1.1 Qualification

The End of Study Visit in the parent study will be the baseline visit for IM011075, and data from the End of Study Visit in the parent study will be the baseline visit data for IM011075. These data will be captured in both databases. Prior to enrollment into IM011075, the investigator will ensure the following:

1) subjects are qualified for participation in IM011075, and must sign a separate consent for IM011075
2) subjects and all relevant study personnel in the parent study remain blinded to parent study treatment prior to switching the subject to open-label BMS-986165 6 mg QD in IM011075

4.1.2 Baseline Visit (V1)

At the End of Study Visit of a subject's parent study, the end of study procedures will be performed per protocol and will become the baseline visit data in IM011075. At the baseline visit, the following investigator-administered and subject-completed assessments will be completed if they were not part of the End of Study Visit in the parent study:

- static Physician's Global Assessment (sPGA)
- Psoriasis Area and Severity Index (PASI)
- scalp-specific PGA (ss-PGA) and PGA-Fingernail (PGA-F) for those with psoriasis involvement of the scalp and nails during the parent study, respectively
- Psoriasis Symptoms and Signs Diary 7-day Recall (PSSD-7d)
- Dermatology Life Quality Index (DLQI)
- EuroQoL Five Dimensions Questionnaire: 3-Level Version (EQ-5D-3L)
- Work Limitation Questionnaire (WLQ)

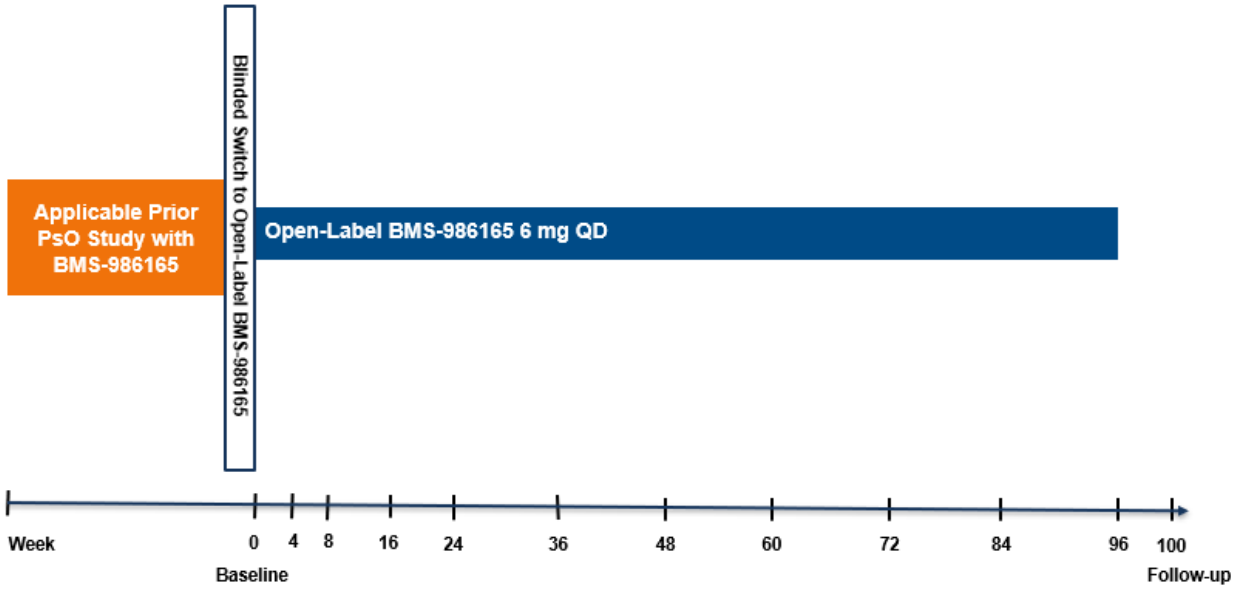
4.1.3 Open-Label Dosing and Assessments

Open-label BMS-986165 6 mg will be dispensed to qualified subjects at the baseline visit. Subjects will be instructed to take BMS-986165 6 mg QD. It is recommended that the first dose of study treatment in Study IM011075 be taken by the subject while the subject is at the site for the Week 52 end of treatment visit in the parent study/Week 0 visit in the IM011075 study.

All subjects will return to the clinic for assessments and routine safety follow-up at Week 4, Week 8, Week 16, Week 24, then every 12 weeks thereafter, as described in the Schedule of Activities (SOA) in Section 1.3.

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



PsO = psoriasis; QD = once daily; WOCBP = women of childbearing potential
Safety follow-up visit includes a pregnancy test for WOCBP.

4.1.4 Adjudication Committees

4.1.4.1 Infection Adjudication Committee

An independent Infection Adjudication Committee, composed of individuals with relevant expertise, will review and adjudicate infection AEs, such as opportunistic infections, influenza, herpes zoster, and tuberculosis (TB), reported in the study per criteria specified in a separate charter. Additional information about these infections may be collected on the case report form in order to characterize and understand them. The structure, responsibilities, and procedures of the Adjudication Committee will be outlined in a charter. The Adjudication Committee members will not be investigators on the study.

4.1.4.2 CV Adjudication Committee

An independent CV Adjudication Committee, composed of individuals with relevant expertise, will review and adjudicate CV and cerebrovascular AEs such as, but not limited to, Major Adverse Cardiovascular Events (MACE) that include death, nonfatal myocardial infarction, nonfatal stroke; revascularization procedures; heart failure; dysrhythmias; heart blocks; and thrombotic events reported in the study per criteria specified in a separate charter. Additional information about CV and cerebrovascular AEs may be collected on the case report form in order to characterize and understand them. The structure, responsibilities, and procedures of the Adjudication Committee

will be outlined in a charter. The Adjudication Committee members will not be investigators on the study.

4.1.4.3 Suicidal Ideation and Behavior Adjudication Committee

An independent Suicidal Ideation and Behavior Adjudication Committee, composed of individuals with relevant expertise, will review and adjudicate suicidal ideation/behavior reported in the study per criteria specified in a separate charter. Additional information about suicidal ideation/behavior may be collected on the case report form. The structure, responsibilities, and procedures of the Adjudication Committee will be outlined in a charter. The Adjudication Committee members will not be investigators on the study.

4.2 Number of Subjects

The total number of subjects will be based on the number who complete the parent studies and continue into IM011075. Any subject from a parent study who does not continue into IM011075 will not be replaced with a new subject.

4.3 End of Study Definition

The duration of study participation for individual subjects is expected to be 96 weeks, with 30 additional days for safety follow-up. To obtain further long-term evaluation of the safety and efficacy of BMS-986165, the duration may be extended to a maximum of 240 weeks with continued assessments every 12 weeks as described for Weeks 60 to 96 in the SOA (Section 1.3).

The start of the study is defined as first visit for first subject completing their parent psoriasis study and enrolling into the IM011075 study. The end of the study is defined as the last visit or scheduled procedure shown in the SOA (Section 1.3) for the last subject. Study completion is defined as the final date on which data were or are expected to be collected.

4.4 Scientific Rationale for Study Design

The primary purpose of this study is to observe the long-term safety and tolerability to BMS-986165 in subjects with psoriasis who have previously been enrolled in an applicable Phase 3 psoriasis study (eg, IM011046, IM011047, IM011065, and IM011066).

4.5 Justification for Dose

The dose selection for BMS-986165 at 6 mg QD, is based on the efficacy and safety results from the Phase 2, placebo-controlled, dose-ranging study of this compound in subjects with moderate-to-severe plaque psoriasis (IM011011).[24] The results from the Phase 2 study demonstrated that doses of BMS-986165 at 3 mg QD, 3 mg BID, 6 mg BID, and 12 mg QD achieved significantly higher PASI 75 responses compared with placebo at Week 12. However, the PASI 75 as well as the PASI 90 responses appeared to plateau at doses of 3 mg BID and above.

Exposure-response modeling showed a significant relationship between the exposure and PASI 75 responder rates at Week 12. Based on the model, average concentration at steady state was found to be the best measure of exposure for predicting PASI 75 responses, one of the coprimary endpoints in Phase 3, regardless of once or twice daily dosing, with near maximal efficacy observed at 3 mg BID, and predicted at 6 mg QD. In addition, the 6 mg QD modeled response rate

is predicted to achieve near maximal effect compared to the maximum effect predicted at 12 mg QD.

