Official Title of Study:

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Phase 2 Study to Evaluate the Clinical Efficacy and Safety of BMS-986322 in Participants with Moderate-to-Severe Psoriasis

NCT Number: NCT05730725

Document Date (Date in which document was last revised): 29 Mar 2023

CLINICAL PROTOCOL IM032041

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Phase 2 Study to Evaluate the Clinical Efficacy and Safety of BMS-986322 in Participants with Moderate-to-Severe Psoriasis

Compound: BMS-986322

Brief Title:

Multiple Dose Study to Evaluate Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of BMS-986322 in Participants with Moderate-to-Severe Psoriasis

Protocol Amendment Number 01

Medical Monitor Name and Contact Information:

[redacted]
Clinical Trial Physician – Medical Monitor
Bristol-Myers Squibb Company
556 Morris Ave
Summit, NJ 07901
Phone: [redacted]
email: [redacted]

24-hr Emergency Telephone Number
USA: 1-866-470-2267
International: +1-248-844-7390

Sponsor Name and Legal Registered Address:

Bristol-Myers Squibb Company
Route 206 & Province Line Road
Lawrenceville, NJ 08543

Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

1-2-1 Otemachi, Chiyoda-ku
Tokyo, 100-0004, Japan

REGULATORY AGENCY IDENTIFIER NUMBER(S)

IND: 145913
EU CT: 2023-504848-34-00
UTN: U1111-1282-3606

DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Protocol Amendment 01	29-Mar-2023	The purpose of Protocol Amendment 01 is to update the European Union Clinical Trial number for this study.
Original Protocol	14-Oct-2022	Not applicable.

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:

The purpose of Protocol Amendment 01 is to update the European Union (EU) Clinical Trial (CT) number for this study and Sponsor address in Japan.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated the EU CT number and the Sponsor address in Japan.	Administrative changes.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title:

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Phase 2 Study to Evaluate the Clinical Efficacy and Safety of BMS-986322 in Participants with Moderate-to-Severe Psoriasis

Brief Title:

Multiple Dose Study to Evaluate Efficacy, Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of BMS-986322 in Participants with Moderate-to-Severe Psoriasis

Rationale:

Tyrosine kinase 2 (TYK2) catalyzes the phosphorylation of signal transducer and activator of transcription (STAT) proteins downstream of the receptors for the p40-containing cytokines interleukin (IL)-12 and IL-23 as well as the Type I interferon (IFN) receptor, resulting in the activation of STAT-dependent transcription and functional responses specific for these receptors.

TYK2-dependent receptors are distinct from those dependent on the Janus kinase (JAK)1/JAK3 (eg, receptors for IL-2, IL-15), JAK1/JAK2 pair (eg, IL-6, IFNγ), or JAK2/JAK2 (eg, erythropoietin, thrombopoietin, granulocyte macrophage colony-stimulating factor). A selective TYK2 inhibitor is expected to have a differentiated profile from inhibitors of other JAK family kinases.

IL-23 is critical in the expansion and survival of pathogenic TH17 cells as well as the induction of innate lymphoid cells in autoimmunity. Thus, IL-23 supports the production of key proinflammatory cytokines by TH17 cells including IL-17 and IL-22, which are effector molecules important for the pathogenesis of immune-mediated conditions such as psoriasis (PsO) and spondyloarthritidies. The receptor signaling pathways regulated by TYK2 play key roles in several immune-mediated disorders. IL-12 is essential for TH1 cell development and drives the production of IFNγ, a major effector molecule in dermatologic autoimmune disorders such as alopecia areata and vitiligo.

Type I IFNs impact many cell types and pathways important in autoimmunity including dendritic cell maturation and expression of major histocompatibility complex and costimulation molecules, B cell differentiation and antibody production, as well as T cell survival. All Type I IFNs act through a common receptor dependent on TYK2 signaling. Type I IFNs have also been implicated in the pathogenesis of PsO (including flares), dermatomyositis, interferonopathies, and systemic sclerosis.

In summary, inhibition of TYK2 impacts PsO through its effects on the IL-23/TH17/TH22 axis, IL-12-mediated TH1 functions, and Type I IFN-driven modulation of a number of immune activities.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare BMS-986322 with placebo on achieving a 75% reduction in PASI score (PASI-75)	• Proportion of participants achieving PASI-75 at Week 12
• To assess the safety and tolerability of BMS-986322	• Type and frequency of TEAEs, SAEs, and TEAEs leading to treatment discontinuation • Severity and causal relationship of TEAEs • Change from baseline and incidence of marked abnormalities in clinical laboratory tests, 12-lead ECG, vital signs, and physical examination
Secondary	
• To compare BMS-986322 with placebo on achieving an sPGA score of 0 ("cleared") or 1 ("minimal")	• Proportion of participants achieving sPGA score of 0 or 1 at Week 12
• To compare BMS-986322 with placebo on achieving a 50% reduction in PASI score (PASI-50)	• Proportion of participants achieving PASI-50 at Week 12
• To compare BMS-986322 with placebo on achieving a 90% reduction in PASI score (PASI-90)	• Proportion of participants achieving PASI-90 at Week 12
• To compare BMS-986322 with placebo on achieving a 100% reduction in PASI score (PASI-100)	• Proportion of participants achieving PASI-100 at Week 12
• To compare BMS-986322 with placebo on achievement of PASI-50, -75, -90, and -100 over time	• Proportion of participants achieving PASI-50, -75, -90, and -100 at various time points from baseline through Week 12
• To compare BMS-986322 with placebo on improvement of continuous PASI measurements over time	• Change from baseline in PASI score at various time points from baseline through Week 12
• To assess Cmax, AUC(TAU), Tmax, and trough concentrations of BMS-986322	• BMS-986322 trough concentrations at various time points through Week 12 • BMS-986322 Cmax, AUC(TAU), and Tmax on Day 15

Abbreviations: AUC(TAU), area under the plasma concentration-time curve over the dosing interval; Cmax, maximum observed plasma concentration; ECG, electrocardiogram; PASI, Psoriasis Area and Severity Index; SAE, serious adverse event; sPGA, static Physician's Global Assessment; TEAE, treatment-emergent adverse event; Tmax, time of maximum observed plasma concentration.

Overall Design:

This is a 12-week, multi-center, randomized, double-blind, placebo-controlled, parallel group, multiple oral dose Phase 2 study of BMS-986322 in participants with moderate-to-severe PsO. Participants will be randomly assigned to receive BMS-986322 (16 mg once daily [QD], 32 mg QD, or 64 mg QD) or placebo. Participants will undergo screening evaluations to determine eligibility within [redacted] days prior to administration of study intervention.

This will be an outpatient study. Participants will receive BMS-986322 and/or placebo tablets to be taken at home. Participants will be provided by the Investigator Site with enough tablets to cover the treatment interval between study visits beginning on Study Day [redacted]. Additional tablets covering the treatment interval between study visits should be supplied by the Investigator Site during each applicable follow-up visit. At follow-up visits (Days [redacted]), doses of BMS-986322 and/or placebo tablets will be administered in the clinic.

Participants will report to the clinic for study visits on Study Days [redacted], and for an Early Termination (ET) visit if needed.

[redacted]

Number of Participants:

Approximately 120 participants will be randomized and treated.

Assuming a screen failure rate of about 20%, it is estimated that approximately 150 screened participants will be required to achieve the planned 120 treated participants.

Study Population:

Key Inclusion Criteria:

- **Type of Participant and Target Disease Characteristics**
  - Male and female participants with a diagnosis of plaque PsO for ≥ 6 months.
  - Body mass index 18 to 40 kg/m^2 and total body weight > 50 kg (110 lbs).
  - Deemed by Investigator to be eligible for phototherapy or systemic therapy.
  - Psoriatic plaques must cover ≥ 10% of body surface area at baseline.

  - Psoriasis Area and Severity Index (PASI) score ≥ 12 and static Physician Global Assessment (sPGA) ≥ 3 at baseline.
  - Willing to discontinue topical and/or systemic therapies, with the exception of topical emollients and low potency topical steroids (rescue) prior to dosing.
- **Age of Participant**
  - Participant must be 18 to 70 years of age inclusive at the time of signing the informed consent form.

Key Exclusion Criteria:

- **Target Disease Exceptions**
  - Diagnosis of non-plaque PsO (guttate, inverse, pustular, erythrodermic).
  - Diagnosis of uveitis, inflammatory bowel disease, or other immune-mediated conditions that are commonly associated with PsO for which a participant requires current systemic (oral, subcutaneous, or intravenous) (including corticosteroids, biologics) immunosuppressant medical treatment. Certain therapies such as non-steroidal anti-inflammatory drugs may be permitted but should be discussed with the Sponsor Medical Monitor prior to determination of participant eligibility.

Intervention Groups and Duration:

Participants will be randomly assigned to receive BMS-986322 (16 mg QD, 32 mg QD, or 64 mg QD) or placebo. Participants will undergo screening evaluations to determine eligibility within [redacted] days prior to administration of study intervention.

Study Intervention:

Study Intervention for IM032-041		
Intervention Name	**Unit Dose Strength(s)**	**IP/IMP/Non-IP/ Non-IMP/AxMP**
BMS-986322-01	[redacted] mg	IMP Blinded
Placebo to Match BMS-986322-01	N/A	IMP Blinded

Abbreviations: AxMP, Auxiliary Medicinal Product; IMP, Investigational Medicinal Product; IP, Investigational Product; N/A, not applicable.

Statistical Methods:

Approximately 120 participants will be randomized in a 1:1:1:1 ratio to receive BMS-986322 (16 mg PO QD, 32 mg PO QD, or 64 mg PO QD) or placebo. Randomization will be stratified by use of previous treatment with a biologic (yes/no). Assuming a screen failure rate of about 20%, it

is estimated that approximately 150 screened participants will be required to achieve the planned 120 treated participants.

The primary objective of this study is to evaluate the response rate in PASI-75 after 12 weeks of treatment with BMS-986322. The response rate in PASI-75 is defined as the proportion of participants with moderate-to-severe PsO experiencing a 75% improvement (reduction from baseline) in PASI score at Week 12 (Day 85) and will be evaluated on the Full Analysis Set.

The safety and tolerability of BMS-986322 will be assessed by the type, frequency, relationship, severity, and seriousness of treatment-emergent adverse events (AEs), clinical laboratory tests, 12-lead electrocardiogram (ECG), vital signs, and physical examination (PE). Treatment-emergent AEs and study intervention-related AEs and SAEs will be summarized using counts and percentages of participants experiencing the event as well as the number of events by system organ class, preferred term, and treatment group. PE findings, vital signs, clinical laboratory test results, and ECG test results will be summarized using descriptive summary statistics for continuous variables and frequency distributions (counts and percentages) for categorical variables. All safety analyses will be performed on the Safety Analysis Set.

Data Monitoring Committee: Yes

An Independent Data Monitoring Committee will be used in the study.

Other Committee: No

Other committees will not be used in this study.

Brief Summary:

The purpose of this study is to compare the proportion of moderate-to-severe PsO participants achieving PASI-75 score (≥ 75% reduction from baseline in PASI) between treatment and placebo groups at Week 12. Study details include the following:

Study Duration: 16 weeks

Study Intervention Duration: 12 weeks

Study Visit Frequency: Participants will report to the clinic for study visits on study Days [redacted], and, if applicable, Early Termination.

2 SCHEDULE OF ACTIVITIES

The schedule of activities are outlined in Table 2-1 (Screening Procedural Outline), Table 2-2 ([redacted] Follow-up Procedural Outline), [redacted]

Table 2-1: Screening Procedural Outline

Procedure	Screening [redacted]	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed; informed consent must be obtained prior to performing any screening procedures. [redacted]
Inclusion/Exclusion Criteria	X	See Section 6.
Medical History	X	All medical history relevant to disease under study. Include findings from PE. Include any toxicities or allergy related to previous treatments. See Section 6.2 Exclusion Criteria for complete eligibility criteria associated with medical history.
Psoriasis-related History	X	Includes scalp symptoms, PsA/joint pain, nail involvement, palmoplantar involvement, genital involvement, history of other forms of psoriasis. See Section 3.
Demographics	X	Some data may be collected via electronic device. See Section 3.
Safety Assessments		
Complete PE	X	See Section 9.4.1.
Physical Measurements	X	Includes height, weight, and BMI.
Vital Signs	X	Includes (ear or oral) body temperature, respiratory rate, seated blood pressure, and seated heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Prior/Concomitant Medication Use	X	Concomitant medications should be reviewed and updated at each visit. See Section 7.7.
12-lead ECG	X	12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes. A single ECG will be collected. See Section 9.4.3.
Chest X-ray	X	Chest x-ray is required if not already performed within 6 months of obtaining written informed consent or if documentation is not on file. See Section 9.4.2.

Table 2-1: Screening Procedural Outline

Procedure	Screening [redacted]	Notes
Laboratory Tests		
Hematology	X	Complete blood count with differential. Participants are required to fast for at least 8 hours prior to the collection of specimens for clinical laboratory tests. See Section 9.4.8.
Chemistry	X	Participants are required to fast for at least 8 hours prior to the collection of specimens for clinical laboratory tests. See Section 9.4.8.
Creatinine Clearance	X	At screening only. See Section 9.4.8.
Serology	X	Serum for hepatitis C antibody, HBsAg, anti-hepatitis B core antibody, anti-HBsAb, HIV-1 and -2 antibody (HIV viral RNA or p24 antigen, if needed) at screening only. See Section 9.4.8.
Urinalysis	X	Participants are required to fast for at least 8 hours prior to the collection of specimens for clinical laboratory tests. See Section 9.4.8.
Test for Drugs of Abuse	X	Urine or serum. See Section 9.4.8.
Tuberculosis Test (Interferon-gamma Release Assay)	X	In accordance with BMS standard testing at screening only. See Section 9.4.2.
Pregnancy Test (Serum)	X	Female participant only (see Appendix 4). Serum (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) to be done at screening visit. The participant must be excluded from participation if the serum pregnancy result is positive.
FSH	X	If needed to document postmenopausal status, as defined in Appendix 4, at screening only. Females under the age of 55 years must have a serum FSH level > 40 mIU/mL to confirm menopause.
SARS-CoV-2 testing	X	PCR testing and other measures (eg, antibody testing, social distancing, temperature readings, personal protective equipment) that may be required by the site will be implemented.
Efficacy Assessments		
[redacted]		

Table 2-1: Screening Procedural Outline

Procedure	Screening [redacted]	Notes
PASI	X	See Section 9.1.3 and Appendix 5 for an illustrative example.
[redacted]		
AE Reporting		
Monitor for AEs and SAEs	X	All AEs and SAEs must be collected from the date of participant's written consent until 30 days following discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time. See Section 9.2 and Appendix 3.

Abbreviations: AE, adverse event; BMI, body mass index; BMS, Bristol-Myers Squibb Company; [redacted]; ECG, electrocardiogram; FSH, follicle-stimulating hormone; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; [redacted]; PASI, Psoriasis Area and Severity Index; PCR, polymerase chain reaction; PE, physical examination; PsA, psoriatic arthritis; [redacted]; RNA, ribonucleic acid; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; [redacted].

Table 2-2: [redacted] Follow-up Procedural Outline

Procedure[a]	[redacted]	Follow-up Visit	Notes
Safety Assessments			
Complete PE	X X X X X X X	X	See Section 9.4.1.
Weight	X X X X X X X	X	
Vital Signs	X X X X X X X	X	Includes (ear or oral) body temperature, respiratory rate, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
12-lead ECG	X X X X X X X	X	12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes. A single ECG will be collected. See Section 9.4.3.
Concomitant Medication Use	Continuously		Concomitant medications should be reviewed and updated at each visit. See Section 7.7.

Table 2-2: [redacted] Follow-up Procedural Outline

Procedure[a]	[redacted]	Follow-up Visit	Notes
Laboratory Tests			
Hematology	X[b]	X	Including complete blood count with differential. Participants are required to fast for at least 8 hours prior to the collection of specimens for clinical laboratory tests on Day [redacted], and ET. See Section 9.4.8.
Chemistry	X[b]	X	Participants are required to fast for at least 8 hours prior to the collection of specimens for clinical laboratory tests on Day [redacted], and ET. Fasting glucose and fasting C-peptide will only be taken on fasting days (Day [redacted], and ET). See Section 9.4.8.
hsCRP	X[b]	X	Participants are required to fast for at least 8 hours prior to the collection of specimens for clinical laboratory tests on Day [redacted], and ET. See Section 9.4.8.

Table 2-2: [redacted] Follow-up Procedural Outline

Procedure[a]	[redacted]	Follow-up Visit	Notes
Fasting Lipid Panel	X[b]	X	Participants are required to fast for at least 8 hours prior to the collection of specimens for clinical laboratory tests on Day [redacted], and ET. See Section 9.4.8.
Urinalysis	X[b]	X	Participants are required to fast for at least 8 hours prior to the collection of specimens for clinical laboratory tests on Day [redacted], and ET. See Section 9.4.8.
Test for Drugs of Abuse	X[b]		Urine or serum. See Section 9.4.8.
[redacted]			
Pregnancy Test (Urine)	X[b]	X	All women must have a negative pregnancy test prior to dosing on Day [redacted].
AE Reporting			
Monitor for AEs and SAEs	Continuously		All AEs and SAEs must be collected from the date of participant's written consent until 30 days following discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later

Table 2-2: [redacted] Follow-up Procedural Outline

Procedure[a]	[redacted]	Follow-up Visit	Notes
			time. See Section 9.2 and Appendix 3.
[redacted]			
Efficacy Assessments			
[redacted]			
PASI	X	X	See Section 9.1.3 and Appendix 5 for an illustrative example.
[redacted]			

Table 2-2: [redacted] Follow-up Procedural Outline

Procedure[a]	[redacted]	Follow-up Visit	Notes
[redacted]			
Study Intervention			
Randomization via IRT	X		See Section 7.2.
Dispense Study Intervention	X		BMS-986322 QD or Placebo QD (see Section 7).
Study Intervention Compliance		X	See Section 7.6.

a In the event that multiple procedures are required at a single time point, the following is the order in which the procedures should be performed, from first to last: [redacted], safety (ECG), safety (vital signs), [redacted], [redacted], safety (clinical laboratory assessments).

b Sample to be taken at predose.