5 STUDY POPULATION

Eligibility criteria for this study have been carefully considered to ensure: 1) safety of the study subjects and 2) potential benefit to subjects. It is imperative that subjects fully meet all eligibility criteria.

The study population will consist of subjects originally considered to have moderate-to-severe plaque psoriasis who have successfully completed the protocol-required treatment period in an applicable study of BMS-986165 (ie, parent study). Applicable parent studies include, but are not limited to, IM011046, IM011047, IM011065, and IM011066. Only study sites that enrolled subjects from applicable parent studies will participate in IM011075.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1) Signed Written Informed Consent

a) Subjects must be willing to participate in IM011075 and must have the ability to sign the informed consent form (ICF).

2) Type of Subject and Target Disease Characteristics

a) Completion of the protocol-required treatment period in an applicable study of BMS-986165 in moderate-to-severe psoriasis

3) Reproductive Status

a) Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin within 24 hours prior to the start of study drug)

b) Women must not be pregnant, lactating, breastfeeding, or planning pregnancy during the study period

c) Not applicable per Revised Protocol 5 (replaced by 3e below)

d) Not applicable per Revised Protocol 5 (replaced by 3f below)

e) WOCBP must agree to use correctly at minimum 1 of the less than highly effective method(s) of contraception for the duration of treatment with study drug BMS-986165. WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements but must still undergo pregnancy testing as described in this protocol (APPENDIX 4).

f) For male subjects who are sexually active with WOCBP, no additional contraceptive measures are required to be used.

Investigators shall advise on the use of less than highly effective methods of contraception, (APPENDIX 4) which, have a failure rate of > 1% when used consistently and correctly.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1) Medical History and Concurrent Diseases

a) Any disease or medical condition that, in the opinion of the investigator, would make the subject unsuitable for this study, would interfere with the interpretation of subject safety or study results, or is considered unsuitable by the investigator for any other reason

b) Prior permanent discontinuation of study treatment in the parent study

2) Findings Related to Possible TB Infection

a) Evidence of active TB (see Section 8.4.3)

5.3 Lifestyle Restrictions

No restrictions are required. However, general skin care measures that are standard for patients with psoriasis are permitted as follows: use of broad spectrum sunscreen (minimum sun protection factor 15 and with inorganic ingredients zinc oxide, titanium dioxide), avoiding excessive sun exposure, wearing sun-protective clothing, avoidance of alcohol-based emollients, avoidance of over-the-counter anti-acne medications and alcohol-based skin care products, and avoidance of perfumed soaps and detergents, and similar measures.

5.3.1 Meals and Dietary Restrictions

Study treatment may be taken without regard to meals.

5.3.2 Caffeine, Alcohol, and Tobacco

No restrictions are required.

5.3.3 Activity

No restrictions are required.

6 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device intended to be administered to a study subject according to the treatment allocation.

Study treatment includes investigational [medicinal] product (IP/IMP) and will consist of BMS-986165.

An IP, also known as IMP in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventive, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IP. Table 3 shows the study treatments for Protocol IM011075.

Table 3: Study Treatments for IM011075

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open-Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986165 Tablet	6 mg	IP	Open-label	Bottle / Pink, plain, round, biconvex, film-coated tablet	Store at 15°C to 25°C; store in a tightly closed container; protect from light

IP = investigational product; IMP = investigational medical product

6.1 Treatments Administered

Study treatment will be administered in an open-label fashion as described in Section 4.1.3. The selection and timing of dose for each subject is provided in Table 4.

Table 4: Selection and Timing of Dose

Study Treatment	Unit Dose Strength/Dosage Level	Dosage Formulation Frequency of Administration	Route of Administration
6 mg QD BMS-986165	6 mg	1 active tablet QD in the morning	oral

QD = once daily

It is recommended that the first dose of study treatment in Study IM011075 be taken by the subject while the subject is at the site for Week 52 end of treatment visit in the parent study/Week 0 visit in the IM011075 study.

6.2 Method of Treatment Assignment

Before the study is initiated, each user (at investigative sites) will receive log-in information and directions on how to access the interactive response technology (IRT) system. At the time of end of treatment visit in the parent protocol, immediately after informed consent is obtained and before any study-related procedures are performed, the investigative site will access the enrollment option of the IRT system for assignment of a new subject number for all subjects. The subject number is assigned sequentially by the system and will be unique across all sites. All enrolled subjects will be assigned subject numbers. The subject number will not be used for any other subject. For continuity purposes, the subject number from the parent study must be recorded for each subject enrolled in Study IM011075.

Open-label BMS-986165 will be dispensed to all enrolled subjects at study visits as shown in the SOA (Section 1.3). Subjects and investigative staff will remain blinded to the treatment that subjects received during the parent studies prior to switching the subject to open-label BMS-986165.

The investigator will confirm subject eligibility based on criteria in Section 5.

6.3 Blinding

This is an open-label study, but individual subjects, and investigative site and study staff will remain blinded to their parent study treatment assignments.

6.4 Dosage Modification

There is no provision for dose-modification of study treatment. If a subject interrupts treatment due to an AE, study treatment can be restarted in consultation with the Medical Monitor.

6.5 Preparation/Handling/Storage/Accountability

The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that the IP is only dispensed to study subjects. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and BMS should be contacted immediately.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Guidance and information for final disposition of unused study treatment are provided in APPENDIX 2.

6.5.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

6.6 Treatment Compliance

Study treatment compliance will be periodically monitored using standard drug accountability procedures (comparing the number of tablets returned to number dispensed, considering the expected regimen and any reported missed doses). Drug accountability will be reviewed by the investigative site staff at each visit to confirm treatment compliance. Site staff will discuss any discrepancies with the subject and remind the subject of the importance of compliance with the assigned regimen.

6.7 Concomitant Therapy

6.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications during the study are described below.

1) Exposure to any investigational drug or placebo outside of the current study

2) Use of any medications/therapy that would aggravate psoriasis. These include agents such as lithium, antimalarials (quinacrine, chloroquine, and hydroxychloroquine), propranolol, indomethacin, and quinidine unless it is considered necessary for the subject's welfare and/or treatment of an AE/SAE.

3) Use of opioid analgesics unless it is considered necessary for the subject's welfare and/or treatment of an AE/SAE

4) Any use of biologic medications (eg, adalimumab, etanercept, infliximab, ustekinumab)

5) Any use of oral psoriasis medications (eg, methotrexate, cyclosporine, retinoids, fumaric acid derivatives) for any indication

6) Any use of oral or injectable corticosteroids (prednisone, methylprednisolone, etc), unless it is considered necessary for the subject's welfare and/or treatment of an AE/SAE

Note: otic, nasal, or inhaled corticosteroids within recommended doses and with no systemic effects are permitted.

7) Live vaccination

8) No new concomitant medications (prescription, over-the-counter, or herbal) are to be administered during the study unless prescribed for treatment of specific clinical events. Any concomitant therapies must be recorded on the eCRF.

The investigator should contact and confirm agreement with the Medical Monitor prior to the administration of any prohibited or restricted concomitant medications.

6.7.2 Permitted Concomitant Medications

Stable doses of concomitant medication for chronic medical conditions are permitted at the discretion of the investigator as long as they do not meet criteria in Section 6.7.1. Dose adjustments of these medications should be avoided during the study unless clinically indicated. If dose adjustments of these medications should occur, they must be recorded on the Concomitant Medications eCRF or the Diagnostic and Medical Procedures eCRF. The investigator should instruct the subject to notify the study site about any new treatments he/she takes after the start of the study treatment. All medications and significant nondrug therapies (including physical therapy and blood transfusions) administered after the subject starts study treatment must be listed on the Concomitant Medications eCRF or the Diagnostic and Medical Procedures eCRF.

6.7.3 Additional Psoriasis Treatments

Topical treatments/medications, medicated shampoos, and phototherapy can be used as additional treatment for psoriasis per the investigator's discretion at any time point during the study. These treatments must be accurately recorded on the Concomitant Medications eCRF or the Diagnostic and Medical Procedures eCRF.

6.8 Treatment After the End of the Study

At the end of the study, the investigator should ensure that subjects continue to receive appropriate standard of care to treat the condition under study. In addition, for subjects who continue to demonstrate clinical benefit, BMS may continue to provide study treatment through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986165 is terminated for other reasons including, but not limited to, lack of efficacy and/or not meeting the study objectives; c) the subject can obtain medication from a government-sponsored or private health program. In all cases BMS will follow local regulations.

7 DISCONTINUATION CRITERIA

7.1 Discontinuation from Study Treatment

Subjects MUST discontinue IP (and non-IP at the discretion of the investigator) for any of the following reasons:

- Subject requests to stop study treatment.

- Any clinically significant AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject. If treatment is discontinued due to an AE, the AE eCRF must be completed to show that the AE caused discontinuation.
- Abnormal liver tests suggestive of drug-induced liver injury (DILI), as defined in Section 8.2.8 or if the investigator believes that it is in the best interest of the subject.
- The subject develops a malignancy, with the exception of a subject who develops nonmelanoma skin cancer who may continue in the study at the discretion of the investigator.
- Pregnancy, positive pregnancy test, or subject expresses an interest in becoming pregnant (refer to Section 8.2.6).
- Subject develops active TB during the study or prematurely discontinues treatment for latent tuberculosis infection (LTBI), or subject is noncompliant with LTBI therapy (refer to Section 8.4.3).
- Termination of the study or program by BMS.
- Inability or failure to comply with protocol requirements in the opinion of the investigator.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Subject reports suicidal ideation, suicidal behavior, or suicide attempts at any time after inclusion. The subject should then be immediately referred to a mental health professional for evaluation of suicide risk. APPENDIX 14 provides categories and definitions of suicidal ideation and behavior.

All subjects who discontinue BMS-986165 treatment will complete the early discontinuation visit and safety follow-up visit (30 days after discontinuation) prior to leaving the study. Refer to the SOA (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up visits. The only exception to this requirement is when a subject withdraws consent for all study procedures including posttreatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). Replacement of subjects is not permitted.

If study treatment is discontinued, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate eCRF page.

7.1.1 Temporary Discontinuation of Study Medication

Temporary study treatment discontinuation is only allowed if the subject develops an AE that, in the opinion of the investigator, indicates that it is in the subject's best interest that the study treatment be placed on hold. Study treatment in this situation should be stopped until the AE is medically treated and has resolved per principal investigator's judgment.

Any temporary study treatment discontinuation as well as restart must be documented on the corresponding eCRF.

7.1.2 PostStudy Treatment Follow-Up

Subjects who discontinue study treatment will complete the early discontinuation visit and safety follow-up visit (30 days after discontinuation) prior to leaving the study.

7.2 Discontinuation from the Study

When a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information, the following applies:

- Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate eCRF page.
- In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Lost to Follow-up

- All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject.
- Lost to follow-up is defined by the inability to reach the subject after a minimum of **3** documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records.
- If it is determined that the subject has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the SOA (Section 1.3) and described in Section 4.1.
- Protocol waivers or exemptions are not allowed.

- All significant safety concerns must be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct.
- Procedures conducted as part of the subject's End of Treatment Visit from the parent study and obtained before signing of informed consent may be utilized for baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the SOA (Section 1.3).
- For several assessments, appropriate training will be provided to investigators and designated personnel at sites. Only those individuals trained and certified to perform these assessments will be performing them during the study.

8.1 Efficacy Assessments

Every effort must be made to ensure that the same evaluator(s) complete the assessment for each subject. If the evaluator(s) is unable to complete the evaluation, then a qualified individual with overlapping experience may perform the evaluation. Documentation of who performed the evaluation is to be recorded in source documents. Assessments are to be performed at approximately the same time of day throughout the duration of the study. All assessments are to be recorded in the electronic device(s) provided by the Sponsor.

Baseline assessments must be performed per protocol. Procedures not specified in the protocol that are part of standard care may be performed if they do not interfere with study procedures; any data arising from such procedures are not to be reported in the eCRF.

8.1.1 Investigator-administered Assessments

8.1.1.1 Static Physician's Global Assessment (sPGA)

The sPGA is a 5-point scale of an average assessment of all psoriatic lesions based on erythema, scale, and induration.[25] The sPGA measure determines psoriasis severity at a single point in time (without taking into account the baseline disease condition) as clear (0), almost clear (1), mild (2), moderate (3), or severe (4). All sPGA assessments should be performed by a trained physician (eg dermatologist) or appropriately trained investigator who is experienced in the assessment of patients with psoriasis. Every effort should be made to ensure that the same physician or designee performs the sPGA for a subject throughout the study (see APPENDIX 5).

8.1.1.2 Psoriasis Area and Severity Index (PASI)

The PASI is a measure of the average redness, thickness, and scaliness of psoriatic skin lesions (each graded on a 0–4 scale), weighted by the area of involvement (head, arms, trunk to groin, and legs to top of buttocks).[26] The PASI produces a numeric score that can range from 0 to 72, with higher PASI scores denoting more severe disease activity. The PASI can also be used to assess response to treatment. The PASI 50 is the proportion of subjects who experience at least a 50% improvement in PASI score as compared with the baseline value. The PASI 75, PASI 90, and PASI 100 are defined similarly. BMS will host a training session prior to initiation of the study to demonstrate proper PASI scoring. All PASI assessments should be performed by a trained

physician (dermatologist) or appropriately trained investigator who is experienced in the assessment of psoriasis patients (see APPENDIX 6).

8.1.1.3 Body Surface Area (BSA)

Measurement of psoriasis BSA involvement is estimated using the handprint method with the size of a subject's handprint (including fingers and thumb) representing 1% of BSA involved.[27,28,29] The total BSA = 100% with breakdown by body region as follows: head and neck = 10% (10 handprints), upper extremities = 20% (20 handprints), trunk including axillae and groin = 30% (30 handprints), lower extremities including buttocks = 40% (40 handprints). All BSA assessments should be performed by a dermatologist or appropriately trained investigator who is experienced in the assessment of psoriasis patients.

8.1.1.4 Scalp-specific Physician's Global Assessment (ss-PGA)

For this assessment in subjects with scalp involvement,[30] scalp lesions are evaluated in terms of clinical signs of redness, thickness, and scaliness and scored on the following 5-point ss-PGA scale:

> 0 = absence of disease, 1 = very mild disease, 2 = mild disease, 3 = moderate disease, 4 = severe disease.

The ss-PGA should be performed by a dermatologist or appropriately trained investigator who is experienced in the assessment of psoriasis patients. An example of the ss-PGA is provided in APPENDIX 7.

8.1.1.5 Physician's Global Assessment-Fingernails (PGA-F)

In this assessment,[31] the overall condition of the fingernails is rated on a 5-point scale:

> 0 = clear, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe

The PGA-F will be performed only in subjects with psoriatic fingernail involvement to assess severity and subsequent improvement. An example is provided in APPENDIX 8. The PGA-F should be performed by a dermatologist or appropriately trained investigator who is experienced in the assessment of psoriasis patients.

8.1.2 Subject-reported Assessments

8.1.2.1 Psoriasis Symptoms and Signs Diary (PSSD)

The PSSD is an 11-item subject-reported instrument that assesses severity of symptoms and subject-observed signs commonly associated in plaque psoriasis.[32,33] It has been shown to be reliable and valid in measuring symptoms and signs of subjects with moderate-to-severe plaque psoriasis in the clinic and has strong psychometric properties in assessing treatment effects in clinical trials.[34] The PSSD assesses severity of 5 symptoms (itch, pain, stinging, burning, skin tightness) and 6 subject-observed signs (skin dryness, cracking, scaling, shedding or flaking, redness, bleeding) using 0–10 numerical ratings. The severity of each item is rated on an 11-point numeric rating scale ranging from 0 (absent) to 10 (worst imaginable). Two versions of the PSSD were developed, one with a 24-hour recall period (PSSD-24h) and one with a 7-day recall period.