[redacted]

Abbreviations: AE, adverse event; [redacted]; ECG, electrocardiogram; ET, Early Termination; hsCRP, high-sensitivity C-reactive protein; [redacted] IRT, Interactive Response Technology; [redacted]; PASI, Psoriasis Area and Severity Index; [redacted]; PE, physical examination; [redacted]; QD, once daily; SAE, serious adverse event; [redacted].

In the event that multiple procedures are required at a single time point, the following is the order in which the procedures should be performed, from first to last:

[redacted]

- Safety (electrocardiogram [ECG])
- Safety (vital signs)
- Pharmacokinetic (PK) sampling
- [redacted]
- Safety (clinical laboratory assessments)

When vital signs measurement or ECG recording coincide with a blood collection, they should preferably be performed before the blood collection, whenever possible. It is expected that every effort be made to collect PK samples at the times indicated in the protocol. However, for flexibility in PK sampling, the following windows serve as a guideline for PK sample collection:

[redacted]

To ensure PK [redacted] samples can be collected on time, the ECG and vital signs may be obtained ± 15 minutes from the nominal postdose time point. Clinical laboratory samples may be obtained ± 15 minutes from the nominal postdose time point.

3 INTRODUCTION

BMS-986322 is an oral tyrosine kinase 2 (TYK2) inhibitor with a highly selective mechanism of action that has the potential to safely and effectively treat a broad spectrum of immune-mediated diseases. TYK2 activates intracellular signal transducer and activator of transcription (STAT)-dependent transcription and functional responses downstream of receptors for critical immune mediators, such as interleukin (IL)-12, IL-23, and Type I interferons (IFNs).[1,2,3] These immune and inflammatory signaling pathways are critical in the pathophysiology of various immune-mediated diseases including psoriasis (PsO), lupus, spondyloarthritis, inflammatory bowel disease (IBD), dermatomyositis, and Type I interferonopathies.[4,5,6,7,8,9]

A comprehensive in vitro and in vivo characterization of BMS-986322 has been established and supports the testing of BMS-986322 in humans. [redacted]

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986322 is provided in the Investigator's Brochure (IB).[10]

PsO is a chronic inflammatory skin disorder, characterized primarily by erythematous scaly plaques, that affects up to 3% of the general population. Men and women are equally affected, and it can present at any age.[11,12] Several studies have observed a bimodal distribution of PsO 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.[13,14,15] The most common form of PsO (58% to 97%) is plaque PsO (PsO vulgaris), with less common forms being guttate, pustular, inverse (flexural), and erythrodermic PsO. The disease can have a fluctuating relapsing course with flares that may be induced by factors such as infections, trauma, smoking, and stress.[13] PsO 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. The scalp is the most commonly affected region of the body in PsO, involved in about 80% of PsO cases.[16] Scalp PsO represents one of the 'special sites,' given its difficult-to-treat nature and disproportionate impact on quality of life. PsO in general has a profound impact on quality of life and can lead to psychological, social, and economic consequences, especially in moderate-to-severe disease.[17,18] Additionally, scalp disease in particular is associated with pain, itching, and bleeding. It has been shown to be associated with a disproportionate impact on quality of life with significant impact on psychosocial impairment.

Effective management of scalp PsO is essential to improving a participant's quality of life.[16] The presence of hair and unacceptable cosmetic appeal of topical therapy are barriers to compliance and satisfaction with the currently available topical interventions. Topical regimens can be complex and are highly dependent on participant preference. Additionally, some participants with severe scalp disease may have minimal body involvement and, hence, may not receive systemic therapy indicated for moderate-to-severe chronic plaque PsO.[16,19,20]

Interventions include topical preparations (eg, corticosteroids, vitamin D analogues, calcineurin inhibitors, salicylic acid, urea, and coal tar), phototherapy modalities (including broad-band and narrow band ultraviolet B), and systemic therapies. In moderate-to-severe disease, systemic interventions 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-IL-12/23p40 antibody (ustekinumab), IL-17 antagonists (secukinumab, ixekizumab, and brodalumab), and anti–IL-23p19 antibody (guselkumab, tildrakizumab and risankizumab). Many of these interventions are associated with increased risk of adverse events (AEs) such as hepatotoxicity and neutropenia (methotrexate),[21] nephrotoxicity (cyclosporine),[22] depression and weight loss (apremilast),[23] serious infections (cytokine inhibitors),[24,25,26,27] and candidiasis and Crohn's disease (IL-17 antagonists).[27, 28, 29]

Although effective therapeutic options are available, undertreatment or nontreatment of PsO has been reported in up to half of surveyed participants (based on absence of intervention and/or dissatisfaction with intervention).[30] Only guselkumab, secukinumab, and apremilast have efficacy data for scalp PsO included in their Food and Drug Administration (FDA) label.[23,27,31] Scalp PsO presents considerable intervention challenges for the patient and practitioner. PsO of this site also contributes to a significant burden on participant quality of life.[16]

3.1 Study Rationale

TYK2 catalyzes the phosphorylation of STAT proteins downstream of the receptors for the p40-containing cytokines IL-12 and IL-23 as well as the Type I IFN receptor, resulting in the activation of STAT-dependent transcription and functional responses specific for these receptors.

TYK2-dependent receptors are distinct from those dependent on the Janus kinase (JAK)1/JAK3 (eg, receptors for IL-2, IL-15), JAK1/JAK2 pair (eg, IL-6, IFNγ), or JAK2/JAK2 (eg, erythropoietin, thrombopoietin, granulocyte macrophage colony-stimulating factor). A selective TYK2 inhibitor is expected to have a differentiated profile from inhibitors of other JAK family kinases.

IL-23 is critical in the expansion and survival of pathogenic TH17 cells as well as the induction of innate lymphoid cells in autoimmunity.[32,33] Thus, IL-23 supports the production of key proinflammatory cytokines by TH17 cells including IL-17 and IL-22, which are effector molecules important for the pathogenesis of immune-mediated conditions such as PsO and spondyloarthritidies. The receptor signaling pathways regulated by TYK2 play key roles in several immune-mediated disorders. IL-12 is essential for TH1 cell development and drives the production

of IFNγ, a major effector molecule in dermatologic autoimmune disorders such as alopecia areata and vitiligo.[34]

Type I IFNs impact many cell types and pathways important in autoimmunity including dendritic cell maturation and expression of major histocompatibility complex and costimulation molecules, B cell differentiation and antibody production, as well as T cell survival.[35,36,37,38,39] All Type I IFNs act through a common receptor dependent on TYK2 signaling. Type I IFNs have also been implicated in the pathogenesis of PsO (including flares), dermatomyositis, interferonopathies, and systemic sclerosis.[40,41,42,43,44]

Monoclonal antibodies directed against either the p19 subunit of IL-23 or the p40 subunit it shares with IL-12 have been clinically validated in autoimmune diseases including PsO, psoriatic arthritis (PsA), and Crohn's disease.[4,5] For example, ustekinumab (anti-p40 antibody) is approved for the treatment of plaque PsO and PsA and produces a 75% reduction in Psoriasis Area and Severity Index (PASI) score (PASI-75) at 12 weeks in approximately 70% of PsO participants versus < 5% of placebo control participants.[45]

Similarly, deucravacitinib, another selective TYK2 inhibitor, was highly effective in the treatment of PsO based on results of recently completed 52-week, randomized, Phase 3, placebo-controlled studies of deucravacitinib (BMS-986165) 6 mg daily versus placebo and apremilast 30 mg twice daily (BID) (POETYK PSO-1 and PSO-2).[46,47] In these 2 Phase 3 studies, in addition to achieving both co-primary clinical efficacy endpoints (PASI-75 and static Physician's Global Assessment [sPGA] 0/1), deucravacitinib also improved DLQI scores. More deucravacitinib-treated participants achieved ≥ 4-point improvement on DLQI meaningful change threshold (MCT ≥ 4) at Week 16 versus placebo-treated and apremilast-treated participants in PSO-1 (77.6% vs 43.4% and 68.8%, respectively) and PSO-2 (78.6% vs 44.9% and 69.3%).

Deucravacitinib, an oral, first in class, selective TYK2 inhibitor, has been approved by the US FDA for treating adults with moderate-to-severe plaque PsO who are candidates for systemic therapy or phototherapy.

In summary, inhibition of TYK2 impacts PsO through its effects on the IL-23/TH17/TH22 axis, IL-12-mediated TH1 functions, and Type I IFN-driven modulation of a number of immune activities.

3.2 Background

BMS-986322 binds to the pseudokinase domain of TYK2, stabilizing an inhibitory interaction between the pseudokinase and catalytic domains of the enzyme, the result of which is blockade of TYK2-mediated functions in vitro and in vivo. The compound is potent and highly selective, blocking responses in human cells induced by IL-12, IL-23, and Type I IFNs, including signal transduction, STAT-dependent gene transcription, and functional responses.

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986322 is provided in the IB.[10]

3.3 Benefit/Risk Assessment

At this early stage in the development of BMS-986322 for the treatment of patients with PsO, assessment of benefit and risk rely on nonclinical data and clinical study experience in healthy volunteers. The proposed dosing regimens reflect correlations between exposures, target engagement, and measures of efficacy in preclinical disease models, safety margins calculated from preclinical toxicology studies, and PK parameters as well as safety and tolerability results from a Phase 1 FIH study.

In the FIH Study IM032007, BMS-986322 was effective in inhibiting in vivo TYK2 activity.

[redacted]

3.3.1 Risk Assessment

Inhibition of TYK2-dependent immune responses by BMS-986322 has the potential to increase the risk of infections in humans. TYK2 inhibition affects multiple cytokine pathways (including IL-12, IL-23, and Type I IFN).

As BMS-986322 is a potential immunosuppressant and in line with standard practice for immunosuppressive therapies, the current study has been designed with study visits that allow for close monitoring and with inclusion/exclusion criteria aimed at minimizing the risk for serious infections.

As with any modulator of the immune system, there is a theoretical risk of increased malignancy with BMS-986322. BMS-986322 was not found to be genotoxic during in vitro and in vivo preclinical studies. Carcinogenicity studies with BMS-986322 have not yet been conducted.

[redacted]

3.3.1.1 Coronavirus Disease 2019-related Risks and Risk Mitigation Measures

Whether BMS-986322 increases the risk for contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or increases the severity or duration of symptoms is currently unknown due to insufficient clinical data. This unknown risk must be considered when enrolling a participant.

Participants with recent or acute infections will have the start of intervention delayed or be excluded as defined in Section 6. If a participant has a confirmed SARS-CoV-2 infection while on study intervention, dose discontinuation is required as described in Section 8.1.

The study includes several features to mitigate this risk of BMS-986322 exposure during active SARS-CoV-2 infection:

- The study entry criteria that exclude participants with recent or active infections (see Section 6.2).
- The clinical research unit has implemented standard monitoring and prevention control measures for risk mitigation.
- The protocol implements SARS-CoV-2 testing (see Section 2), as stipulated by the clinical site at which the study is being conducted, in order to prevent participants who are shedding the virus from entering into the research unit and from being dosed with BMS-986322.

3.3.1.2 General COVID-19-related Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with clinical research site's monitoring and prevention control procedures and relevant governmental and Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-associated requirements. Such measures aim to minimize the prevalence and transmission of SARS-CoV-2 among site staff and participants, and include distancing, sanitization, testing, and the use of personal protective equipment. The risk mitigation measures are part of the research site's generic informed consent and, when and where applicable, may be amended based on emerging guidance.

3.3.2 Benefit Assessment

Inhibition of TYK2 is expected to provide therapeutic benefit for participants with PsO 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) are involved in the pathogenesis of PsO.[48] 2) Biologic agents targeting the IL-17, IL-23p19, and IL-12/23 p40 pathways have been approved for and are highly efficacious in the treatment of PsO. Further, participants with PsO may sustain a durable therapeutic response after repeated dosing with BMS-986322. A recent study using only a single dose of a monoclonal antibody targeting the IL-23 p19 subunit resulted in rapid and sustained response for up to 66 weeks in participants with moderate-to-severe PsO.[49] Similarly, deucravacitinib, another selective TYK2 inhibitor, was highly effective in the treatment of PsO.[46,47]

Based on its mechanism of action as an inhibitor of TYK2-mediated signaling pathways downstream of well-characterized pharmaceutical targets for the treatment of PsO, the p19 subunit of IL-23 or the p40 subunit it shares with IL-12, and the demonstration of extended inhibition of IL-23 signaling in healthy participants (clinical study IM0032007), it is likely that participants with moderate-to-severe PsO will benefit from the treatment with BMS-986322.

3.3.3 Overall Benefit/Risk Conclusion

In summary, existing preclinical data (see the IB[10] or toxicology data) and clinical experience in healthy participants in combination with the design and doses selected for the current Phase 2 study indicate an overall favorable benefit/risk assessment of investigating BMS-986322 as an oral treatment of participants with moderate-to-severe PsO.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of BMS-986322 may be found in the IB.[10]

4 OBJECTIVES AND ENDPOINTS

To examine the effects of BMS-986322 16 mg, 32 mg, and 64 mg, when orally (PO) administered once daily (QD), compared with placebo, after 12 weeks of treatment in participants with moderate-to-severe PsO, the following objectives and endpoints as outlined in Table 4-1 will be assessed.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare BMS-986322 with placebo on achieving a 75% reduction in PASI score (PASI-75)	• Proportion of participants achieving PASI-75 at Week 12
• To assess the safety and tolerability of BMS-986322	• Type and frequency of TEAEs, SAEs, and TEAEs leading to treatment discontinuation • Severity and causal relationship of TEAEs • Change from baseline and incidence of marked abnormalities in clinical laboratory tests, 12-lead ECG, vital signs, and physical examination
Secondary	
• To compare BMS-986322 with placebo on achieving an sPGA score of 0 (“cleared”) or 1 (“minimal”)	• Proportion of participants achieving sPGA score of 0 or 1 at Week 12
• To compare BMS-986322 with placebo on achieving a 50% reduction in PASI score (PASI-50)	• Proportion of participants achieving PASI-50 at Week 12
• To compare BMS-986322 with placebo on achieving a 90% reduction in PASI score (PASI-90)	• Proportion of participants achieving PASI-90 at Week 12
• To compare BMS-986322 with placebo on achieving a 100% reduction in PASI score (PASI-100)	• Proportion of participants achieving PASI-100 at Week 12
• To compare BMS-986322 with placebo on achievement of PASI-50, -75, -90, and -100 over time	• Proportion of participants achieving PASI-50, -75, -90, and -100 at various time points from baseline through Week 12
• To compare BMS-986322 with placebo on improvement of continuous PASI measurements over time	• Change from baseline in PASI score at various time points from baseline through Week 12
• To assess Cmax, AUC(TAU), Tmax, and trough concentrations of BMS-986322	• BMS-986322 trough concentrations at various time points through Week 12 • BMS-986322 Cmax, AUC(TAU), and Tmax on Day 15
[redacted]	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Abbreviations: AUC(TAU), area under the plasma concentration-time curve over the dosing interval; [redacted] Cmax, maximum observed plasma concentration; [redacted]; ECG, electrocardiogram; [redacted] PASI, Psoriasis Area and Severity Index; [redacted]; [redacted]; [redacted]; SAE, serious adverse event; sPGA,

static Physician's Global Assessment; TEAE, treatment-emergent adverse event; Tmax, time of maximum observed plasma concentration.

5 STUDY DESIGN

5.1 Overall Design

This is a 12-week, multi-center, randomized, double-blind, placebo-controlled, parallel group, multiple oral dose Phase 2 study of BMS-986322 in participants with moderate-to-severe PsO. Participants will be randomly assigned to receive BMS-986322 (16 mg QD, 32 mg QD, or 64 mg QD) or placebo. Participants will undergo screening evaluations to determine eligibility within [redacted] days prior to administration of study intervention.

This will be an outpatient study. Participants will receive BMS-986322 and/or placebo tablets to be taken at home. Participants will be provided by the Investigator Site with enough tablets to cover the treatment interval between study visits beginning on Study Day [redacted]. Additional tablets covering the treatment interval between study visits should be supplied by the Investigator Site during each applicable follow-up visit. At follow-up visits (Days [redacted]), doses of BMS-986322 and/or placebo tablets will be administered in the clinic (see Section 2).

Participants will report to the clinic for study visits on Study Days [redacted] and for an Early Termination (ET) visit if needed.

Physical examinations (PEs), clinical disease activity assessments (PASI, [redacted], sPGA), vital sign measurements, PK evaluations, clinical laboratory evaluations, ECG, [redacted] evaluations will be performed at selected times throughout the dosing interval. AEs will be recorded and assessed by the Investigator (or designee as documented in the Delegation of Authority) at study visits and throughout the study period. Participants will be required to return to the clinic for additional (unscheduled) safety follow-up visits as deemed necessary by the investigator.

[redacted]

5.1.1 Data Monitoring Committee and Other Committees

The Independent Data Monitoring Committee (IDMC) charter will describe the procedures related to the committee operations in greater detail.

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of participants enrolled in this study, to ensure the integrity of the blinded nature of the study, [redacted]. An IDMC charter will be developed that will specify the roles and responsibilities of the members and interim decision rules. Sponsor Steering Committee will receive and act on the recommendations from the IDMC. A firewall will be established to ensure the maintenance of the study blind for the Sponsor, the investigational site staff, and study participants and their study partners.

Data summaries and listings will be provided to the IDMC to facilitate their safety assessment at the regularly scheduled times and on an ad hoc basis if needed. The safety review includes SAEs and events of special interest, focusing on early signal detection. Further details on the frequency, content, and methods of data reports to the IDMC will be outlined in the IDMC Charter along with the processes and procedures the committee will follow.

5.2 Number of Participants

Approximately 120 participants will be randomized and treated.

Assuming a screen failure rate of about 20%, it is estimated that approximately 150 screened participants will be required to achieve the planned 120 treated participants.