The PSSD-7d will be administered in this trial to assess long-term impact on patient-reported signs and symptoms (see APPENDIX 9).

8.1.2.2 Dermatology Life Quality Index (DLQI)

The DLQI[35] is a subject-reported quality of life index which consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work, school, personal relationships, and treatment during the last week. Each question is scored on a scale of 0 to 3 by a tick box: 0 - "not at all", 1 - "a little", 2 - "a lot", or 3 - "very much". The scores are summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment) (see APPENDIX 10).

8.1.2.3 Euro Quality of Life Five Dimensions Questionnaire: 3-Level Version (EQ-5D-3L)

The EQ-5D-3L is an instrument widely used in cost-utility analysis.[36] Using a system of 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and three levels (1 = no problems, 2 = some/moderate problems, and 3 = extreme problems) for each dimension, it provides utility values for a total of 243 health states. The utility values are measured from the general population using the time trade-off method. The EQ-5D-3L has demonstrated good validity, reliability, and responsiveness in patients with plaque psoriasis.[37] An example is provided in APPENDIX 11.

8.1.2.4 Work Limitation Questionnaire (WLQ)

The WLQ is a 25-item self-report that measures the on-the-job impact of chronic health conditions and treatment with a focus on assessing limitations while performing specific job demands from the following 4 domains:[38]

1) Time management: difficulty with handling time and scheduling demands (5 items)
2) Physical demands: ability to perform job tasks that involve bodily strength, movement, endurance, coordination, and flexibility (6 items)
3) Mental-interpersonal demands: cognitively demanding tasks and on-the-job social interactions (9 items)
4) Output demands: concerns reduced work productivity (5 items)

The score can be used to calculate a percent of lost work productivity due to a particular disease state. An example is provided in APPENDIX 12.

8.2 Adverse Events

The definitions of an AE and SAE can be found in APPENDIX 3.

All AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue before completing the study.

Adverse events that start in the parent study and are continuing at the time of the first dose in the IM011075 study will be recorded as ongoing in the parent study eCRF. In addition,

- if the event worsens within 30 days of the last dose of study drug in the parent study, then the outcome and resolution date will be updated in the parent study eCRF and the worsening event will be recorded as a new event in the IM011075 eCRF.
- if the event resolves within 30 days of the last dose of study drug in the parent study, then the outcome and resolution date will be updated in the parent study eCRF.

Adverse events that start on or after the date of the first dose in the IM011075 study will be recorded in the IM011075 eCRF.

Contacts for SAE reporting are specified in APPENDIX 3**.**

8.2.1 Adverse Events of Interest

Adverse events of interest (AEIs) are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. Adverse events of interest may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the BMS-986165 clinical development program, certain skin-related AEs (eg, acne), infection AEs, and CK elevation have been identified as potential AEIs; however, there has been no definitive assessment on the causal relationship between these events and treatment with BMS-986165. Additionally, given a potential association between treatment for autoimmune diseases and increased risk for cancer, malignancy has been identified as a potential AEI. Therefore, additional information about certain skin-related AEs, infection AEs, CK elevation, and malignancy may be collected on the case report form in order to better characterize and understand them.

8.2.2 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until discharge from the study (ie, final study visit for a given subject), at the timepoints specified in the SOA (Section 1.3).

The Reference Safety Information in Sections 5.6.1 and 5.6.2 of the IB should be used to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

- Medical occurrences that begin after obtaining informed consent but before the first dose of open-label BMS-986165 will be recorded as medical history on the appropriate section of the eCRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in APPENDIX 3.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in APPENDIX 3.

8.2.3 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs).

8.2.4 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization or reported as SAEs if they become serious (see APPENDIX 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the eCRF. Completion of supplemental eCRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 7.3).

Further information on follow-up procedures is given in APPENDIX 3.

8.2.5 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the Investigational Review Board/Independent Ethics Committee (IRB/IEC), if appropriate according to local requirements.

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

8.2.6 Pregnancy

In the event a subject becomes pregnant during the trial, the study treatment must be discontinued immediately. If the subject becomes pregnant while on treatment or within 3 days of discontinuing study treatment, the investigator must immediately notify PRA Drug Safety of this event and complete and forward a Pregnancy Surveillance Form to PRA Drug Safety within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in APPENDIX 3. The investigator must also notify the Medical Monitor or designee of this event within 24 hours of awareness of pregnancy.

The pregnant subject will need to be followed up until the conclusion of the pregnancy for pregnancy outcomes. The safety data of the subject will continue to be collected under the same rules as instructed in Section 7.1.

Any pregnancy that occurs in a female partner of a male study subject should be reported to PRA Drug Safety. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

8.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia vs low hemoglobin value).

8.2.8 Potential Drug-Induced Liver Injury (DILI)

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 8.2 and APPENDIX 3 for reporting details). Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event.

Potential DILI is defined as:

1) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of liver function test elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.2.9 Other Safety Considerations

Any significant worsening of a preexisting medical condition noted during interim or final physical examination (PE), electrocardiogram (ECG), or any other potential safety assessment required or not required by protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

8.3 Overdose

For this study, taking > 24 mg of BMS-986165 within a 24-hour time period will be considered an overdose.

In the event of an overdose, the investigator should:

1) Contact the Medical Monitor immediately

2) Closely monitor the subject for AEs/SAEs and laboratory abnormalities

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.4 Safety

Planned time points for all safety assessments are listed in the SOA (Section 1.3).

8.4.1 Physical Examinations

A complete PE will include general appearance, vital signs, eyes, ears, nose mouth, throat, neck, CV, respiratory, gastrointestinal/abdomen, lymphatic, musculoskeletal, skin, psychiatric, and neurologic exams. A targeted physical examination will only include any organ system associated with an AE or a laboratory abnormality.

8.4.2 Vital Signs

Refer to SOA (Section 1.3).

8.4.3 Tuberculosis Assessment

To be eligible for the study, a subject must not have active signs or symptoms of TB, as judged by the investigator.

At the baseline visit and approximately yearly thereafter, in addition to a complete PE and medical history to evaluate exposure to TB, all subjects will complete a TB questionnaire APPENDIX 13.

If based on the TB risk assessment tool (APPENDIX 13), a subject is identified as needing an Interferon Gamma Release Assay (IGRA) test, they can still roll over into IM011075 at the baseline visit. Study treatment should be started as per protocol at this baseline visit. However, IGRA testing must be performed at this visit and the result obtained in the shortest possible timeframe.

If IGRA results are:

a) Negative; no further action is needed.

b) Positive; subject must stop study treatment immediately and initiate and complete prophylaxis treatment per local guidelines. Study treatment will be held until subject has been on prophylaxis treatment for 30 days.

c) Indeterminate; an IGRA retest will be required. If the second test is either indeterminate or positive, the subject must initiate and complete prophylaxis treatment per local guidelines. Study treatment will be held until subject has been on prophylaxis treatment for 30 days.

8.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Hematology	
Hemoglobin (Hgb) Hematocrit (Hct) White Blood Cell Count, including differential Platelet Count	
Chemistry	
AST ALT Total Bilirubin Direct Bilirubin (if total bilirubin >ULN) Alkaline Phosphatase Lactate Dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) Uric Acid Glucose	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Creatine Kinase (CK)[a]
Lipid Panel	
Cholesterol (total) High Density Lipoprotein (HDL) Low Density Lipoprotein (LDL) Triglycerides	
Other Analyses	
Urine Pregnancy Test (WOCBP only) Interferon Gamma Release Assay	

[a] If CK > 2.5 × ULN, then reflex testing (ie, CK-MB, Troponin I) will be required.

8.5 Pharmacokinetics

The PK of BMS-986165 and metabolites (if applicable) will be derived from plasma concentration vs time data. The PK parameter to be assessed will be trough observed plasma concentration (Ctrough).

Plasma samples will be analyzed for BMS-986165 by a validated assay. Actual times will be used for the analyses.

In addition, plasma samples will be archived for potential metabolite analysis, if the need arises and to the extent possible. Detailed instructions for PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the Study Reference Manual.

8.5.1 Sampling Schedule

The sampling schedule for the assessment of PK is provided in Table 5. Predose samples must be drawn before the dose on visit days. The timing of other procedures at a given visit can be adjusted so that PK sampling can be performed at the scheduled time. If possible, PK samples should be collected for subjects who discontinue treatment due to an AE.

Table 5: Pharmacokinetic Sampling Schedule for BMS-986165

Study Visit of Sample Collection	Event	Time (Relative to Dose) Hour: Min	Blood Sample for PK	Notes
Week 4	predose	00:00	X	
Week 24	predose	00:00	X	
Week 48	predose	00:00	X	
Week 72	predose	00:00	X	
Week 96	predose	00:00	X	

min = minute; PK = pharmacokinetic

Note: Predose samples must be drawn before the dose of study treatment on the visit day, ie, study treatment will be taken at the site on those days.

8.5.2 Sampling Windows

It is expected that every effort is made to collect PK samples at the times indicated. Predose samples must be drawn before the morning dose on the visit day.

All samples should be collected using the timepoint labels provided even if they are outside of the suggested window. Actual sample times must be recorded. Any missed PK sample collections must be noted in the source documents.

8.6 Exploratory Biomarker Assessments

Biomarker testing may be performed to assess the stability of the markers over time and to compare the marker levels between other treatments given in parent studies (eg, IM011046, IM011047, and IM011066). Markers of interest include inflammatory markers including but not limited to cytokines, (eg, IFNα, IFNβ, IL-17, IL-22, beta-defensin), chemokines, (eg, IP-10, CCL20, CXCL13), and soluble receptors, (eg, CD25, TNF ligand superfamily member 6). Markers of extracellular matrix damage may be assessed. Additionally, markers of CV and metabolic disorder such as HBA1c, C-peptide, cholesterol, and others may be assessed. RNA samples may be analyzed for, but not limited to, IFN-regulated gene expression, steroid regulated genes, by RNA-sequencing or quantitative reverse transcription polymerase chain reaction. Blood samples will be drawn for serum and plasma predose on the days indicated in Table 1.

Blood samples will not be drawn for any exploratory biomarker assessments where country or local practices don't allow for it.

8.6.1 Additional Research Collection

This protocol will include residual sample storage for additional research.

For All US Sites:

Additional research is required for all study subjects, except where prohibited by IRBs/IECs, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study subject must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study subjects may opt out of the additional research retention and/or collection.

For non-US Sites

Additional research is optional for all study subjects, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational Research and Development (R&D) capability at BMS and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, and response to treatment, etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study Sponsor's senior leaders in R&D (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

- Residual PK, plasma for inflammation and CV Markers, serum for inflammation and CV markers, blood RNA, (see Table 6) will be retained for additional research purposes.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 15 years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research Sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion and no researcher will have access to the key. The key is securely held by the investigator at the study site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Table 6: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for Which Residual Samples Will be Retained
PK	All
Serum for Inflammation and CV Markers	All
Plasma for Inflammation and CV Markers	All
Blood RNA	All

CV = cardiovascular; DNA = deoxyribonucleic acid; PK = pharmacokinetic; RNA = ribonucleic acid

8.7 Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

As this LTE study is for observational purposes only, no formal calculations of sample size and power determination will be made. All qualified subjects who complete the final treatment visit from an applicable parent study will be eligible to participate. The expected number of subjects participating from each applicable parent study is as follows: 600 subjects from IM011046; 1000 subjects from IM011047; 180 subjects from IM011065; 80 subjects from IM011066. Sample size is determined by the number of subjects with the potential to enroll into IM011075.

9.2 Populations for Analyses

For purposes of analysis, the following analysis sets will be used in this trial:

Enrolled Population: All subjects who signed informed consent for entry into IM011075

As-treated Population: All enrolled subjects who took at least one dose of study treatment in IM011075

Biomarker Population: All enrolled subjects who took at least one dose of study treatment in IM011075 and have at least 1 posttreatment biomarker measurement

Pharmacokinetic Population: All enrolled subjects who took at least one dose of study treatment in IM011075 and have any available exposure data

9.3 Endpoints

9.3.1 Primary Endpoint

The primary objective of this LTE study is to characterize the long-term safety and tolerability of BMS-986165 in subjects with moderate-to-severe plaque psoriasis. The following assessments will be summarized for the evaluation of this objective:

- AEs, SAEs, AEs leading to study discontinuation, and deaths

9.3.2 Secondary Endpoints

The secondary endpoints evaluated over time for long-term maintenance of response of BMS-986165 are defined as:

- sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1
- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from parent study baseline in the PASI score

9.3.3 Additional Endpoints

Additional endpoints evaluated over time for long-term maintenance of response of BMS-986165 are defined as:

- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score
- PASI 100 response assessed as a proportion of subjects who achieve a 100% improvement from baseline in the PASI score
- Change from baseline and percent change from baseline in BSA
- Change from baseline in PSSD total score
- Change from baseline in PSSD symptom score
- Change from baseline in PSSD sign score
- PSSD total score of 0 among subjects with a baseline PSSD total score ≥1
- PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥1
- PSSD sign score of 0 among subjects with a baseline PSSD sign score ≥1
- Change from baseline in DLQI score
- DLQI 0/1 assessed as a proportion of subjects with a DLQI score of 0 or 1 among subjects with a baseline DLQI score ≥ 2
- sPGA 0 response assessed as a proportion of subjects with an sPGA score of 0
- Change from baseline in the EQ-5D-3L utility scores
- Change from baseline in the WLQ score

- ss-PGA 0/1 assessed as a proportion of subjects with a ss-PGA score 0 or 1 among subjects with a parent study baseline ss-PGA score ≥ 3
- PGA-F 0/1 assessed as a proportion of subjects with a PGA-F score of 0 or 1 among subjects with a parent study baseline PGA-F score ≥ 3

9.3.4 PK Endpoints

- Plasma concentration values

9.3.5 PD Endpoints

- Exploratory Biomarkers

9.4 Efficacy Analyses

As this study is for observational purposes, no statistical tests for treatment comparisons will be conducted. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified. Efficacy variables will be summarized for all visits in which the variable is assessed. Complete details of the planned analyses will be documented in the statistical analysis plan (SAP) and finalized before database lock. Efficacy summaries will be provided for the 'As-treated' population. Baseline values for change from baseline calculations will be defined in the SAP.

Summaries will be presented for the following groups:

- BMS-986165 6 mg QD (last treatment from previous study)→BMS-986165 6 mg QD
- Apremilast 30 mg BID (last treatment from previous study)→BMS-986165 6 mg QD
- Placebo (last treatment from previous study)→BMS-986165 6 mg QD

9.5 Safety Analyses

Safety data will be analyzed for AEs and SAEs. Safety will be summarized using the 'As-treated' population. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified. Baseline values for change from baseline calculations will be defined in the SAP.

Summaries will be presented for the following groups:

- BMS-986165 6 mg QD (last treatment from previous study)→BMS-986165 6 mg QD
- Apremilast 30 mg BID (last treatment from previous study)→BMS-986165 6 mg QD
- Placebo (last treatment from previous study)→BMS-986165 6 mg QD

9.5.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are events that occur after the first dose of study drug is given in the IM011075 study and prior to 30 days after the last dose of study drug in the

IM011075 study. Events that were ongoing during the parent study and worsen once the study drug is initiated in the IM011075 study will also be considered TEAEs.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented by system organ class and preferred term. Serious AEs and deaths, AEs leading to study treatment discontinuation, AEs by maximum severity, and AEs by relationship will also be summarized by the MedDRA system organ class and preferred term. All TEAEs will also be summarized by preferred term sorted by decreasing frequency.

9.6 Other Analyses

Other analysis summaries will be presented similar to as defined in Section 9.5.

9.6.1 Demographics and Baseline Data

Demographics and baseline data obtained during the screening visit of the parent studies will be summarized for subjects entering the LTE for each applicable analysis population. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

9.6.2 Prior and Concomitant Medications

Prior and concomitant medications, categorized by medication group and subgroup according to the World Health Organization Drug Dictionary, will be summarized for the 'As-treated' population. Medications with an end date prior to the first dose of LTE study drug will be considered prior medications.