5.3 End of Study Definition

The start of the study is defined as the first participant's first visit.

The primary completion date is defined as the date on which the last data point is collected for the study's primary endpoint. If the study has multiple primary endpoints, the primary completion date is the date on which the last data point is collected for the last primary endpoint.

End of study is defined as the last participant's last visit.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last procedure/assessment shown in the Schedule of Activities.

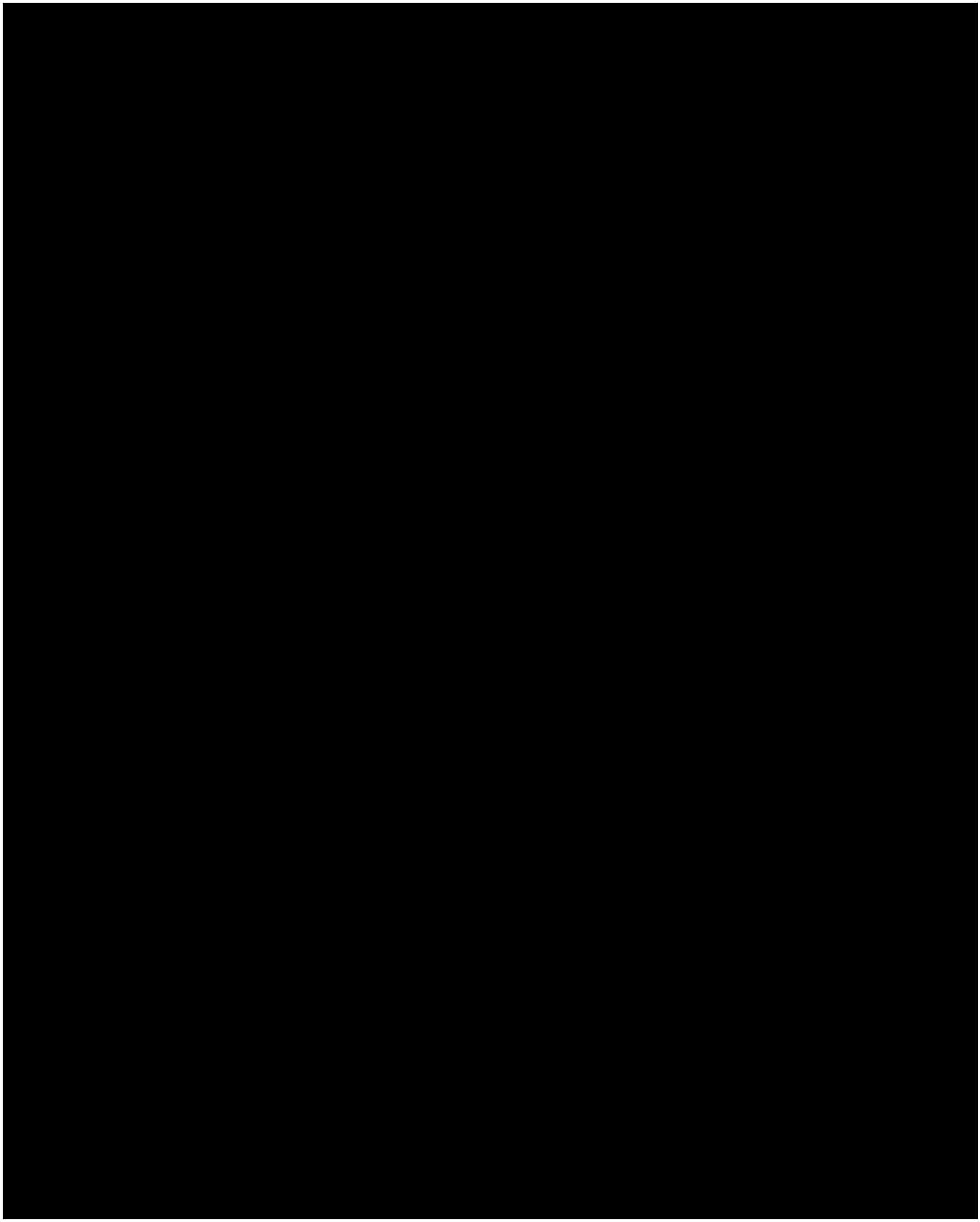
5.4 Scientific Rationale for Study Design

The proposed Phase 2 study in participants with PsO is being conducted to provide safety data and evidence of clinical efficacy of BMS-986322 in a relevant disease population, [redacted] Psoriasis is an ideal condition to evaluate the safety and efficacy of the TYK2 inhibitor BMS-986322 for multiple reasons. 1) Many of the pathways in the TYK2 signaling cascade (IFNα, IL-12/-23, and the downstream mediators IL-17 and IL-22) have been implicated in psoriatic disease pathogenesis. 2) Biologic agents targeting the IL-17, IL-23p19, and IL-12/-23 p40 pathways are currently available and highly effective in the treatment of PsO. 3) The use of deucravacitinib, another selective TYK2 inhibitor, was highly effective in the treatment of moderate-to-severe PsO.[46,47,52] 4) Psoriasis is a prevalent systemic inflammatory condition, yet some patients remain untreated or undertreated. This allows for evaluation of drug safety and efficacy without interactions from multiple background therapies. [redacted]

Deucravacitinib, an oral, first in class, selective TYK2 inhibitor, has been approved by the US FDA for treating adults with moderate-to-severe plaque PsO who are candidates for systemic therapy or phototherapy.

In this study, data will be collected from participants such as race, ethnicity, sexual orientation, and gender/gender they identify with. Participation in the main study is not contingent upon providing responses to race, ethnicity, sexual orientation, or gender identity questions.

[redacted]



6 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

a) Participants must have signed and dated an IRB-/IEC-approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

2) Type of Participant and Target Disease Characteristics

a) Male and female participants with a diagnosis of plaque PsO for ≥ 6 months.

b) Body mass index (BMI) 18 to 40 kg/m^2 and total body weight > 50 kg (110 lbs).

c) Deemed by Investigator to be eligible for phototherapy or systemic therapy.

d) Psoriatic plaques must cover ≥ 10% of BSA at baseline.

e) PASI score ≥ 12 and sPGA ≥ 3 at baseline.

f) Willing to discontinue topical and/or systemic therapies, with the exception of topical emollients and low potency topical steroids (rescue) prior to dosing.

3) Age of Participant

a) Participant must be 18 to 70 years of age inclusive at the time of signing the ICF.

4) Reproductive Status

- Investigators shall counsel women of childbearing potential (WOCBP) (as defined in Appendix 4) participants, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy.
- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants:

i) Female participants must have documented proof that they are not of childbearing potential.

(1) Women who are not of childbearing potential (as defined in Appendix 4) are exempt from contraceptive requirements.

ii) WOCBP must have a negative highly sensitive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study intervention.

- Additional requirements for pregnancy testing during and after study intervention are in Section 2: Schedule of Activities.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to potentially decrease the risk for inclusion of a woman with an undetected pregnancy.

iii) WOCBP and male participants who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception as described below and included in the ICF.

- WOCBP are not permitted to use hormonal contraception methods alone as a highly effective method (as described in Appendix 4).

iv) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP
OR

(2) Is a WOCBP and using at least a non-hormonal contraceptive method that is highly effective (ie, intrauterine device), AND another highly effective user independent method (ie, vasectomized partner, sexual abstinence), or a less than highly effective non-hormonal contraceptive method (ie, male or female condom,

diaphragm with spermicide, cervical cap with spermicide, vaginal sponge spermicide) during the intervention period and for at least 5 days after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same period. Definitions are provided in Appendix 4.

b) Male Participants:

i) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

ii) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant or breastfeeding. Male participants should continue to use a condom during the intervention period and for at least 5 days after the last dose of study intervention.

iii) Female partners of male participants should be advised to use a highly effective method of contraception during the intervention period and for at least 5 days after the last dose of study intervention for the male participant.

iv) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral), even if the participant has undergone a successful vasectomy, during the intervention period and for at least 5 days after the last dose of study intervention.

v) Male participants must refrain from donating sperm during the intervention period and for at least 5 days after the last dose of study intervention.

vi) Breastfeeding partners of male participants should be advised to consult their health care provider about using appropriate highly effective contraception during the time the male participant is required to use condoms.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1) Target Disease Exceptions

a) Diagnosis of non-plaque PsO (guttate, inverse, pustular, erythrodermic).

b) Diagnosis of uveitis, inflammatory bowel disease, or other immune-mediated conditions that are commonly associated with PsO for which a participant requires current systemic (oral, subcutaneous, or intravenous [IV]) (including corticosteroids, biologics) immunosuppressant medical treatment. Certain therapies such as non-steroidal anti-inflammatory drugs may be permitted but should be discussed with the Sponsor Medical Monitor prior to determination of participant eligibility.

2) Infectious/Immune-related Exclusions

a) History or evidence of active infection and/or febrile illness within 7 days of screening (eg, bronchopulmonary, urinary, gastrointestinal, etc).

b) History of serious bacterial, fungal, or viral infections that led to hospitalization and IV antibiotic treatment within 90 days prior to screening, or any recent serious infection requiring antibiotic treatment within 30 days of Study Day [redacted].

c) History of administration of live vaccines within 60 days prior to Day [redacted], or plans to receive a live vaccine during the study, or within 60 days after completing study intervention.

d) Immunization with non-live vaccines (including COVID-19) within 1 month prior to dosing or planning to receive immunization with a non-live vaccine within 21 days following dosing.

e) Has a history of an infected joint prosthesis or has received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.

f) Active herpes infection, including herpes simplex 1 and 2 and herpes zoster (demonstrated on PE and/or medical history within 2 months of administration of study intervention).

g) History of disseminated or complicated herpes zoster infection (including, but not limited to, multi-dermatomal involvement, ophthalmic zoster, central nervous system involvement, or post-herpetic neuralgia).

h) Positive hepatitis B virus (HBV) surface antigen (HBsAg) or HBV DNA by polymerase chain reaction (PCR).

i) Positive hepatitis-C virus (HCV) antibody.

j) Active COVID-19 infection as documented by a positive SARS-CoV-2 antigenic test or PCR test prior to dosing, regardless of signs or symptoms, and post-acute SARS-CoV-2 infection sequelae that may be configured as chronic medical illness (as in Exclusion Criterion 4a).

3) Participants with any history or risk for tuberculosis (TB), specifically participants with the following:

a) Current clinical radiographic or laboratory evidence of active TB.

b) History of active TB up to 10 years, unless there is documentation that prior anti-TB treatment was appropriate in duration and type according to current World Health Organization Guidelines.

c) Latent TB defined as Positive Quantiferon G or other diagnostic test in the absence of clinical manifestations, unless participant has received at least 1 month of treatment with isoniazid, or other agents recommended by local Health Authority guidelines, and an interferon gamma release assay (IGRA) test (eg, Quantiferon G or T-spot) is negative before Day [redacted].

d) Any history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the participant's immune status (eg, history of splenectomy, primary immunodeficiency, human immunodeficiency virus [HIV] infection, etc).

4) Medical History and Concurrent Diseases

a) Any significant acute or chronic medical illness.

b) Any major surgery (ie, requiring anesthesia, intubation and penetration in body cavities) within 4 weeks of study intervention administration.

c) Blood transfusion within 4 weeks of study intervention administration.

d) Recent (within 6 months of study intervention administration) drug or alcohol abuse as determined by the Investigator.

e) Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic, or local active infection/infectious illness) that, in the Investigator's judgment will substantially increase the risk to the participant if he or she participates in the study.

f) Has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months.

g) Class III or IV congestive heart failure by New York Heart Association Criteria.

h) Has been hospitalized in the past 3 months for asthma, ever required intubation for treatment of asthma, currently require oral corticosteroids for the treatment of asthma, or required more than one short-term (≤ 2 weeks) course of oral corticosteroids for asthma within the previous 6 months.

i) History of cancer (solid organ or hematologic including myelodysplastic syndrome) or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell or squamous cell carcinoma that has been treated with no evidence of recurrence).

j) Inability to tolerate oral medication.

k) Inability to be venipunctured and/or tolerate venous access.

[redacted]

u) Is currently receiving lithium, antimalarials, or has received lithium, antimalarials within 4 weeks of the first administration of study intervention.

[redacted]

5) Reproductive Status

a) Women who are breastfeeding.

b) Women who have a positive serum pregnancy test result at screening.

6) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7: Concomitant Therapy.

7) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in PE, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population.

b) Urinalysis findings suspicious of infection (eg, pyuria, bacteriuria) in a non-contaminated sample collected at screening. Participants may be rescreened and if deemed eligible, may be randomized within 14 days of completing an appropriate course of antibiotic treatment for urinary tract infection.

c) Chest x-ray findings suspicious of infection at screening. Participants may be rescreened if deemed eligible and may be randomized within [redacted] days of completing an appropriate course of antibiotic treatment for pulmonary infection.

d) Leukopenia defined as absolute white blood cell count < 3000/mm^3 within [redacted] days of dosing with study intervention on Day [redacted].

e) Lymphopenia defined as absolute lymphocyte count < 500/mm^3 within [redacted] days of dosing with study intervention on Day [redacted].

f) Neutropenia defined as absolute neutrophil count < 1000/mm^3 within [redacted] days of dosing with study intervention on Day [redacted].

g) Moderate-to-severe thrombocytopenia defined as platelet count < 100,000/mm^3 within [redacted] days of dosing with study intervention on Day [redacted].

h) Moderate-to-severe anemia defined as hemoglobin < 9 g/dL within [redacted] days of dosing with study intervention on Day [redacted].

i) Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3× upper limit of normal (ULN) within [redacted] days of dosing with study intervention on Day [redacted].

j) Total, unconjugated, and/or conjugated bilirubin > 1.5× ULN within [redacted] days of dosing with study intervention on Day [redacted].

k) Any other significant laboratory or procedure abnormalities that, in the opinion of the Investigator, might place the participant at unacceptable risk for participation in this study.

l) Positive blood screen for hepatitis C antibody, HBsAg, or HIV-1 and -2 antibody.

8) Allergies and Adverse Drug Reactions

a) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

9) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required.)

b) Inability to comply with restrictions as listed in Section 6.3: Lifestyle Restrictions.

c) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

d) Participation in another clinical trial concurrent with this study.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Participants are advised to protect against sun exposure through sun avoidance, use of protective clothing (long sleeves, pants, hats, etc), and use of sunscreen from at least 1 week prior to the first dose of study intervention until the safety follow-up visit. Participants should avoid excessive sun exposure or use of tanning booths or other ultraviolet light sources and avoid risks that are known to provoke flare of psoriasis.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs) that occurred following consent.

6.4.1 Re-testing During Screening

This study permits the re-enrollment of a participant who has discontinued the study as a screen failure (ie, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented.

Re-testing of laboratory parameters and/or other assessments within any single screening or lead-in period will be permitted once (in addition to any parameters that require a confirmatory value).

The most current result prior to randomization is the value by which study inclusion will be assessed because it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline, may be repeated in an effort to find all possible well-qualified participants. Consultation with the Sponsor Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, procedure(s), or medical device intended to be administered to a study participant according to the study protocol.

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1-1.

An IP, also known as an 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 from the authorized form, 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 preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis may be considered Non-IMPs/AxMPs.

7.1 Study Interventions Administered

Participants will receive BMS-986322 and/or placebo tablets to be taken at home. Participants will be provided by the Investigator Site with enough tablets to cover the treatment interval between study visits beginning on Study Day [redacted]. Additional tablets covering the treatment interval between study visits should be supplied by the Investigator Site during each applicable follow-up visit. At follow-up visits (Days [redacted]), doses of BMS-986322 and/or placebo tablets will be administered in the clinic (see Section 2).

In the morning of visits on Days [redacted] (Table 2-2), each participant will receive a single oral dose of BMS-986322 and/or placebo at approximately 9:00 AM. Participants will be required to fast for at least 8 hours prior to study visit on Days [redacted].

At the time of dosing, 240 mL of water will be administered to the participant along with his/her dose of study intervention. The time of dose administration will be called "0" hour.

Table 7.1-1: Study Intervention(s) Administered

Type/ Intervention Name/Dose Formulation	Unit Dose Strength(s)	IMP/Non-IMP/AxMP Blinded or Open-label Use	Sourcing	Packaging and Labeling	Current/ Former Name(s) or Alias(es)	Storage Conditions (Per Label)
BMS-986322-01	[redacted] mg	IMP Blinded	Provided centrally by the Sponsor	Study interventions will be provided in bottles [redacted]	BMS-986322-01	Refer to the label on the container and/or Pharmacy Manual.
Placebo to Match BMS-986322-01	N/A	IMP Blinded	Provided centrally by the Sponsor	Study interventions will be provided in bottles [redacted]	BMS-986322-01	Refer to the label on the container and/or Pharmacy Manual.

Abbreviations: AxMP, Auxiliary Medicinal Product; IMP, Investigational Medicinal Product; N/A, not applicable.

Table 7.1-2: Study Arm(s)

Arm Title/ Arm Type	[redacted]	Route of Administration
Placebo		Oral
16 mg BMS-986322		Oral
32 mg BMS-986322		Oral
64 mg BMS-986322		Oral

The BMS-986322 tablets (active or placebo) are provided in a kit [redacted]

7.2 Assignment to Study Intervention

All participants will be centrally randomized using Interactive Response Technology (IRT). Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

During the screening visit, the investigative site will call into the enrollment option of the IRT designated by Bristol-Myers Squibb Company (BMS) for assignment of a participant number that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted] Sequential numbering may restart at [redacted] for each participating site as the distinct participant identification number (PID) will ultimately be composed of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number [redacted] will have a PID of [redacted].

Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to randomize the participant. Randomization numbers will be assigned prior to dosing. Participants will be randomized to receive either BMS-986322 at one of the doses being evaluated (16 mg PO QD, 32 mg PO QD, 64 mg PO QD) or placebo according to a computer-generated randomization scheme prepared by an IRT Manager within the Drug

Supply Management Department of BMS Research and Development. Randomization will be stratified by previous treatment with a biologic (yes/no). Block randomization with fixed block size per stratum will be employed in this study.