9.6.3 Pharmacokinetics

Ctrough will be summarized by timepoint for the PK population.

9.6.4 Biomarkers

Selected biomarkers will be summarized by time point for the biomarker population. Summaries will be provided for raw, change from baseline, and percent change from baseline.

9.7 Interim Analyses

No interim analysis is currently planned.

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11 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
AEI	adverse event of interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BID	twice daily
BMS	Bristol-Myers Squibb
BSA	body surface area
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CK	creatine kinase
CTA	clinical trial agreement
Ctrough	trough observed plasma concentration
CV	cardiovascular
CYP450	cytochrome P450
DC	discontinuation
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-3L	Euro Quality of Life Five Dimensions Questionnaire: 3-Level Version
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
Hct	hematocrit
HCV	hepatitis C virus
HDL	high density lipoprotein

Term	Definition
Hgb	hemoglobin
IB	Investigator Brochure
IC50	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IFNγ	interferon gamma
Ig	immunoglobulin
IGRA	interferon gamma release assay
IL	interleukin
IMD	Innovative Medicines Development
IMP	investigational medicinal product
IP	investigational product
IRB	Investigational Review Board
IRT	interactive response technology
JAK	Janus kinase
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LTBI	latent tuberculosis infection
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
PASE	psoriatic arthritis screening and evaluation
PE	physical examination
PGA-F	Physician Global Assessment- Fingernails
PK	pharmacokinetics
PPS	Per Protocol Set
PsA	psoriatic arthritis
PsO	psoriasis

Term	Definition
PSSD	Psoriasis Symptoms and Signs Diary
PSSD-7d	Psoriasis Symptoms and Signs Diary 7-day Recall
PSSI	Psoriasis Scalp Severity Index
PUVA	Psoralens with ultraviolet A
QD	once daily
QOD	every other day
R&D	Research and Development
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SOA	Schedule of Activities
sPGA	static Physician Global Assessment
ss-PGA	scalp-specific Physician's Global Assessment
STAT	signal transducer and activator of transcription
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TYK2	tyrosine kinase 2
UK	United Kingdom
ULN	upper limit of normal
UVB	ultraviolet B
VAS	visual analog scale
WLQ	Work Limitations Questionnaire
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

Regulatory and Ethical Considerations

Good Clinical Practice

This study will be conducted in accordance with:

- Good Clinical Practice (GCP)
- as defined by the International Council for Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations (CFR), Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure (IB) or product labeling information to be provided to subjects and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to Bristol-Myers Squibb (BMS).

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form (ICF), which will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the ICF approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

Source Documents

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved,

or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), AE tracking/reporting, protocol-required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

Study Treatment Records

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a health authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product

If	Then
	dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and paper Pregnancy Surveillance Form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

Monitoring

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

Records Retention

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

Return of Study Treatment

For this study, study treatments (those supplied by BMS, a vendor or sourced by the investigator) such as partially-used study treatment containers, vials, and syringes may be destroyed on site.

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of nonstudy treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing study site or investigator participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP AND REPORTING

Adverse Events

Adverse Event Definition:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

Serious Adverse Events

Serious Adverse Event Definition: Any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below) Note: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department <24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability or permanent damage
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event (see Section 8.2.8 for the definition of potential DILI).

Pregnancy and potential DILI must follow the same transmission timing and processes to BMS as used for SAEs (see Section 8.2.6 for reporting pregnancies).

Evaluating AEs and SAEs

Assessment of Intensity
The intensity of AEs is determined by a physician and will use the following levels: • Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. A "reasonable possibility of a relationship" conveys that there are facts, evidences, and/or arguments to suggest a causal relationship rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. Note: Follow-up SAE reports must include the same investigator term(s) initially reported.

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

Reporting of SAEs to Sponsor or Designee

SAEs, whether related or not related to study drug, and pregnancies must be reported to PRA Drug Safety within 24 hours of awareness of the event.

SAEs must be recorded on the SAE Report Form. For studies capturing SAEs through electronic data capture, electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: BMSSafety@prahs.com

SAE Fax Number:

Americas: 1-888-772-6919 (or 1-434- 951-3482)

Europe/East Asia-Pacific: +44-1792-525-720

SAE Telephone Contact - For questions on SAE/pregnancy reporting, please call:

Americas: 1-800 772 2215 (or 1-434-951-3489)

Europe/East Asia-Pacific: +49-621-878-2154.

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels.

- 1-week minimum for vaginal hormonal products (rings, creams, gels)
- 4-week minimum for transdermal products
- 8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILD-BEARING POTENTIAL

At minimum, one of the less than highly effective methods of contraception listed below is required during study duration and until the end of study treatment.

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation[b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[b,c] • Bilateral tubal occlusion
• Vasectomized partner *Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 5.1.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP subjects choose to forego complete abstinence.

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine hormone-releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of > 1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action

Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • Lactation amenorrhea method

CONTRACEPTION GUIDANCE FOR MALE SUBJECTS WITH PARTNER(S) OF CHILD-BEARING POTENTIAL

For male subjects eligible to participate in the study with female partners of childbearing potential, no additional contraceptive measures are required to be used; however, these subjects must:

- Inform any and all partner(s) of their participation in a clinical drug study.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 8.2.6 and APPENDIX 3.

APPENDIX 5 STATIC PHYSICIAN'S GLOBAL ASSESSMENT OF PSORIASIS (sPGA)

The static PGA is used to determine the subject's psoriasis lesions overall at a given time point. Overall lesions will be graded for erythema, induration, and scaling based on the scales below. The average of the 3 scales, which is rounded to the nearest whole number, is the final sPGA score.

Characteristics	Score	Rating Score
Erythema (E) (averaged over the whole body)		0 = No evidence of erythema, but post inflammatory hyper/hypopigmentation changes may be present 1 = Faint erythema 2 = Light red coloration 3 = Moderate red coloration 4 = Bright red coloration
Induration (I) (averaged over the whole body)		0 = No evidence of plaque elevation 1 = Minimal plaque elevation, barely palpable, = 0.25 mm 2 = Mild plaque elevation, slight but definite elevation, indistinct edge, = 0.5 mm 3 = Moderate plaque elevation, elevated with distinct edges, = 0.75 mm 4 = Severe plaque elevation, hard/sharp borders, ≥ 1 mm
Scaling (S) (averaged over the whole body)		0 = No evidence of scaling 1 = Minimal; occasional fine scale 2 = Mild; fine scale dominates 3 = Moderate; coarse scale predominates 4 = Severe; thick scale predominates

E + I + S / 3 = (Total Average)

Physician's Static Global Assessment based upon above Total Average

0 = Clear, except for residual discoloration
1 = Almost clear -majority of lesions have individual scores for E + I + S / 3 that averages 1
2 = Mild -majority of lesions have individual scores for E + I + S / 3 that averages 2
3 = Moderate -majority of lesions have individual scores for E + I + S / 3 that averages 3
4 = Severe -majority of lesions have individual scores for E + I + S / 3 that averages 4

Note: Scores should be rounded to the nearest whole number. If total ≤ 1.49, score = 1; if total ≥ 1.50, score = 2.

APPENDIX 6 PSORIASIS AREA AND SEVERITY INDEX (PASI)

Psoriasis Area and Severity Index (PASI); a quantitative rating scale for measuring the severity of psoriatic lesions based on area coverage and plaque appearance. Please complete **all** sections of the table.

Plaque Characteristic	**Rating score**	**Body region (and weighting factor)**			
		Head	**Upper Extremities**	**Trunk**	**Lower Extremities**
Erythema (Redness)	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Infiltration (Thickness)					
Desquamation (Scaling)					
Add together each of the 3 scores for each of the body regions to give 4 separate sub totals.					
	Sub Totals	A1 =	A2 =	A3 =	A4 =
Multiply each subtotal by amount of body surface area represented by that region i.e. A1 x 0.1 for head, A2 x 0.2 for upper extremities, A3 x 0.3 for trunk, A4 x 0.4 for lower extremities to give a value B1, B2, B3, and B4 for each body region respectively					
		A1 x 0.1 = B1	A2 x 0.2 = B2	A3 x 0.3 = B3	A4 x 0.4 = B4
		B1 =	B2 =	B3 =	B4 =
Degree of involvement as % for each body region affected; (score each region with score between 0-6)	0 = None 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50 -69% 5 = 70-89% 6 = 90-100%				
For each body region multiply sub total B1, B2, B3 and B4 by the score (0-6) of the % of body region involved to give 4 subtotals C1, C2, C3, and C4					
		B1 x score = C1	B2 x score = C2	B3 x score = C3	B4 x score = C4
		C1 =	C2 =	C3 =	C4 =
The patient's PASI score is the sum of C1 + C2 + C3 + C4				**PASI=**	

APPENDIX 7 SCALP-SPECIFIC PHYSICIAN'S GLOBAL ASSESSMENT (ss-PGA)

Please rate overall scalp psoriasis severity by selecting the overall score based on the following rating scale:

Score	Category	Description
0	Absence of Disease	No evidence of redness, no evidence of thickness, and no evidence of scaliness on the scalp
1	Very Mild Disease	The overall clinical picture consists of flat lesions with barely perceptible erythema, with or without a trace of overlying fine scale
2	Mild Disease	The overall clinical picture consists of lesions with mild erythema, slight, but definite, thickness, and a thin scale layer
3	Moderate Disease	The overall clinical picture consists of lesions with moderate erythema, a moderate thickness, and a moderate scaled layer
4	Severe Disease	The overall clinical picture consists of lesions with bright erythema, severe thickness, and a severe, coarse thick scale layer

APPENDIX 8 PHYSICIAN'S GLOBAL ASSESSMENT-FINGERNAILS (PGA-F)

For this assessment in subjects with psoriasis fingernail involvement, the overall condition of the fingernails is rated by the investigator on a 0-4 (5-point) scale. The overall score assigned based on the higher of the nail bed/nail matrix score:

		Nail Bed Signs	Nail Matrix Signs
Clear	0	Onycholysis- consistent with a normal nail **AND** Hyperkeratosis- none **AND** Splinter Hemorrhages-consistent with nonpsoriatic splinter hemorrhages **AND** Nail Bed Erythema- none	No nonpsoriatic nail plate irregularities including pitting, crumbling, Beau's lines, senile onychorrhexis, and nonpsoriatic leukonychia
Minimal	1	Onycholysis- < 10% involved on all nails **OR** Hyperkeratosis- present, but barely detectable elevation of nail plate **OR** Nail Bed Erythema- faint **AND** Splinter Hemorrhages- consistent with nonpsoriatic splinter hemorrhages	No more than 5 pits or psoriatic leukonychia on any nail **AND** No crumbling
Mild	2	Onycholysis- >10% on five or more nails **OR** Hyperkeratosis- present with mild elevation of nail plate **OR** Splinter Hemorrhages- present on four or fewer nails **OR** Nail Bed Erythema- mild	Five or more nails with mild pitting (eg, >10 pits/nail) or psoriatic leukonychia **AND** No crumbling
Moderate	3	Onycholysis- >30% on at least one nail **OR** Hyperkeratosis- present with moderate elevation of nail plate **OR** Splinter Hemorrhages- scattered and present on five or more nails **OR** Nail Bed Erythema- moderate	Five or more nails with moderate pitting (eg, >25 pits/nail) **AND** ≤ 25% crumbling on any nails
Severe	4	Onycholysis- >50% on at least one nail **OR** Hyperkeratosis- present with severe elevation of nail plate **OR** Splinter Hemorrhages- numerous and present on five or more nails **OR** Nail Bed Erythema- severe	Five or more nails with severe pitting (>50 pits/nail) **OR** >25% crumbling on any nail

APPENDIX 9 PSORIASIS SYMPTOMS AND SIGNS DIARY (PSSD)

Please answer each question to the best of your ability. There are no right or wrong answers. Please pay close attention to the time period of interest. These questions ask you to think about the **past 7 days**.

Individuals with psoriasis may experience a range of symptoms. Please indicate how severe each of the following skin symptoms was in the **past 7 days.** Please select only one number for each item on the 0 to 10 scale (0=Absent and 10= Worst imaginable).

1. Rate the severity of itch in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
2. Rate the severity of dryness in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
3. Rate the severity of cracking in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
4. Rate the severity of skin tightness in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
5. Rate the severity of scaling (build-up of skin) in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
6. Rate the severity of shedding or flaking in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
7. Rate the severity of redness in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
8. Rate the severity of bleeding in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
9. Rate the severity of burning in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
10. Rate the severity of stinging in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
11. Rate the severity of pain from your psoriasis lesions in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable

APPENDIX 10 DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: Date: Score:

Name: Diagnosis:

Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful, or stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	☐ Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	☐ Not relevant
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	☐ Not relevant ☐

Please check you have answered EVERY question. Thank you

APPENDIX 11 EURO QUALITY OF LIFE FIVE DIMENSIONS QUESTIONNAIRE: 3-LEVEL VERSION (EQ-5D-3L)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ❑
- I have some problems in walking about ❑
- I am confined to bed ❑

Self-Care

- I have no problems with self-care ❑
- I have some problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

Usual Activities (eg work, study, housework, family, or leisure activities)

- I have no problems with performing my usual activities ❑
- I have some problems with performing my usual activities ❑
- I am unable to perform my usual activities ❑

Pain/Discomfort

- I have no pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have extreme pain or discomfort ❑

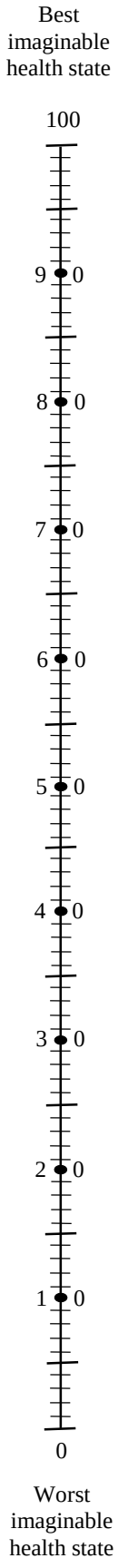
Anxiety/Depression

- I am not anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX 12 WORK LIMITATIONS QUESTIONNAIRE (WLQ)

Work Limitations Questionnaire©

Self-Administered Long-Form

Fill in Today's Date

Month		Day		Year	

Instructions

Health problems can make it difficult for working people to perform certain parts of their jobs. We are interested in learning about how your health may have affected you at work during the past 2 weeks.

(1) The questions will ask you to think about your physical health or emotional problems. These refer to any ongoing or permanent medical conditions you may have and the effects of any treatments you are taking for these. Emotional problems may include feeling depressed or anxious.

(2) Most of the questions are multiple choice. They ask you to answer by placing a mark in a box.

For example:

How satisfied are you with each of the following . . .?

(Mark one box on each line a. and b.)

	Not At All Satisfied	Moderately Satisfied	Very Satisfied
a. Your local schools.	☐1	☐2	■3
b. Your local police department. . .	☐1	■2	☐3

These marks tell us you are very satisfied with your local schools and moderately satisfied with your local police department.

OPTIONAL PAGE

3. Before you begin answering any questions, we would like you to write some information on the calendar.

   - Find today's date. Mark that box.
   - Count back 2 weeks and mark that box too.

This 2-week period is the subject of most of the questions. Feel free to mark other important dates such as birthdays, family events, or work deadlines. Please use the calendar to help you answer correctly.

Insert calendar here

Questions 1 through 5 ask about how your health has affected you at work during the past 2 weeks. Please answer these questions even if you missed some workdays.

- *Mark the "Does not apply to my job" box only if the question describes something that is not part of your job.*
- *If you have more than one job, report on your **main** job only.*

1. In the past 2 weeks, how much of the time did your physical health or emotional problems make it difficult for you to do the following?