Study intervention will be dispensed at the study visits listed in the Schedule of Activities (Section 2).

Participants will not be replaced if they are discontinued from the study secondary to an AE unless the AE can be determined to be unrelated to treatment. If a participant is replaced after dosing, then the replacement participant will be assigned the original participant's number plus [redacted]. The replacement participant will receive the same treatment as the participant being replaced, but a new randomization number will be assigned to him/her. For example, Participant [redacted] would be replaced by Participant data [redacted].

7.3 Blinding

This is a randomized, double-blind, placebo-controlled study. Blinded intervention assignments will be managed using IRT. IP supply will be controlled by IRT at each visit. Access to treatment codes will be restricted from all site and Sponsor personnel and participants prior to database lock for the final analysis with exceptions as specified below. Treatment codes may be shared with sites and participants after finalization of the CSR.

Randomization schedules will be shipped directly to a pharmacist or other individual(s) who will be responsible for the dispensing of blinded study intervention. This (these) individual(s) will be unblinded to study intervention identification but will not be involved in any other aspect of study conduct. The randomization schedules will be maintained in a secure location with access limited to authorized personnel.

Blinding of study intervention assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining whether a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary (ie, that it will alter the participant's immediate management). In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving the IP. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual task of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only perform the emergency unblinding after the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is IRT.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to minimize additional disclosure and the impact of unblinding.

Any request to unblind a participant for non-emergency purposes should be discussed with the Medical Monitor.

If a participant is unblinded for any reason, the participant will be discontinued from study intervention.

In case of an emergency, the investigator(s) has unrestricted access to randomization information via the IRT system and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. Following the unblinding, the investigator shall notify the Sponsor Medical Monitor or designee that the unblinding took place as soon as possible.

A scientist in the Non-clinical Disposition and Bioanalysis department or the Sponsor (and/or a designee in the external bioanalytical laboratory) will be unblinded to the randomized treatment assignments to minimize unnecessary bioanalytical analysis of samples. Any results shared by the Non-clinical Disposition and Bioanalysis group with the Sponsor's study team will be blinded to ensure integrity of the study.

Blind break (IRT)	The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining whether unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment unless doing so could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.
Blinded study with unblinded site pharmacist who is dispensing drug	Participants will be randomly assigned in a 1:1:1:1 ratio to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense study intervention following randomization. This third party will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study intervention with the investigator. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

Abbreviations: CRF, Case Report Form; IRT, Interactive Response Technology.

7.4 Dosage Modification

There is no provision for dose modification of study intervention. If a participant interrupts intervention due to an AE, study intervention can be restarted in consultation with the Sponsor Medical Monitor or designee.

7.5 Preparation/Handling/Storage/Accountability

The IP/Non-IMP/AxMP must be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, to ensure that IP/IMP/Non-IMP/AxMP is only dispensed to study participants. The IP/IMP/Non-IMP/AxMP must be dispensed only from official study sites by authorized personnel according to local regulations.

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

Study intervention not supplied by the Sponsor will be stored in accordance with the package insert.

IP/IMP/Non-IMP/AxMP documentation (whether supplied by the Sponsor or not) must be maintained and must include all processes required to ensure the 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).

- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition of records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

7.6 Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets, etc during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded in the Case Report Form (CRF).

A record of the quantity of BMS-986322/placebo dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records.

Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study intervention administration in the study are described below in Table 7.7.1-1. Medications taken within 4 weeks prior to study intervention administration must be recorded on the CRF.

Table 7.7.1-1: Prohibited and/or Restricted Treatments

Prohibited Treatments	**Washout Period (Before Randomization)**
[redacted]	
Lithium, antimalarials	4 weeks
[redacted]	
Metformin or statins	Restrict dose of metformin to 500 mg twice a day or 850 mg once a day with plasma lactate monitoring or switch to other glucose-lowering agents; restrict dose of statins as follows:

Table 7.7.1-1: Prohibited and/or Restricted Treatments

Prohibited Treatments	Washout Period (Before Randomization)
	atorvastatin (≤ 20 mg) rosuvastatin (≤ 10 mg) simvastatin (≤ 20 mg) Pravastatin (≤ 20 mg) lovastatin (≤ 20 mg) Fluvastatin (≤ 40 mg) pitavastatin (≤ 2 mg)

Abbreviations: [redacted];

[redacted] Therefore, drugs that are sensitive substrates of these transporters are recommended to be used with caution or their dose restricted for the duration of the study. Additional references[54,55] and individual drug labels should be referred to for further information on PK drug-drug interactions.

In addition, the use of concomitant medications (prescription, over-the-counter) should be limited during the study unless they are prescribed by the investigator for treatment of specific clinical events and after consultation with the Sponsor Medical Monitor. Any changes to or new concomitant therapies must be recorded on the CRF.

The use of herbal products is prohibited during and up to 30 days after the completion of the study.

7.7.2 Other Restrictions and Precautions

See Section 6.3 for details regarding sun exposure restrictions.

7.8 Continued Access to Study Intervention After the End of the Study

At the end of the study, the Sponsor will not continue to provide Sponsor-supplied study intervention to participants/investigators unless the Sponsor chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

The Sponsor reserves the right to terminate access to Sponsor-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986322 is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; or c) the participant can obtain medication from a government-sponsored or other health program. In all cases, the Sponsor will follow local regulations.

8 DISCONTINUATION CRITERIA

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 2.

8.1 Discontinuation of Study Intervention

Participants MUST discontinue IP/IMP (and Non-IMP/AxMP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.
- Any clinical AE, laboratory test result 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 participant.
- Termination of the study by the Sponsor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness (eg, infectious disease). (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required.)
- Significant noncompliance with protocol (eg, procedures, assessments, medications, etc). The investigator should discuss such issues with the Sponsor Medical Monitor.
- Any current evidence of SARS-CoV-2 infection.
- If a participant is unblinded for any reason.
- Permanent discontinuation of the study intervention for abnormal liver tests should be considered by the Investigator when a participant meets one of the conditions outlined in Section 9.2.7 or if the Investigator believes that it is in best interest of the participant.
- Pregnancy (see Section 9.2.5).

Refer to the Section 2: Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All participants who discontinue study intervention should comply with protocol-specified follow-up procedures as outlined in Section 2: Schedule of Activities. The only exception to this requirement is when a participant withdraws consent for all study procedures, including post-treatment study follow-up, or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study intervention is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.1.1 Post-study Intervention Study Follow-up

Participants who discontinue study intervention may continue to be followed.

8.2 Discontinuation From the Study

Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up.
- The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant 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 participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an ET visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from both the study intervention and the study at that time. No follow-up visit will be performed where a participant withdraws consent.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.2 Study Termination for Unexpectedly Unfavorable Risk/Benefit Balance

The DMC will evaluate the risk/benefit profile of the study on an ongoing basis. This evaluation will be based on all available unblinded data with particular attention to: (1) AEs or other safety trends in this or any other clinical study of BMS-986322 whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; (2) new nonclinical data suggesting unreasonable and significant risk of illness or injury. In addition, the Sponsor will evaluate the blinded data on an ongoing basis for unexpected/unusual safety findings/signals and increases in PsO disease activity and/or discontinuations not anticipated in a clinical trial of similar participant populations. Any concerns

will be escalated promptly to the DMC for further evaluation. [redacted]

If such evaluation suggests that the risk/benefit profile of the study or an individual dose group has become unfavorable to the study participants, the Sponsor will pause enrollment and/or dosing until further assessment of data and interaction with the appropriate Health Auhtority(ies) can take place on potential actions. Such actions may include, but are not limited to, study continuation without change, continuation with modification, or termination of the study.

8.3 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails, as well as lack of response by participant to **1** registered mail letter. All attempts should be documented in the participant's medical records.
- If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data, such as public health registries and databases, 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, to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities, see Section 2.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities (see Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a

screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, complete blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the time frame defined in the Schedule of Activities, see Section 2.
- 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.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- As part of the online questionnaire, the study sponsor may collect and use information about the gender that participants identify with, sexual orientation, and intersex status. At the conclusion of the study, summaries of this information, including information already collected about race, ethnicity, and gender, across all study participants will be developed to understand the populations that participated in the study. In addition, in the future, this data may be combined with data from other BMS studies to conduct subsequent research on how the disease or treatment impacts certain populations. Answering the questions about the gender you identify with, sexual orientation, and intersex status is voluntary, and participants are not required to answer these questions in the questionnaire to take part in this clinical study.

9.1 Efficacy Assessments

9.1.1 Efficacy Assessment for the Study

Every effort must be made to ensure that the same evaluator(s) complete the assessment for each participant. If the evaluator(s) is/are 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.

Baseline assessments must be performed per protocol (standard of care assessments may not be used for baseline). 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 electronic CRF (eCRF).

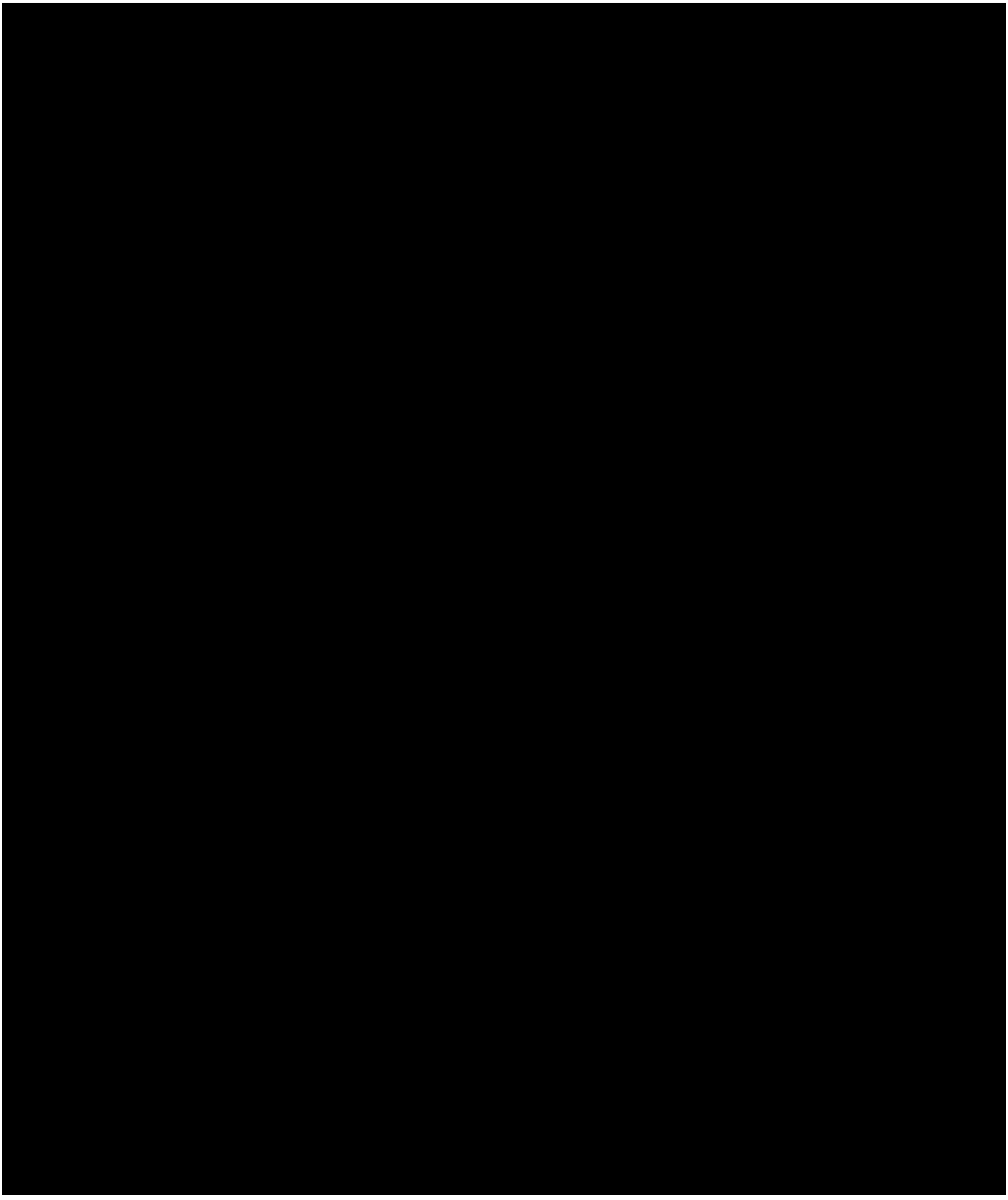
[redacted]

[redacted]

9.1.3 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).[59] The PASI produces a numeric score that can range from 0 to 72, with higher PASI scores denoting more severe disease activity. PASI can also be used to assess response to treatment. The PASI-50 is the proportion of participants who experience at least a 50% improvement in PASI score as compared with 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. PASI assessments should be performed by a dermatologist or appropriately trained investigator who is experienced in the assessment of PsO patients (see Appendix 5 for an illustrative example).

[redacted]



[redacted]

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver or a surrogate).

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

Refer to Appendix 3 for SAE reporting.

9.2.1 Period and Frequency for Collecting AE and SAE Information

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

The investigator must report any SAE that occurs after these periods and that is believed to be related to a study intervention or protocol-specified procedure (eg, a follow-up [redacted]).

- All SAEs will be recorded and reported to the Sponsor or designee, promptly and not to exceed 24 hours of awareness of the event , as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study intervention 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.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or

SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Non-serious 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 non-serious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory test result abnormalities that are reported/identified during the study.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3: Lost to Follow-up).

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

9.2.4 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 participants 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

This section is not applicable for women not of childbearing potential.

If, following initiation of the study intervention, it is discovered that a participant is pregnant or may have been pregnant at the time of study intervention exposure, including at least 5 days after study intervention administration, the investigator must immediately notify the Sponsor Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the Sponsor designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

In all cases, the study intervention will be discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety).

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed.

Any pregnancy that occurs in a female partner of a male participant at the time of study intervention exposure, including at least 5 days after study intervention administration, should be reported to the Sponsor or designee. For the 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 and recorded on the Pregnancy Surveillance Form.

If any sexual activity involving penile intercourse (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and for at least 5 days after study intervention administration, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the Adverse Events – Non-serious and Serious Events CRF page. 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 requires the participant to have study intervention discontinued or interrupted
- Any laboratory test result abnormality that requires the participant to receive specific corrective therapy

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

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory test result abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see Section 9.2: Adverse Events and Appendix 3: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING for reporting details).

A potential DILI is defined as follows:

- Aminotransferase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) elevation > 3× upper limit of normal (ULN)

  AND

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

  AND

- No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

9.2.8 Other Safety Considerations

Any significant worsening of conditions noted during interim or final physical examinations, ECG, radiographic imaging, or any other potential safety assessment required or not required by the protocol should also be recorded as a non-serious AE or SAE, as appropriate, and reported accordingly.

9.3 Overdose

[redacted]. Overdoses that meet the regulatory definition of an SAE will be reported as SAEs (see Appendix 3).

9.4 Safety

Planned time points for all safety assessments are listed in Section 2: Schedule of Activities.

9.4.1 Physical Examinations

A complete PE will be obtained at specified time points as outlined in Section 2: Schedule of Activities. The complete PE will consist of evaluation of the following systems: general, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, psychiatric, skin, and musculoskeletal. Complete PEs may be performed by a Doctor of Medicine, Doctor of Osteopathy, Physician's Assistant, or a Nurse Practitioner.

9.4.2 Tuberculosis Screening and Chest X-Ray

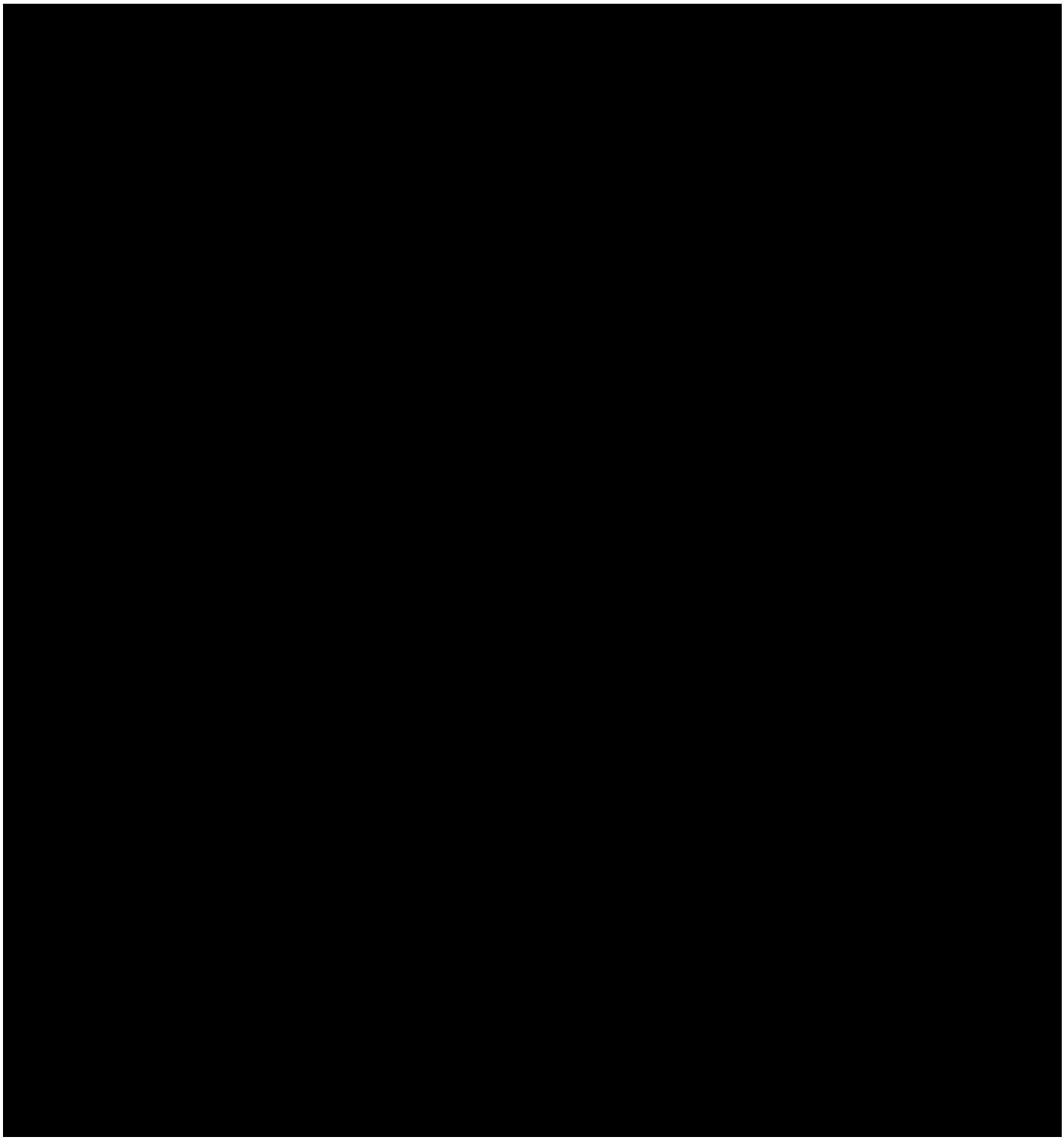
A chest x-ray and PE are considered part of the process to assess a participant's eligibility as outlined in Section 6. Chest x-ray at the screening visit is required if not already performed within 6 months of obtaining written informed consent or if documentation is not on file.

In addition to a complete PE and medical history to evaluate exposure to TB, all participants will have a screening test, an IGRA (eg, T-spot®, QuantiFERON®), preferably performed centrally. If unable to obtain central lab results (eg, repeated test due to indeterminate result), an IGRA test could be obtained locally, after consultation with the Sponsor Medical Monitor.

Participants with a positive screening test will not be eligible for the study unless they have completed at least 1 month of treatment for latent TB prior to dosing of study intervention, and the participant has a negative chest x-ray done at screening that reveals no evidence of active TB and a negative IGRA test (Quantiferon or T-spot) is confirmed prior to Day [redacted].

9.4.3 Electrocardiograms

12-lead ECGs should be collected at times specified in Table 2-1 and Table 2-2. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position. When the timing of the measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, blood pressure, and pulse rate.



[redacted]

9.4.7 Vital Signs

Refer to Section 2: Schedule of Activities.

9.4.8 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.

Participants should fast for at least 8 hours prior to sample collection at screening, on Day [redacted], and ET only. A central/local laboratory will perform the analyses and will provide reference ranges for these tests.

Table 9.4.8-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen or serum urea Uric acid Fasting glucose (Day [redacted], and ET only) Fasting C-peptide (Day [redacted], and ET only)	Total protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase Creatinine clearance – screening only
Fasting Lipid Panel	
Total C (mg/dL, mmol/L) Reflex testing will occur for direct LDL-C if TG > 400 mg/dL (4.52 mmol/L) HDL-C (mg/dL, mmol/L) TG (mg/dL, mmol/L) Note: A participant should be fasting at least 8 hours (Day [redacted], and ET only).	
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	

Table 9.4.8-1: Clinical Laboratory Assessments

pH
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick
Serology
Serum for hepatitis C antibody, HBsAg, anti-hepatitis B core antibody, anti-HBsAb, HIV-1 and -2 antibody (HIV viral RNA or p24 antigen, if needed). At screening only.
Other Analyses
Test for drugs of abuse (urine or serum) (screening and predose on Day)
Pregnancy test (women only: serum at screening, urine at Days)
Follicle stimulating hormone (screening only for women only)
[redacted]
hsCRP - abnormalities in hsCRP levels present at baseline do not necessarily warrant participant exclusion. Please discuss with the Sponsor Medical Monitor.
[redacted]
Tuberculosis test (at screening only)

Abbreviations: ET, early termination; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; hsCRP, high sensitivity C-reactive protein; [redacted]; LDL-C, low-density lipoprotein cholesterol; RNA, ribonucleic acid; [redacted]; TG, triglycerides.

[redacted]

[redacted]

9.6 Immunogenicity Assessments

Not applicable.

[redacted]

[redacted]

9.8 Optional Future Research

This protocol will include residual sample storage for optional future research, from consented participants only, [redacted]:

[redacted]

Samples kept for future research will be stored at the Sponsor-designated storage facility.

The manager of these samples will ensure that they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 20 years after the end of the study or the maximum period allowed by applicable law.

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

Further details of sample collection and processing will be provided to the site in the Laboratory Manual.

9.9 Other Assessments

Not applicable.

9.10 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.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

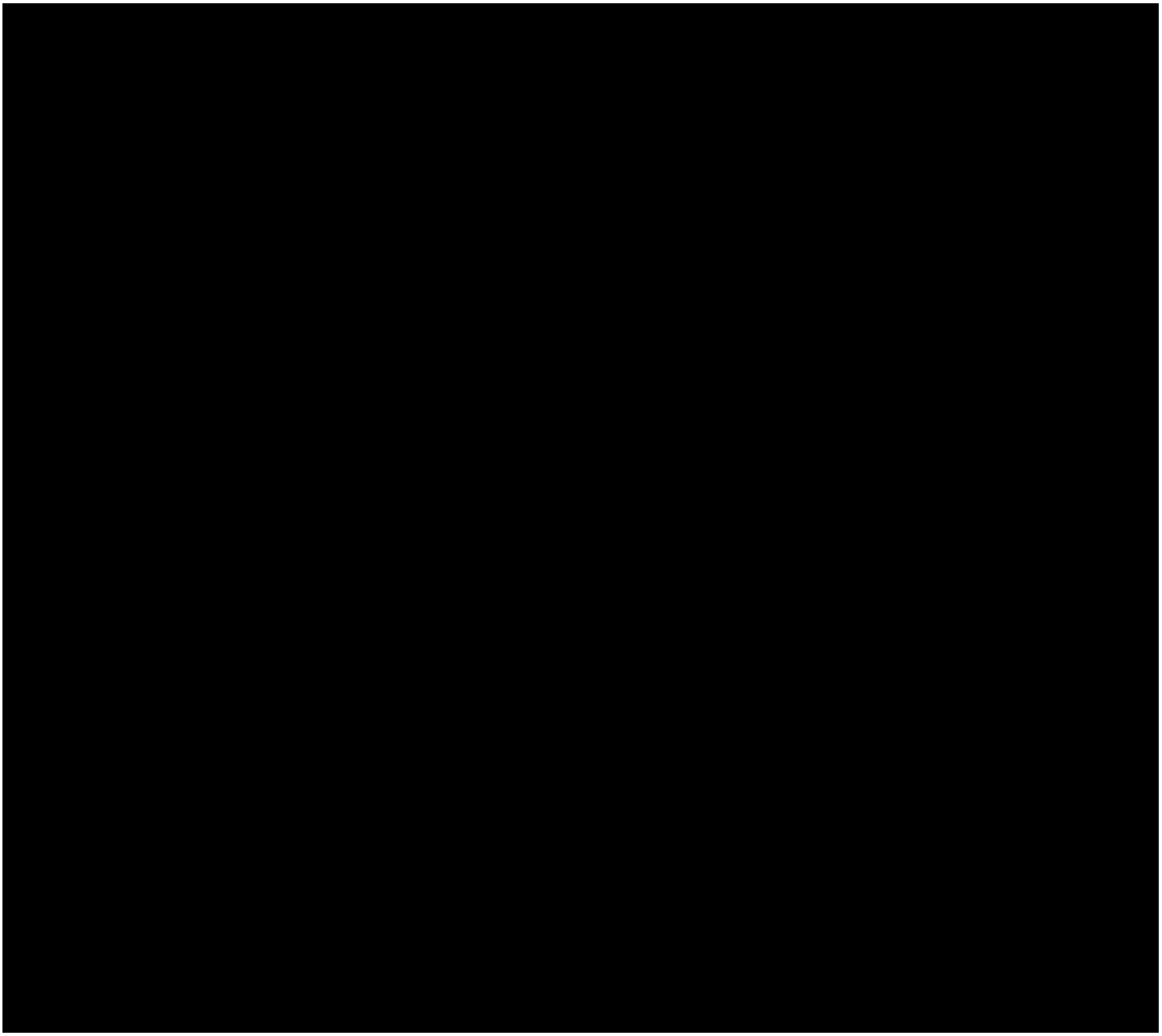
The primary efficacy hypothesis of this study stipulates that the proportion of participants with moderate-to-severe PsO achieving a 75% reduction in PASI score from baseline after 12 weeks of treatment with BMS-986322 will be higher than after 12 weeks of treatment with placebo.

10.2 Sample Size Determination

The sample size calculation is driven by several considerations.

The first consideration is to compare the response rate in PASI-75, the proportion of participants with moderate-to-severe PsO experiencing a 75% improvement (reduction from baseline) in PASI score from baseline after 12 weeks, between BMS-986322 and placebo arms. With a 2-sided, 2-sample Fisher's exact test at a significant level of 5%, a sample size of [redacted] participants per arm will provide at least 99% power to detect a 60% increase in the PASI-75 response rate in an active arm (ie, 70% response rate) compared to placebo assuming the response rate is 10% in the placebo arm after 12 weeks of treatment. The second consideration is to assess the response rate in PASI-75 in active dose arms. With a probability of at least 99%, data from [redacted] treated participants per active arm will produce a 2-sided 95% exact confidence interval (CI) with a margin of error (half-width) of at most 18.8%. In addition, administration of BMS-986322 to [redacted] participants in each active treatment group provides approximately 26%, 79%, and 96% probability of observing at least one occurrence of any treatment-emergent AE that would occur with 1%, 5%, or 10% incidence rate, respectively.

[redacted]



Therefore, approximately 120 participants will be randomized in a 1:1:1:1 ratio to receive BMS-986322 (16 mg PO QD, 32 mg PO QD, or 64 mg PO QD) or placebo. Randomization will be stratified by use of previous treatment with a biologic (yes/no). Assuming a screen failure rate of about 20%, it is estimated that approximately 150 screened participants will be required to achieve the planned 120 treated participants.

10.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Population	Description
All Enrolled Participants	All participants who have agreed to participate in a clinical study following completion of the informed consent process, unless otherwise specified by the protocol.
All Randomized Participants	All participants who were randomized using IRT.
Full Analysis Set	All participants who were randomized and have received at least one dose of study intervention. This population will be used for efficacy analyses and will be analyzed as per randomized treatment.
Per Protocol Population	All participants who were randomized and have no relevant protocol deviation. The primary efficacy analysis will be repeated using this population if there are more than 10% of participants with relevant protocol deviations. Participants will be analyzed as per randomized treatment.
Safety Population	All participants who were randomized and have received at least one dose of study intervention. This population will be used for safety analyses and will be analyzed as per actual treatment received.

[redacted]

Abbreviation: IRT, Interactive Response Technology.

10.4 Statistical Analyses

The SAP will be developed and finalized prior to final database lock and subsequent unblinding, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

A description of the participant population will be included in the CSR, including subgroups of age, gender, gender identity, race, and other study-specific populations and demographic characteristics. A description of participant disposition will also be included in the CSR.

Participant characteristics and/or demographic data may be pooled across studies for future analysis.

10.4.1 General Considerations

Categorical variables will be summarized using counts and percentages of participants falling into each category by treatment group and visit, as applicable. Continuous variables will be summarized using number of participants, mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum by treatment group and visit, as applicable and unless otherwise specified. Descriptive summaries of PK data will additionally include geometric mean and

arithmetic percentage coefficient of variation (%CV). Tmax and similar parameters will be described by median, minimum, and maximum statistics. Change from baseline will be derived as difference of the observed value to its corresponding baseline value, where baseline is defined as the last non-missing observation prior to first administration of any study intervention and will be presented by descriptive summary statistics. Details on statistical considerations will be included in the SAP.

10.4.2 Planned Analyses

[redacted]

The final analysis will be conducted after conclusion of the study (ie, when the last participant has completed the study as defined in Section 5.3) and final database lock has occurred.

10.4.3 Primary Endpoint(s)

The primary objective of this study is to evaluate the response rate in PASI-75 after 12 weeks of treatment with BMS-986322. The response rate in PASI-75 is defined as the proportion of participants with moderate-to-severe PsO experiencing a 75% improvement (reduction from baseline) in PASI score at Week 12 (Day 85) and will be evaluated on the Full Analysis Set.

The safety and tolerability of BMS-986322 will be assessed by the type, frequency, relationship, severity, and seriousness of treatment-emergent AEs, clinical laboratory tests, 12-lead ECG, vital signs, and PE. Treatment-emergent AEs and study intervention-related AEs and SAEs will be summarized using counts and percentages of participants experiencing the event as well as the number of events by system organ class, preferred term, and treatment group. PE findings, vital signs, clinical laboratory test results, and ECG test results will be summarized using descriptive summary statistics for continuous variables and frequency distributions (counts and percentages) for categorical variables. All safety analyses will be performed on the Safety Analysis Set. An overview of primary efficacy and safety endpoints is given in Table 10.4.3-1.

Table 10.4.3-1: Primary Efficacy and Safety Endpoints

Primary Endpoint	Description	Time Frame
Achievement of PASI-75	At least 75% improvement in PASI score as compared to baseline, ie, percent change from baseline less than or equal to -75%	Week 12
Incidence of TEAEs	Type and frequency of TEAEs, SAEs, and TEAEs leading to treatment discontinuation Severity and causal relationship of TEAEs	30 days after last dose of study intervention or date of last follow-up, whichever is later
Clinical laboratory tests	Change from baseline and incidence of marked abnormalities	30 days after last dose of study intervention or date of last follow-up, whichever is later

Table 10.4.3-1: Primary Efficacy and Safety Endpoints

Primary Endpoint	Description	Time Frame
12-lead ECG	Change from baseline and incidence of abnormal findings	30 days after last dose of study intervention or date of last follow-up, whichever is later
Vital signs	Change from baseline and incidence of marked abnormalities	30 days after last dose of study intervention or date of last follow-up, whichever is later
Physical examination	Change from baseline (weight), and incidence of abnormal findings	30 days after last dose of study intervention or date of last follow-up, whichever is later

Abbreviations: ECG, electrocardiogram; PASI, Psoriasis Area and Severity Index; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

To compare the response rates between each treatment group and placebo, the achievement of PASI-75 at Week 12 will be analyzed by 2-sample Fisher's exact test or Chi-square test based on the observed counts. Fisher's exact test will be employed if at least one cell count is smaller than 5. If a participant discontinues from the study prior to Week 12 but has available PASI assessment at the ET visit, the record will be included into the statistical analysis if the ET visit occurred after at least [redacted] Otherwise, participants without evaluable response due to missing PASI scores at baseline and/or Week 12 will be imputed as non-responder for analysis. The number of participants with imputed response will be provided per treatment group. The absolute count and proportion of participants with moderate-to-severe PsO achieving PASI-75 at Week 12 along with corresponding 2-sided 95% asymptotic and Clopper-Pearson exact CIs will be provided for each treatment group. Table 10.4.3-2 provides a summary of the primary estimand.

Table 10.4.3-2: Primary Estimand

Estimand attribute	**Primary definition**		
Treatment	BMS-986322 16 mg QD vs Placebo BMS-986322 32 mg QD vs Placebo BMS-986322 64 mg QD vs Placebo		
Population	Adult male and female participants with moderate-to-severe PsO with or without previous use of biologics		
Endpoint	Percent change from baseline in PASI score ≤ -75% at Week 12 (yes/no)		
Intercurrent event	**Event**	**Strategy**	**Rationale**
	Participant discontinuation prior to Week 12	[redacted]	To provide a conservative estimate of the treatment effect assuming early discontinuation due to deterioration of disease

Table 10.4.3-2: Primary Estimand

Estimand attribute	Primary definition	
Population-level summary	Proportion of participants achieving PASI-75 at Week 12	

Abbreviations: [redacted]; PASI, Psoriasis Area and Severity Index; PsO, psoriasis; QD, once daily.

The unstratified odds ratio versus placebo and the difference in the response rates (unstratified risk difference), their associated 2-sided 95% CIs, and p-value from Fisher's exact test or Chi-square test will be provided. There will be no adjustment for multiplicity. All comparisons will be performed in a pre-specified hierarchical procedure starting from the highest dose arm to the lowest dose arm. If a comparison is not significant at level 0.05, all p-values in subsequent comparisons will be considered nominal. As a supportive analysis, the primary efficacy endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factor prior use of biologics (yes/no) to compare each BMS-986322 treatment group versus placebo. The 2-sided p-values from the CMH test, the adjusted difference in response rates (stratified risk difference) using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated 2-sided 95% CIs using a normal approximation to the weighted average will be provided.

A Cochran-Armitage trend test will be performed to assess a positive trend between treatment groups of BMS-986322 and PASI-75 response rates at Week 12.

As a secondary analysis of the primary endpoint, a logistic regression model analysis will be performed to evaluate the impact of treatment on PASI-75 at Week 12, with treatment group, age, gender, weight, BMI, baseline PASI score, and prior use of biologics (yes/no) as covariates, if applicable. Similar to above, PASI scores observed at ET visits [redacted] will be included into the analysis. Otherwise, missing observations at Week 12 will not be imputed for analysis. Adjusted odds ratios for each treatment group versus placebo will be provided along with associated 2-sided 95% CIs. Details of the tests and models as well as further analyses of the primary endpoint will be given in the SAP.

Primary safety endpoints will be analyzed by observed incidence and percentage as well as descriptive summary statistics of observed value and change from baseline per treatment group and visit, as applicable. Further details will be given in the SAP.

10.4.4 Secondary Endpoint(s)

The statistical analysis of dichotomous secondary endpoints, such as achievement of PASI-50, 90, and 100, and achievement of sPGA score of 0 or 1 at Week 12 will in general follow the primary endpoint analysis. To assess dichotomous endpoints over time, a repeated measures logistic regression model analysis will be performed using a generalized estimating equations model.