(*Mark one box on each line a. through e.*)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult** a slight bit of the time	**Difficult** none of the time (0%)	Does not apply to my job
a. work the required number of hours	☐1	☐2	☐3	☐4	☐5	☐6
b. get going easily at the beginning of the workday	☐1	☐2	☐3	☐4	☐5	☐6
c. start on your job as soon as you arrived at work	☐1	☐2	☐3	☐4	☐5	☐6
d. do your work without stopping to take breaks or rests	☐1	☐2	☐3	☐4	☐5	☐6
e. stick to a routine or schedule	☐1	☐2	☐3	☐4	☐5	☐6

PLEASE READ CAREFULLY

These questions ask you to rate the amount of time you were able to handle certain parts of your job without difficulty.

2. a. In the past 2 weeks, how much of the time were you **able** to walk or move around different work locations (for example, go to meetings), without difficulty caused by physical health or emotional problems?

(*Mark one box.*)

Able all of the time (100%)	☐1
Able most of the time	☐2
Able some of the time (about 50%)	☐3
Able a slight bit of the time	☐4
Able none of the time (0%)	☐5
Does not apply to my job	☐6

b. In the past 2 weeks, how much of the time were you **able** to lift, carry, or move objects at work weighing more than 10 lbs., without difficulty caused by physical health or emotional problems?

(*Mark one box.*)

Able all of the time (100%)	☐1
Able most of the time	☐2
Able some of the time (about 50%)	☐3
Able a slight bit of the time	☐4
Able none of the time (0%)	☐5
Does not apply to my job	☐6

c. In the past 2 weeks, how much of the time were you **able** to sit, stand, or stay in one position for longer than 15 minutes while working, without difficulty caused by physical health or emotional problems?

(*Mark one box.*)

Able all of the time (100%)	☐1
Able most of the time	☐2
Able some of the time (about 50%)	☐3
Able a slight bit of the time	☐4
Able none of the time (0%)	☐5
Does not apply to my job	☐6

d. In the past 2 weeks, how much of the time were you **able** to repeat the same motions over and over again while working, without difficulty caused by physical health or emotional problems?

(*Mark one box.*)

Able all of the time (100%)	☐1
Able most of the time	☐2
Able some of the time (about 50%)	☐3
Able a slight bit of the time	☐4
Able none of the time (0%)	☐5
Does not apply to my job	☐6

d. In the <u>past 2 weeks</u>, how much of the time were you **able** to bend, twist, or reach while working, without difficulty caused by physical health or emotional problems?

(*Mark one box.*)

Able all of the time (100%)	☐1
Able most of the time	☐2
Able some of the time (about 50%)	☐3
Able a slight bit of the time	☐4
Able none of the time (0%)	☐5
Does not apply to my job	☐6

e. In the <u>past 2 weeks</u>, how much of the time were you **able** to use hand-held tools or equipment (eg, a phone, pen, keyboard, computer mouse, drill, hair dryer, or sander), without difficulty caused by physical health or emotional problems?

(*Mark one box.*)

Able all of the time (100%)	☐1
Able most of the time	☐2
Able some of the time (about 50%)	☐3
Able a slight bit of the time	☐4
Able none of the time (0%)	☐5
Does not apply to my job	☐6

PLEASE READ CAREFULLY

These questions ask about difficulties you may have had at work.

3. In the past 2 weeks, how much of the time did your physical health or emotional problems make it difficult for you to do the following?

(Mark one box on each line a. through f.)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult** a slight bit of the time	**Difficult** none of the time (0%)	Does not apply to my job
a. keep your mind on your work	☐1	☐2	☐3	☐4	☐5	☐6
b. think clearly when working	☐1	☐2	☐3	☐4	☐5	☐6
c. do work carefully	☐1	☐2	☐3	☐4	☐5	☐6
d. concentrate on your work	☐1	☐2	☐3	☐4	☐5	☐6
e. work without losing your train of thought	☐1	☐2	☐3	☐4	☐5	☐6
f. easily read or use your eyes when working	☐1	☐2	☐3	☐4	☐5	☐6

The next questions ask about difficulties in relation to the people you came in contact with while working. These may include employers, supervisors, coworkers, clients, customers, or the public.

4. In the past 2 weeks, how much of the time did your physical health or emotional problems make it difficult for you to do the following?

(Mark one box on each line a. through c.)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult** a slight bit of the time	**Difficult** none of the time (0%)	Does not apply to my job
a. speak with people in-person, in meetings or on the phone	☐1	☐2	☐3	☐4	☐5	☐6
b. control your temper around people when working	☐1	☐2	☐3	☐4	☐5	☐6
c. help other people to get work done	☐1	☐2	☐3	☐4	☐5	☐6

These questions ask about how things went at work overall.

5. In the past 2 weeks, how much of the time did your physical health or emotional problems make it difficult for you to do the following?

(Mark one box on each line a. through e.)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult** a slight bit of the time	**Difficult** none of the time (0%)	Does not apply to my job
a. handle the workload	☐1	☐2	☐3	☐4	☐5	☐6
b. work fast enough	☐1	☐2	☐3	☐4	☐5	☐6
c. finish work on time	☐1	☐2	☐3	☐4	☐5	☐6
d. do your work without making mistakes	☐1	☐2	☐3	☐4	☐5	☐6
e. feel you've done what you are capable of doing	☐1	☐2	☐3	☐4	☐5	☐6

APPENDIX 13 TUBERCULOSIS RISK ASSESSMENT TOOL

A subject with any of the 3 following high risk factors will have an interferon gamma release assay (IGRA) test:

	Yes	No
1. Recent close or prolonged contact with someone with infectious tuberculosis (TB) disease (defined as within 12 months)		
2. High-risk profession or situations, like being patient-facing, eg, healthcare providers		
3. Recent travel to or from a high burden country for TB OR residing in a high burden country for TB (please see country list from United Nations partner website [Stop TB]): http://www.stoptb.org/countries/tbdata.asp		

APPENDIX 14 SUICIDAL IDEATION AND BEHAVIOR CATEGORIES AND DEFINITIONS

Suicidal Ideation

Passive suicidal ideation: wish to be dead

Patient has thoughts about a wish to be dead or not alive anymore or wishes to fall asleep and not wake up.

Active suicidal ideation: nonspecific (no method, intent, or plan)

General nonspecific thoughts of wanting to end one's life or commit suicide (eg, "I've thought about killing myself") without general thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.

Active suicidal ideation: method, but no intent or plan

Patient has thoughts of suicide and has thought of at least one method during the assessment period. This situation is different than a specific plan with time, place, or method details worked out (eg, thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose, but I never made a specific plan as to when, where, or how I would actually do it…and I would never go through with it."

Active suicidal ideation: method and intent, but no plan

Active suicidal thoughts of killing oneself, and patient reports having some intent to act on such thoughts, as opposed to "I have the thoughts, but I definitely will not do anything about them."

Active suicidal ideation: method, intent, and plan

Thoughts of killing oneself with details of plan fully or partially worked out and patient has some intent to carry it out (ie, some degree of intent is implicit in the concept of plan).

Suicidal Behavior

Completed suicide

A self-injurious behavior that resulted in fatality and was associated with at least some intent to die as a result of the act. Evidence that the individual intended to kill him- or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance.

Suicide attempt

A potentially self-injurious behavior associated with at least some intent to die as a result of the act. Evidence that the individual intended to kill him- or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury.

Interrupted suicide attempt

When the person is interrupted (by an outside circumstance) from starting a potentially self-injurious act (if not for that, actual attempt would have occurred).

Aborted suicide attempt

When person begins to take steps toward making a suicide attempt, but stops before actually engaging in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops before being stopped by something else.

Preparatory acts toward imminent suicidal behaviors

This category can include anything beyond a verbalization or thought, but it stops short of a suicide attempt, an interrupted suicide attempt, or an aborted suicide attempt. This might include behaviors related to assembling a specific method (eg, buying pills, purchasing a gun) or preparing for one's death by suicide (eg, giving things away, writing a suicide note).

Self-Injurious Behavior Without Suicidal Intent

Self-injurious behavior associated with no intent to die. The behavior is intended purely for other reasons, either to relieve distress (often referred to as self-mutilation [eg, superficial cuts or scratches, hitting or banging, or burns]) or to effect change in others or the environment.