Continuous secondary endpoints, such as continuous PASI score and BMS-986322 Cmax, AUC(TAU), Tmax, and trough concentrations, will be presented by descriptive summary statistics of value and change from baseline by treatment group and time point, as applicable per parameter.

A mixed model for repeated measurements (MMRM) will be employed to assess PASI scores over time. Further details of secondary endpoint analyses including covariates used for model adjustment will be given in the SAP.

[redacted]

10.4.6 Other Safety Analyses

Other safety analyses not covered in Section 10.4.3 will be described in the SAP.

[redacted]

11 REFERENCES

1 Watford WT, Hissong BD, Bream JH, et al. Signaling by IL-12 and IL-23 and the immunoregulatory roles of STAT4. Immunol Rev 2004;202:139-56.

2 Tokarski JS, Zupa-Fernandez A, Tredup JA, et al. Tyrosine kinase 2-mediated signal transduction in T lymphocytes is blocked by pharmacological stabilization of its pseudokinase domain. J Biol Chem 2015;290:11061-74.

3 Shaw MH, Boyartchuk V, Wong S, et al. A natural mutation in the Tyk2 pseudokinase domain underlies altered susceptibility of B10.Q/J mice to infection and autoimmunity. Proc Natl Acad Sci 2003;100:11594-9.

4 Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med 2012;367:1519-28.

5 Strober BE, Crowley JJ, Yamauchi PS, et al. Efficacy and safety results from a Phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. Br J Dermatol 2011;165:661-8.

6 Ryan C, Thrash B, Warren RB, et al. The use of ustekinumab in autoimmune disease. Expert Opin Biol Ther 2010;10:587-604.

7 Gordon KB, Blauvelt A, Foley P, et al. Efficacy of guselkumab in subpopulations of patients with moderate-to-severe plaque psoriasis: a pooled analysis of the phase III VOYAGE 1 and VOYAGE 2 studies. Br J Dermatol 2018;178:132-9.

8 Petri M, Wallace DJ, Spindler A, et al. Sifalimumab, a human anti-interferon-alpha monoclonal antibody, in systemic lupus erythematosus: a phase I randomized, controlled, dose-escalation study. Arthritis Rheum 2013;65:1011-21.

9 Furie R, Khamashta M, Merrill JT, et al. Anifrolumab, an anti-interferon-alpha receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. Arthritis Rheumatol 2017;69:376-86.

10 BMS-986322 Investigator's Brochure, Version 03. Bristol-Myers Squibb Company; 2022. Document Control No. 930143799.

11 Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013;133:377-85.

12 Kupetsky EA, Keller M. Psoriasis vulgaris: an evidence-based guide for primary care. J Am Board Fam Med 2013;26:787-801.

13 World Health Organization. Global Report on psoriasis. WHO 2016.

14 Langely RG, Kruger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis 2005;64:ii18-ii23.

[15] Quiero R, Tejon P, Alonso S, et al. Age at disease onset: a key factor for understanding psoriatic disease. Rheumatology (Oxford) 2014;53:1178-85.

[16] Mosca M, Hong J, Hadeler E, et al. Scalp psoriasis: A literature review of effective therapies and updated recommendations for practical management. Dermatol Ther 2021;11:769–97.

[17] Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol 1999;41:401-7.

[18] Nestle FO, Kaplan DH, Barker J. Mechanisms of disease: Psoriasis. N Engl J Med 2009;361:496-509.

[19] van de Kerkhof PC, Franssen ME. Psoriasis of the scalp. Diagnosis and management. Am J Clin Dermatol 2001;2:159-165.

[20] Merola JF, Qureshi A, Husni ME. Underdiagnosed and undertreated psoriasis: Nuances of treating psoriasis affecting the scalp, face, intertriginous areas, genitals, hands, feet, and nails. Dermatol Ther 2018;31:e12589.

[21] Novartis. Rheumatrex® (methotrexate). United States Prescribing Information. 2016.

[22] Novartis. Neoral® (cyclosporine). United States Prescribing Information. 2009.

[23] Celgene. Otezla® (apremilast). United States Prescribing Information. 2017.

[24] Abbvie. Humira® (adalimumab). United States Prescribing Information. 2017.

[25] Janssen Biotech. Remicade® (infliximab). United States Prescribing Information. 2013.

[26] Janssen Biotech. Stelara® (ustekinumab). United States Prescribing Information. 2016.

[27] Novartis. Cosentyx® (sekukinumab). United States Prescribing Information. 2015.

[28] Eli Lilly. Taltz® (ixekizumab). United States Prescribing Information. 2017.

[29] Valeant. Siliq® (brodalumab). United States Prescribing Information. 2017.

[30] Armstrong AW, Robertson AD, Wu J, et al. Undertreatment, treatment trends, and treatment dissatisfaction among subjects with psoriasis and psoriatic arthritis in the United States. Findings from the National Psoriasis Foundation surveys, 2003-2011. JAMA Dermatol 2013;149:1180–5.

[31] Janssen Biotech. TREMFYA® (guselkumab). United States Prescribing Information. 2017.

[32] Volpe, E, Servant, N, Zollinger, R, et al. A critical function for transforming growth factor-beta, interleukin 23 and proinflammatory cytokines in driving and modulating human T(H)-17 responses. Nat Immunol 2008;9:650–7.

[33] Geremia A, Arancibia-Carcamo CV, Fleming MP, et al. IL-23-responsive innate lymphoid cells are increased in inflammatory bowel disease. J Exp Med 2011;208:1127–33.

[34] Tucci M, Lombardi L, Richards HB, et al. Overexpression of interleukin-12 and T helper 1 predominance in lupus nephritis. Clin Exp Immunol 2008;154:247-54.

[35] Simmons DP, Wearsch PA, Canaday DH, et al. Type I IFN drives a distinctive dendritic cell maturation phenotype that allows continued class II MHC synthesis and antigen processing. J Immunol 2012;188:3116-26.

[36] Blanco P, Palucka AK, Gill M, et al. Induction of dendritic cell differentiation by IFN-alpha in systemic lupus erythematosus. Science 2001;294:1540-3.

[37] Braun D, Caramalho I, Demengeot J. IFN-alpha/beta enhances BCR-dependent B cell responses. Int Immunol 2002;14:411-9.

[38] Jego G, Palucka AK, Blanck JP, et al. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. Immunity 2003;19:225-34.

[39] Marrack P, Kappler J, Mitchell T. Type I interferons keep activated T cells alive. J Exp Med 1999;189:521-30.

[40] Nestle FO, Conrad C, Tun-Kyi A, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. J Exp Med 2005;202:135-43.

[41] Liu Y, Jesus AA, Marrero B, et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med 2014;371:507-18.

[42] Wong D, Kea B, Pesich R, et al. Interferon and biologic signatures in dermatomyositis skin: specificity and heterogeneity across diseases. PLoS One 2012;7:e29161.

[43] Coelho LF, de Oliveira JG, Kroon EG. Interferons and scleroderma-a new clue to understanding the pathogenesis of scleroderma? Immunol Lett 2008;118:110-5.

[44] Zhang LJ, Sen GL, Ward NL, et al, Antimicrobial peptide LL37 and MAVS signaling drive interferon-β production by epidermal keratinocytes during skin injury. Immunity 2016;45:119-30.

[45] Cingoz O. Ustekinumab. MAbs. 2009;1:216-21.

[46] A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Phase 2 Study to Evaluate the Clinical Efficacy and Safety of BMS-986165 in Subjects with Moderate to Severe Psoriasis (IM011011). Bristol-Myers Squibb Co., Research and Development, 2008; Document Control No. 930129274.

[47] A Multi-Center, Randomized, Double-Blind, Placebo- and Active Comparator-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of BMS-986165 in Subjects with Moderate-to Severe Plaque Psoriasis (IM011046). Bristol-Myers Squibb Co., Research and Development, 2021; Document Control No. 930164984.

[48] Nestle FO, Kaplan DH, Barker J. Mechanisms of disease: Psoriasis. N Engl J Med 2009;361:496-509.

[49] Krueger JG, Ferris LK, Menter A, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: Safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunology 2015;136:116-24.

[redacted]

52 Sotyktu [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2022.

[redacted]

54 Guidance for Industry: Drug Interaction Studies (FDA Center for Drug Evaluation and Research). http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm.

55 Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/CLINPHARM/ddis/maintable.

[redacted]

59 Fredriksson T, Pettersson U. Severe psoriasis-oral therapy with a new retinoid. Dermatologica 1978;157:238-44.

[redacted]

[redacted]

12 APPENDICES

APPENDIX 1 ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(TAU)	area under the plasma concentration-time curve over the dosing interval
BMI	body mass index
BMS	Bristol-Myers Squibb Company
BSA	body surface area
[redacted]	[redacted]
CI	confidence interval
Cmax	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CRF	Case Report Form, paper or electronic
CSR	clinical study report
[redacted]	[redacted]
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
ET	Early Termination
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein

Term	Definition
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
[redacted]	[redacted]
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	interferon
[redacted]	[redacted]
IGRA	interferon gamma release assay
IL	interleukin
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
[redacted]	[redacted]
IRT	Interactive Response Technology
IV	intravenous(ly)
JAK	Janus kinase
[redacted]	
MMRM	mixed model for repeated measurements
[redacted]	
PASI	Psoriasis Area and Severity Index
PCR	polymerase chain reaction
[redacted]	[redacted]
PE	physical examination
[redacted]	
PID	participant identification number
PK	pharmacokinetic(s)
PO	orally
[redacted]	

Term	Definition
PsA	psoriatic arthritis
PsO	psoriasis
[redacted]	
RNA	ribonucleic acid
[redacted]	[redacted]
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAE	serious adverse event
SAP	statistical analysis plan
sPGA	static Physician's Global Assessment
STAT	signal transducer and activator of transcription
TB	tuberculosis
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
TYK2	tyrosine kinase 2
ULN	upper limit of normal
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws, regulations, and requirements

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

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a quality issue (eg, protocol deviation) that is likely to affect, to a significant degree, 1 or more of the following: (1) the rights, physical safety, or mental integrity of 1 or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

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, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

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

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines
- United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union (EU) Directive 2001/20/EC
- European Regulation 536/2014 for clinical studies (if applicable)
- European Medical Device Regulation 2017/745 for clinical device research (if applicable)
- the IRB/IEC
- all other applicable local regulations

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, by the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study participants.

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 the following:

- IRB/IEC
- Regulatory authority(ies), if applicable according to 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, by the local Health Authority must be sent to Bristol-Myers Squibb Company (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF 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 participants 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 participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with 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 study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform the participant that his/her participation is voluntary. The participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for the participant to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the participant and by the person who conducted the informed consent discussion.
- Include a statement in the participant's medical record that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent the participant to the most current version of the ICF(s) during his/her participation.
- Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

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

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections

5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the source data location list/map or equivalent document.

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten 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 records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an 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 INTERVENTION RECORDS

Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention 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 the following: • 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 participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • non-study disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include Investigational Product sourced from the site's stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study intervention integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its 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 test result abnormalities that are reported or identified during the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and

pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify participants 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 and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

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

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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 source documents.

In addition, the study may be evaluated by the 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 the 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 its 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 its 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 its designee.

RETURN OF STUDY INTERVENTION

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

If	Then
Study interventions supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study intervention containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxic or biologic agents). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused Investigational Medicinal Product must be reconciled by the site monitor/clinical research associate prior to destruction. If study interventions will be returned, the return will be arranged by the responsible study monitor.
Study interventions sourced by site, not supplied by BMS (or its vendors; eg, study interventions sourced from the site's 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 of study interventions, 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 standard operating procedures 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 (eg, 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 Study 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 interventions provided by BMS (or its vendors). Destruction of non-study interventions sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

STUDY AND SITE CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

To benefit potential study participants, patients, health care providers, and researchers and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public per regulatory and BMS requirements. BMS will post study information on local, national, or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

In the European Union (EU, the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in the EU/European Economic Area and third countries.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

- Participant recruitment (eg, among the top quartile of enrollers)
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

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

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at the Sponsor is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). Authorship selection is based on significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights, and conclusion)
2) Drafting the work or revising it critically for important intellectual content
3) Final approval of the version to be published

4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Those who make the most significant contributions, as defined above, will be considered by the Sponsor for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

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 pre-existing medical condition occurring in a clinical investigation participant after signing of informed consent, whether or not considered related to the study intervention.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory test result), symptom, or disease temporally associated with the study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal laboratory test results or other safety assessment findings 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 pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though the condition 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/serious adverse event (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 the definition above, then it cannot be an SAE, even if serious conditions are met.

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event that 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 department or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery that was planned prior to signing consent. • Admissions 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 enrollment in 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/incapacity.
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 results in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant 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 department or at home for allergic bronchospasm and 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 9.2.7: Potential Drug-induced Liver Injury of the protocol for the definition of a potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as those used for SAEs. (See Section 9.2.5: Pregnancy of the protocol for reporting pregnancies.)

EVALUATING AES AND SAES

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, evidence, 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's Brochure 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 the 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 the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, 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.

An event is defined as "serious" when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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 intervention or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or the designee) using the same procedure used for transmitting the initial SAE report. All AEs/SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study intervention, and pregnancies must be reported to BMS (or the designee) promptly and not to exceed 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the electronic Case Report Form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or the designee).
    - In this case, the paper form is transmitted via email or confirmed fax transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed fax transmission.

SAE Email Address: worldwide.safety@BMS.com

SAE Fax Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Women of Childbearing Potential (WOCBP) and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1: Inclusion Criteria of the protocol. Only the contraception methods as described in Section 6.1: Inclusion Criteria of the protocol are acceptable for this study.

DEFINITIONS

Women 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
- Pre-menopausal 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 participant's medical records, medical examination, or medical history interview.

- Post-menopausal female
  - A post-menopausal state is defined as 12 months of amenorrhea in a woman over the age of 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 to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. 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.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the time point at which the study intervention (Investigational Medicinal Product [IP/IMP] and other study interventions ie, Non-IMP/AxMP required for study) or any active major metabolites have decreased to a concentration that is no longer considered relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the study intervention to pass.

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *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. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – 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. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[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. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device.

• Intrauterine system (IUS). (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[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. Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is pregnant or breastfeeding.
• 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 intervention. 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 participant.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy. • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2 of the protocol. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence. • Periodic abstinence (including, but not limited to, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation amenorrhea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the Investigational Medicinal Product 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. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria and Section 7.7.1: Prohibited and/or Restricted Treatments of the protocol. [c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this

study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria and Section 7.7.1: Prohibited and/or Restricted Treatments of the protocol.

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. (This method of contraception cannot be used by WOCBP participants in studies in which hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5: Pregnancy of the protocol and Appendix 3.

APPENDIX 5 PSORIASIS AREA AND SEVERITY INDEX (PASI)

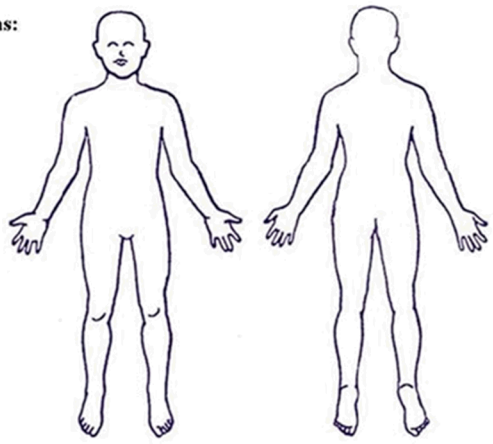
Psoriasis Area and Severity Index (PASI)

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 and shade in the affected areas on the body diagrams below.

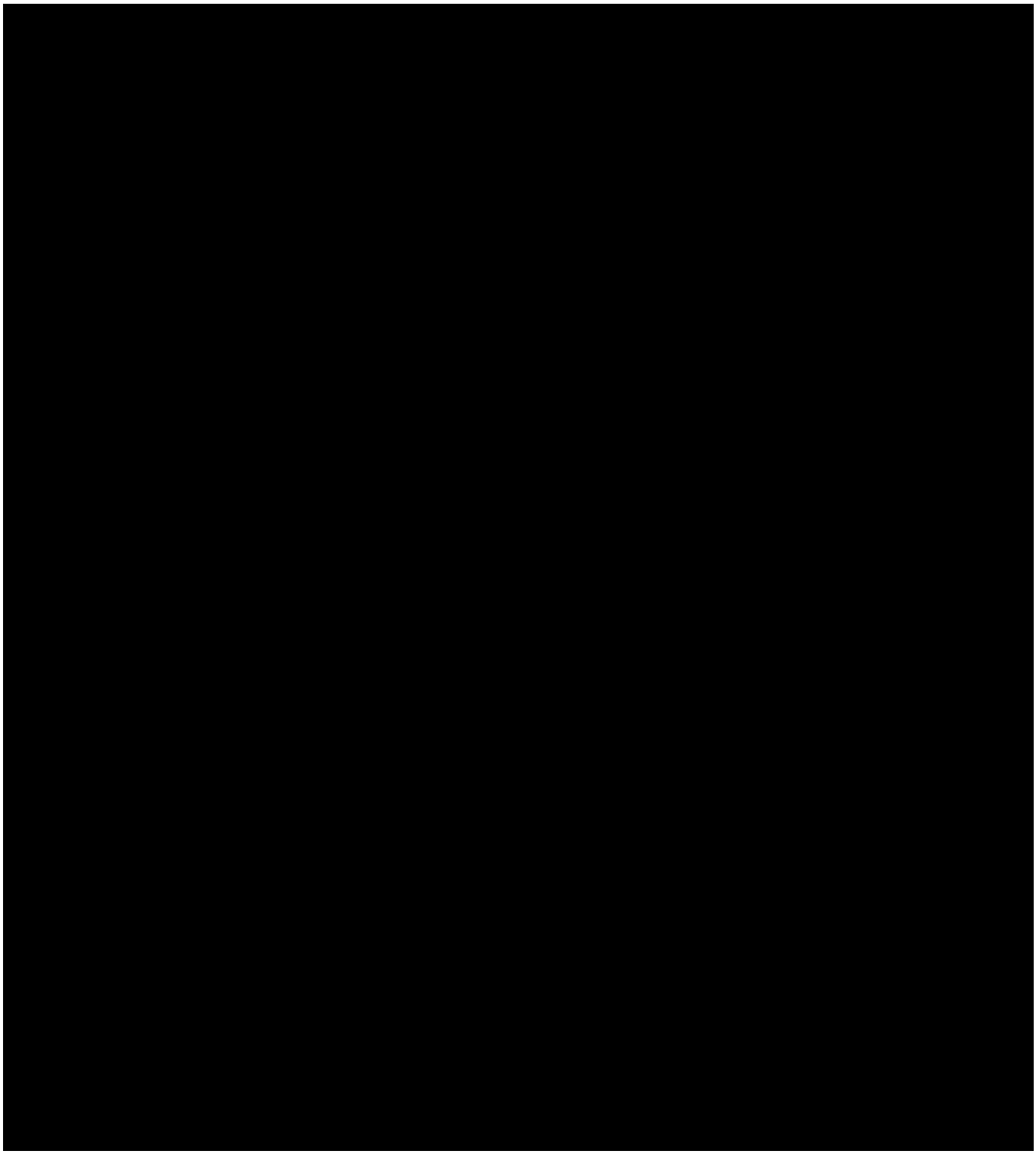
Plaque Characteristic	Rating score	Body region (and weighting factor)			
		Head	Upper Extremities	Trunk	Lower Extremities
Erythema (Redness)	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Induration (Thickness)					
Desquamation (Scaling)					
Add together each of the 3 scores for each of the body regions to give 4 separate sub totals.					
Sub Totals		A1 =	A2 =	A3 =	A4 =
Multiply each sub total 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=**	

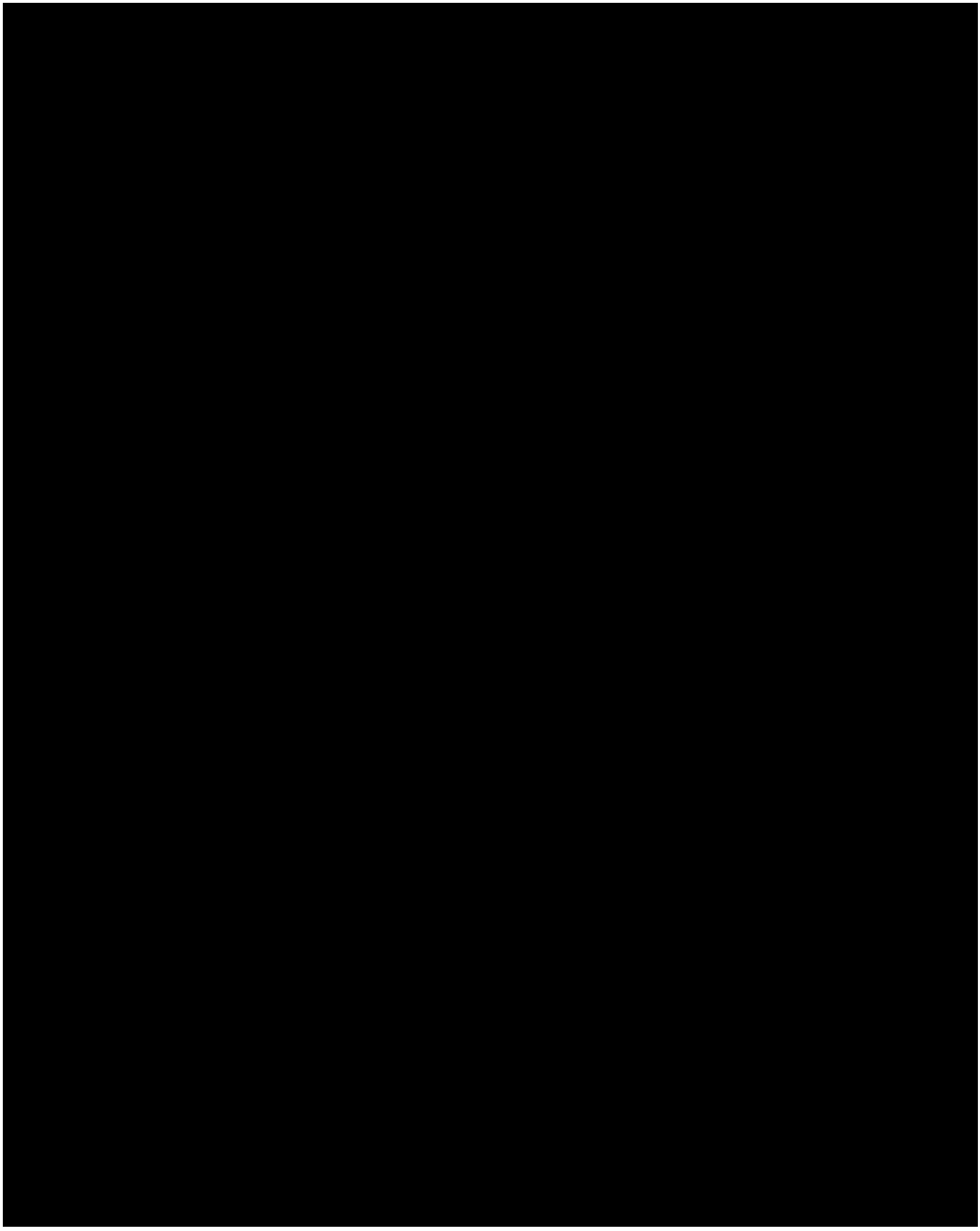
Percent (%) Total Body Surface Area (BSA) of psoriasis: ____%

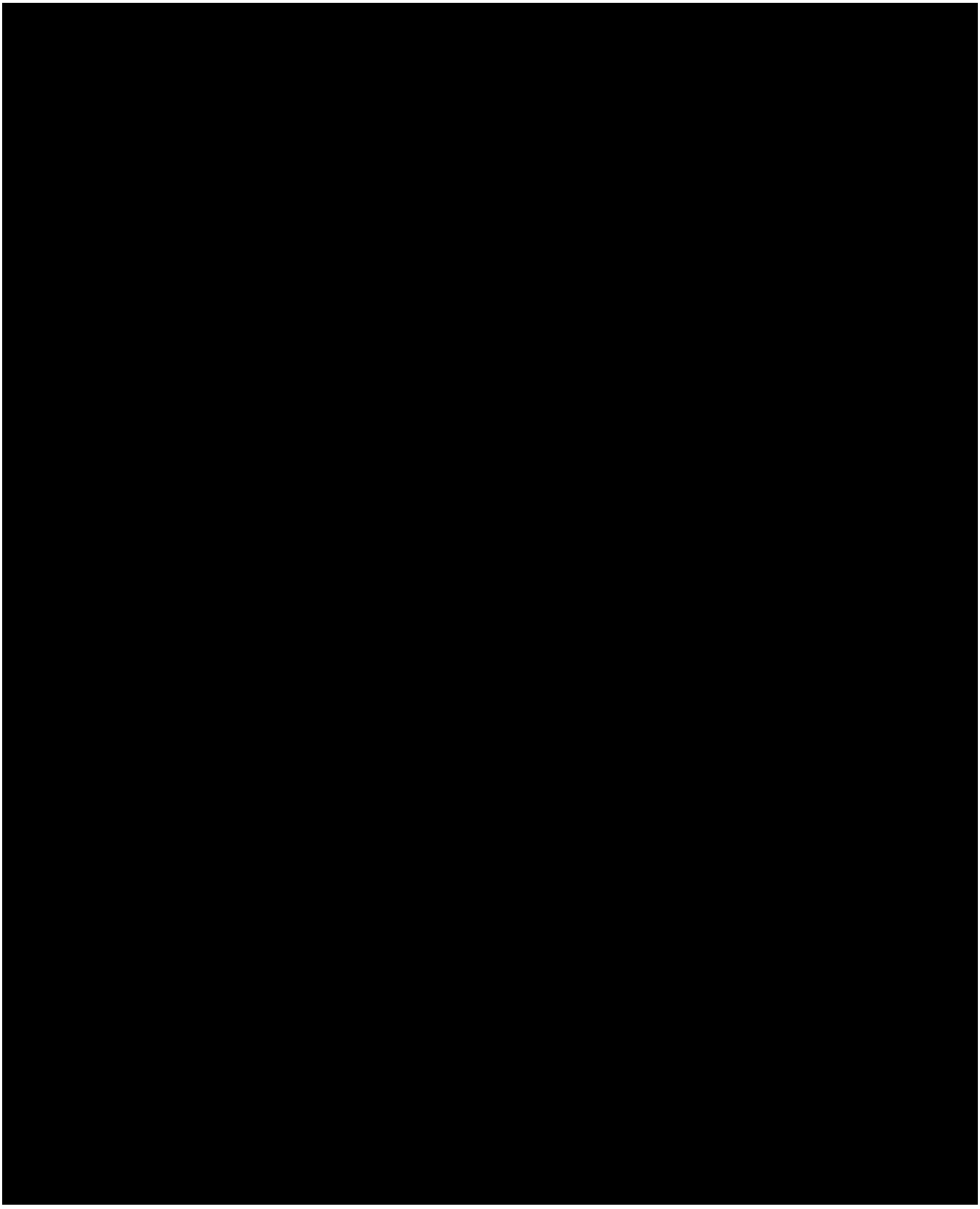
Please shade in the affected areas:

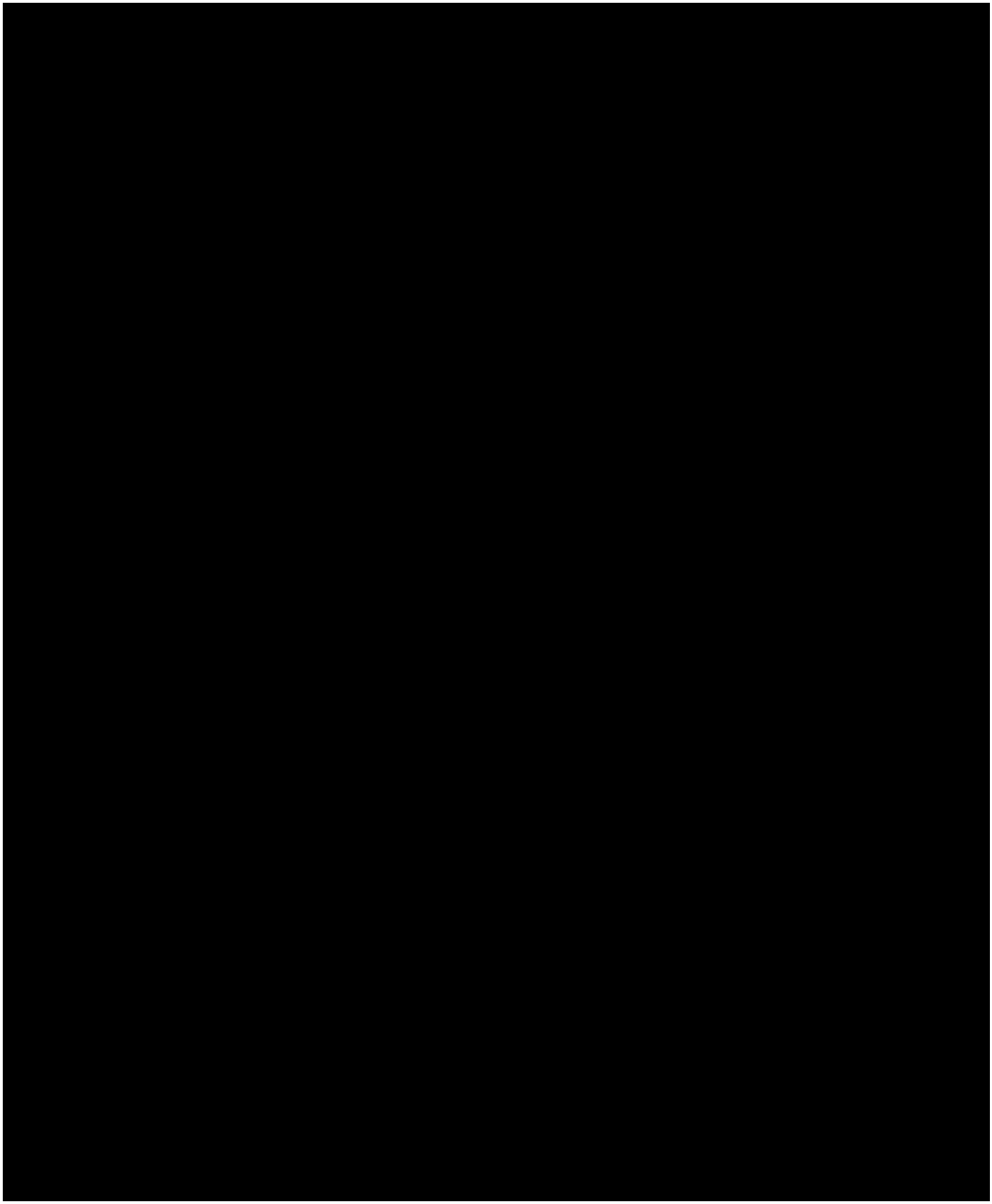


English for USA









APPENDIX 14 ADME GENE LIST (FROM HTTP://PHARMAADME.ORG)

CORE ADME GENE LIST

Gene Symbol	Full Gene Name	Class
ABCB1	ATP-binding cassette, subfamily B (MDR/TAP), member 1	Transporter
ABCC2	ATP-binding cassette, subfamily C (CFTR/MRP), member 2	Transporter
ABCG2	ATP-binding cassette, subfamily G (WHITE), member 2	Transporter
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	Phase I
CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2	Phase I
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6	Phase I
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6	Phase I
CYP2C19	cytochrome P450, family 2, subfamily C, polypeptide 19	Phase I
CYP2C8	cytochrome P450, family 2, subfamily C, polypeptide 8	Phase I
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9	Phase I
CYP2D6	cytochrome P450, family 2, subfamily D, polypeptide 6	Phase I
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1	Phase I
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4	Phase I
CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5	Phase I
DPYD	dihydropyrimidine dehydrogenase	Phase I
GSTA1	glutathione S-transferase A1	Phase II
GSTM1	glutathione S-transferase M1	Phase II
GSTP1	glutathione S-transferase pi	Phase II
GSTT1	glutathione S-transferase theta 1	Phase II
NAT1	N-acetyltransferase 1 (arylamine N-acetyltransferase)	Phase II
NAT2	N-acetyltransferase 2 (arylamine N-acetyltransferase)	Phase II
SLC15A2	solute carrier family 15 (H+/peptide transporter), member 2	Transporter
SLC22A1	solute carrier family 22 (organic cation transporter), member 1	Transporter
SLC22A2	solute carrier family 22 (organic cation transporter), member 2	Transporter
SLC22A6	solute carrier family 22 (organic anion transporter), member 6	Transporter
SLCO1B1	solute carrier organic anion transporter family, member 1B1	Transporter
SLCO1B3	solute carrier organic anion transporter family, member 1B3	Transporter
SULT1A1	sulfotransferase family, cytosolic, 1 A, phenol-preferring, member 1	Phase II
TPMT	thiopurine S-methyltransferase,	Phase II
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	Phase II

UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15	Phase II
UGT2B17	UDP glucuronosyltransferase 2 family, polypeptide B17	Phase II
UGT2B7	UDP glucuronosyltransferase 2 family, polypeptide B7	Phase II

EXTENDED ADME GENE LIST

Rank	Gene Symbol	Full Gene Name	Class
7	ABCB8	ATP-binding cassette, subfamily B (MDR/TAP), member 8	Transporter
7	ABCC12	ATP-binding cassette, subfamily C (CFTR/MRP), member 12	Transporter
7	ABCC3	ATP-binding cassette, subfamily C (CFTR/MRP), member 3	Transporter
7	ABCC4	ATP-binding cassette, subfamily C (CFTR/MRP), member 4	Transporter
7	AHR	aryl hydrocarbon receptor	Modifier
7	ALDH4A1	aldehyde dehydrogenase 4 family, member A1	Phase I
7	ALDH5A1	aldehyde dehydrogenase 5 family, member A1	Phase I
7	ALDH6A1	aldehyde dehydrogenase 6 family, member A1	Phase I
7	CES1	carboxylesterase 1 (monocyte/macrophage serine esterase 1)	Phase I
7	CES2	carboxylesterase 2 (intestine, liver)	Phase I
7	CYP7A1	cytochrome P450, family 7, subfamily A, polypeptide 1	Phase I
7	EPHX1	epoxide hydrolase 1, microsomal (xenobiotic)	Phase I
7	FMO3	flavin containing monooxygenase 3	Phase I
7	GSTA1	glutathione S-transferase A1	Phase II
7	GSTA2	glutathione S-transferase A2	Phase II
7	GSTA3	glutathione S-transferase A3	Phase II
7	GSTA4	glutathione S-transferase A4	Phase II
7	GSTA5	glutathione S-transferase A5	Phase II
7	GSTM2	glutathione S-transferase M2 (muscle), glutathione S-transferase M4	Phase II
7	GSTM3	glutathione S-transferase M3 (brain)	Phase II
7	GSTM4	glutathione S-transferase M4	Phase II
7	GSTO1	glutathione S-transferase omega 1, glutathione S-transferase omega 2	Phase II
7	GSTO2	glutathione S-transferase omega 2	Phase II
7	GSTT2	glutathione S-transferase theta 2	Phase II
7	SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	Transporter
7	SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1	Transporter

Rank	Gene Symbol	Full Gene Name	Class
7	SLC22A11	solute carrier family 22 (organic anion/cation transporter), member 11	Transporter
7	SLC22A8	solute carrier family 22 (organic anion transporter), member 8	Transporter
7	SLC7A5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	Transporter
7	SLCO1A2	solute carrier organic anion transporter family, member 1A2	Transporter
7	SLCO2B1	solute carrier organic anion transporter family, member 2B1	Transporter
7	SULT1A2	sulfotransferase family, cytosolic, 1 A, phenol-preferring, member 2	Phase II
7	SULT1A3	sulfotransferase family, cytosolic, 1 A, phenol-preferring, member 3	Phase II
7	SULT1B1	sulfotransferase family, cytosolic, 1B, member 1	Phase II
7	UGT1A3	UDP glucuronosyltransferase 1 family, polypeptide A3	Phase II
7	UGT1A6	UDP glucuronosyltransferase 1 family, polypeptide A6	Phase II
7	UGT1A7	UDP glucuronosyltransferase 1 family, polypeptide A7	Phase II
7	UGT1A8	UDP glucuronosyltransferase 1 family, polypeptide A8	Phase II
7	UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	Phase II
7	UGT2A1	UDP glucuronosyltransferase 2 family, polypeptide A1	Phase II
7	UGT2B11	UDP glucuronosyltransferase 2 family, polypeptide B11	Phase II
7	UGT2B28	UDP glucuronosyltransferase 2 family, polypeptide B28	Phase II
7	UGT2B4	UDP glucuronosyltransferase 2 family, polypeptide B4	Phase II
6	ABCA1	ATP-binding cassette, subfamily A (ABC1), member 1	Transporter
6	ABCA4	ATP-binding cassette, subfamily A (ABC1), member 4	Transporter
6	ABCB11	ATP-binding cassette, subfamily B (MDR/TAP), member 11	Transporter
6	ABCB4	ATP-binding cassette, subfamily B (MDR/TAP), member 4	Transporter
6	ABCB5	ATP-binding cassette, subfamily B (MDR/TAP), member 5	Transporter

Rank	Gene Symbol	Full Gene Name	Class
6	ABCB6	ATP-binding cassette, subfamily B (MDR/TAP), member 6	Transporter
6	ABCB7	ATP-binding cassette, subfamily B (MDR/TAP), member 7	Transporter
6	ABCC1	ATP-binding cassette, subfamily C (CFTR/MRP), member 1	Transporter
6	ABCC10	ATP-binding cassette, subfamily C (CFTR/MRP), member 10	Transporter
6	ABCC11	ATP-binding cassette, subfamily C (CFTR/MRP), member 11	Transporter
6	ABCC5	ATP-binding cassette, subfamily C (CFTR/MRP), member 5	Transporter
6	ABCC6	ATP-binding cassette, subfamily C (CFTR/MRP), member 6	Transporter
6	ABCC8	ATP-binding cassette, subfamily C (CFTR/MRP), member 8	Transporter
6	ABCC9	ATP-binding cassette, subfamily C (CFTR/MRP), member 9	Transporter
6	ABCG1	ATP-binding cassette, subfamily G (WHITE), member 1	Transporter
6	ADH1A	alcohol dehydrogenase 1 A (class I), alpha polypeptide	Phase I
6	ADH1B	alcohol dehydrogenase IB (class I), beta polypeptide	Phase I
6	ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	Phase I
6	ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide	Phase I
6	ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide, methionyl aminopeptidase 1	Phase I
6	ADH6	alcohol dehydrogenase 6 (class V)	Phase I
6	ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	Phase I
6	ALDH1A1	aldehyde dehydrogenase 1 family, member A1	Phase I
6	ALDH1A2	aldehyde dehydrogenase 1 family, member A2	Phase I
6	ALDH1A3	aldehyde dehydrogenase 1 family, member A3	Phase I
6	ALDH1B1	aldehyde dehydrogenase 1 family, member B1	Phase I
6	ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	Phase I
6	ALDH3A1	aldehyde dehydrogenase 3 family, memberA1	Phase I
6	ALDH3A2	aldehyde dehydrogenase 3 family, member A2	Phase I
6	ALDH3B1	aldehyde dehydrogenase 3 family, member B1	Phase I
6	ALDH3B2	aldehyde dehydrogenase 3 family, member B2	Phase I
6	ALDH7A1	aldehyde dehydrogenase 7 family, member A1	Phase I

Rank	Gene Symbol	Full Gene Name	Class
6	ALDH8A1	aldehyde dehydrogenase 8 family, member A1	Phase I
6	ALDH9A1	aldehyde dehydrogenase 9 family, member A1	Phase I
6	AOX1	aldehyde oxidase 1	Phase I
6	ARNT	aryl hydrocarbon receptor nuclear translocator	Modifier
6	CBR1	carbonyl reductase 1	Phase I
6	CBR3	carbonyl reductase 3	Phase I
6	CDA	cytidine deaminase	Modifier
6	CYB5R3	cytochrome b5 reductase 3	Phase I
6	CYP11A1	cytochrome P450, family 11, subfamily A, polypeptide 1	Phase I
6	CYP11B1	cytochrome P450, family 11, subfamily B, polypeptide 1	Phase I
6	CYP11B2	cytochrome P450, family 11, subfamily B, polypeptide 2	Phase I
6	CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1	Phase I
6	CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	Phase I
6	CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
6	CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
6	CYP21A2	cytochrome P450, family 21, subfamily A, polypeptide 2	Phase I
6	CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	Phase I
6	CYP26A1	cytochrome P450, family 26, subfamily A, polypeptide 1	Phase I
6	CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1	Phase I
6	CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	Phase I
6	CYP2A7	cytochrome P450, family 2, subfamily A, polypeptide 7	Phase I
6	CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18	Phase I
6	CYP2F1	cytochrome P450, family 2, subfamily F, polypeptide 1	Phase I
6	CYP2J2	cytochrome P450, family 2, subfamily J, polypeptide 2	Phase I
6	CYP39A1	cytochrome P450, family 39, subfamily A, polypeptide 1	Phase I

Rank	Gene Symbol	Full Gene Name	Class
6	CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43	Phase I
6	CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7	Phase I
6	CYP4B1	cytochrome P450, family 4, subfamily B, polypeptide 1	Phase I
6	CYP4F11	cytochrome P450, family 4, subfamily F, polypeptide 11	Phase I
6	CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	Phase I
6	EPHX2	epoxide hydrolase 2, cytoplasmic	Phase I
6	FMO1	flavin containing monooxygenase 1	Phase I
6	FMO2	flavin containing monooxygenase 2	Phase I
6	FMO4	flavin containing monooxygenase 4	Phase I
6	FMO5	flavin containing monooxygenase 5	Phase I
6	GPX2	glutathione peroxidase 2 (gastrointestinal)	Phase I
6	GPX3	glutathione peroxidase 3 (plasma)	Phase I
6	GPX7	glutathione peroxidase 7	Phase I
6	GSR	glutathione reductase	Phase I
6	GSTK1	glutathione S-transferase kappa 1	Phase II
6	GSTM5	glutathione S-transferase M5	Phase II
6	GSTZ1	glutathione transferase zeta 1 (maleylacetoacetate isomerase)	Phase II
6	NNMT	nicotinamide N-methyltransferase	Phase II
6	NR1I2	nuclear receptor subfamily 1, group I, member 2	Modifier
6	NR1I3	nuclear receptor subfamily 1, group I, member 3	Modifier
6	PNMT	phenylethanolamine N-methyltransferase	Phase II
6	PON1	paraoxonase 1	Phase I
6	PON2	paraoxonase 2	Phase I
6	PON3	paraoxonase 3	Phase I
6	POR	P450 (cytochrome) oxidoreductase	Modifier
6	PPARD	peroxisome proliferative activated receptor, delta	Modifier
6	PPARG	peroxisome proliferative activated receptor, gamma	Modifier
6	RXRA	retinoid X receptor, alpha	Modifier
6	SLC10A2	solute carrier family 10 (sodium/bile acid cotransporter family), member 2	Transporter
6	SLC13A1	solute carrier family 13 (sodium/sulfate symporters), member 1	Transporter
6	SLC13A2	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	Transporter

Rank	Gene Symbol	Full Gene Name	Class
6	SLC13A3	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3	Transporter
6	SLC16A1	solute carrier family 16 (monocarboxylic acid Transporter), member 1	Transporter
6	SLC19A1	solute carrier family 19 (folate transporter), member 1	Transporter
6	SLC22A10	solute carrier family 22 (organic anion/cation transporter), member 10	Transporter
6	SLC22A12	solute carrier family 22 (organic anion/cation transporter), member 12	Transporter
6	SLC22A13	solute carrier family 22 (organic cation transporter), member 13	Transporter
6	SLC22A14	solute carrier family 22 (organic cation transporter), member 14	Transporter
6	SLC22A15	solute carrier family 22 (organic cation transporter), member 15	Transporter
6	SLC22A16	solute carrier family 22 (organic cation transporter), member 16	Transporter
6	SLC22A17	solute carrier family 22 (organic cation transporter), member 17	Transporter
6	SLC22A18	solute carrier family 22 (organic cation transporter), member 18	Transporter
6	SLC22A18AS	solute carrier family 22 (organic cation transporter), member 18 antisense	Transporter
6	SLC22A3	solute carrier family 22 (extraneuronal monoamine transporter), member 3	Transporter
6	SLC22A4	solute carrier family 22 (organic cation transporter), member 4	Transporter
6	SLC22A5	solute carrier family 22 (organic cation transporter), member 5	Transporter
6	SLC22A7	solute carrier family 22 (organic anion transporter), member 7	Transporter
6	SLC22A9	solute carrier family 22 (organic anion/cation transporter), member 9	Transporter
6	SLC27A1	solute carrier family 27 (fatty acid transporter), member 1	Transporter
6	SLC28A1	solute carrier family 28 (sodium-coupled nucleoside transporter), member 1	Transporter
6	SLC28A2	solute carrier family 28 (sodium-coupled nucleoside transporter), member 2	Transporter
6	SLC28A3	solute carrier family 28 (sodium-coupled nucleoside transporter), member 3	Transporter
6	SLC29A1	solute carrier family 29 (nucleoside Transporter), member 1	Transporter

Rank	Gene Symbol	Full Gene Name	Class
6	SLC29A2	solute carrier family 29 (nucleoside Transporter), member 2	Transporter
6	SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	Transporter
6	SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5	Transporter
6	SLC5A6	solute carrier family 5 (sodium-dependent vitamin transporter)	Transporter
6	SLC6A6	solute carrier family 6 (neurotransmitter transporter, taurine), member 6	Transporter
6	SLC7A8	solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	Transporter
6	SLCO1C1	solute carrier organic anion transporter family, member 1C1	Transporter
6	SLCO2A1	solute carrier organic anion transporter family, member 2A1	Transporter
6	SLCO3A1	solute carrier organic anion transporter family, member 3A1	Transporter
6	SLCO4A1	solute carrier organic anion transporter family, member 4A1	Transporter
6	SLCO4C1	solute carrier organic anion transporter family, member 4C1	Transporter
6	SLCO5A1	solute carrier organic anion transporter family, member 5A1	Transporter
6	SLCO6A1	solute carrier organic anion transporter family, member 6A1	Transporter
6	SULT1C1	sulfotransferase family, cytosolic, 1C, member 1	Phase II
6	SULT1C2	sulfotransferase family, cytosolic, 1C, member 2	Phase II
6	SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	Phase II
6	SULT2A1	sulfotransferase family, cytosolic, 2 A, DHEA preferring, member 1	Phase II
6	SULT2B1	sulfotransferase family, cytosolic, 2B, member 1	Phase II
6	TAP1	transporter 1, ATP-binding cassette, subfamily B (MDR/TAP)	Transporter
6	UGT1A10	UDP glucuronosyltransferase 1 family, polypeptide A10	Phase II
6	UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4	Phase II
6	UGT1A5	UDP glucuronosyltransferase 1 family, polypeptide A5	Phase II
6	UGT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10	Phase II

Rank	Gene Symbol	Full Gene Name	Class
5	ABCC13	ATP-binding cassette, subfamily C (CFTR/MRP), member 13	Transporter
5	ARSA	arylsulfatase A	Modifier
5	CAT	catalase	Modifier
5	CHST8	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8	Phase II
5	CYP19A1	cytochrome P450, family 19, subfamily A, polypeptide 1	Phase I
5	CYP26C1	cytochrome P450, family 26, subfamily C, polypeptide 1	Phase I
5	CYP27B1	cytochrome P450, family 27, subfamily B, polypeptide 1	Phase I
5	CYP2R1	cytochrome P450, family 2, subfamily R, polypeptide 1	Phase I
5	CYP2S1	cytochrome P450, family 2, subfamily S, polypeptide 1	Phase I
5	CYP46A1	cytochrome P450, family 46, subfamily A, polypeptide 1	Phase I
5	CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11	Phase I
5	CYP4F12	cytochrome P450, family 4, subfamily F, polypeptide 12	Phase I
5	CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	Phase I
5	CYP4F3	cytochrome P450, family 4, subfamily F, polypeptide 3	Phase I
5	CYP4F8	cytochrome P450, family 4, subfamily F, polypeptide 8	Phase I
5	CYP4Z1	cytochrome P450, family 4, subfamily Z, polypeptide 1	Phase I
5	CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1	Phase I
5	CYP8B1	cytochrome P450, family 8, subfamily B, polypeptide 1	Phase I
5	DHRS13	dehydrogenase/reductase (SDR family) member 13	Phase I
5	DHRS2	dehydrogenase/reductase (SDR family) member 2	Phase I
5	GPX1	glutathione peroxidase 1	Phase I
5	GPX4	glutathione peroxidase 4 (phospholipid hydroperoxidase)	Phase I
5	GPX5	glutathione peroxidase 5 (epididymal androgen-related protein)	Phase I
5	GPX6	glutathione peroxidase 6 (olfactory)	Phase I
5	GSS	glutathione synthetase	Phase I

Rank	Gene Symbol	Full Gene Name	Class
5	GSTCD	glutathione S-transferase, C-terminal domain containing	Phase II
5	HNF4A	hepatocyte nuclear factor 4, alpha	Modifier
5	HNMT	histamine N-methyltransferase	Phase II
5	HSD11B1	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
5	HSD17B11	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
5	HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14	Phase I
5	LOC731356	similar to dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
5	MGST1	microsomal glutathione S-transferase 1	Phase II
5	MGST2	microsomal glutathione S-transferase 2	Phase II
5	MGST3	microsomal glutathione S-transferase 3	Phase II
5	MPO	myeloperoxidase	Modifier
5	NOS1	nitric oxide synthase 1 (neuronal)	Phase I
5	NOS2A	nitric oxide synthase 2 A (inducible, hepatocytes)	Phase I
5	NOS3	nitric oxide synthase 3 (endothelial cell)	Phase I
5	PPARA	peroxisome proliferator-activated receptor alpha	Modifier
5	SERPINA7	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 7	Modifier
5	SLC7A7	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7	Transporter
5	SOD1	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	Modifier
5	SOD2	superoxide dismutase 2, mitochondrial	Modifier
5	SOD3	superoxide dismutase 3, extracellular precursor	Modifier
5	SULF1	sulfatase 1	Phase I
5	SULT4A1	sulfotransferase family 4 A, member 1	Phase II
5	TAP2	transporter 2, ATP-binding cassette, subfamily B (MDR/TAP)	Transporter
5	UGT8	UDP glycosyltransferase 8 (UDP-galactose ceramide galactosyltransferase)	Phase II
5	XDH	xanthine dehydrogenase	Phase I
4	ADHFE1	alcohol dehydrogenase, iron containing, 1	Phase I
4	CHST1	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1	Phase II
4	CHST10	carbohydrate sulfotransferase 10	Phase II
4	CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	Phase II
4	CHST12	carbohydrate (chondroitin 4) sulfotransferase 12	Phase II
4	CHST13	carbohydrate (chondroitin 4) sulfotransferase 13	Phase II
4	CHST2	carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2	Phase II

Rank	Gene Symbol	Full Gene Name	Class
4	CHST3	carbohydrate (chondroitin 6) sulfotransferase 3	Phase II
4	CHST4	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 4	Phase II
4	CHST5	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 5	Phase II
4	CHST6	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6	Phase II
4	CHST7	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7	Phase II
4	CHST9	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9	Phase II
4	CYP2D7P1	cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1	Phase I
4	DDO	D-aspartate oxidase	Phase I
4	DHRS1	dehydrogenase/reductase (SDR family) member 1	Phase I
4	DHRS12	dehydrogenase/reductase (SDR family) member 12	Phase I
4	DHRS3	dehydrogenase/reductase (SDR family) member 3	Phase I
4	DHRS4	dehydrogenase/reductase (SDR family) member 4	Phase I
4	DHRS4L1	dehydrogenase/reductase (SDR family) member 4 like 1	Phase I
4	DHRS4L2	dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
4	DHRS7	dehydrogenase/reductase (SDR family) member 7	Phase I
4	DHRS7B	dehydrogenase/reductase (SDR family) member 7B	Phase I
4	DHRS7C	dehydrogenase/reductase (SDR family) member 7C	Phase I
4	DHRS9	dehydrogenase/reductase (SDR family) member 9	Phase I
4	DHRSX	dehydrogenase/reductase (SDR family) X-linked	Phase I
4	DPEP1	dipeptidase 1 (renal)	Phase I
4	FMO6P	flavin containing monooxygenase 6	Phase I
4	HAGH	hydroxyacylglutathione hydrolase	Phase I
4	IAPP	islet amyloid polypeptide	Modifier
4	KCNJ11	potassium inwardly-rectifying channel, subfamily J, member 11	Modifier
4	LOC728667	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
4	LOC731931	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
4	MAT1A	methionine adenosyltransferase I, alpha	Modifier
4	METAP1	methionyl aminopeptidase 1	Phase I
4	PDE3A	phosphodiesterase 3A, cGMP-inhibited	Phase I
4	PDE3B	phosphodiesterase 3B, cGMP-inhibited	Phase I

Rank	Gene Symbol	Full Gene Name	Class
4	PLGLB1	plasminogen-like B1	Phase I
3	ATP7A	ATPase, Cu++ transporting, alpha polypeptide (Menkes syndrome)	Modifier
3	ATP7B	ATPase, Cu++ transporting, beta polypeptide	Modifier
3	CFTR	cystic fibrosis transmembrane conductance regulator	Modifier