Protocol Number: IM011011
IND Number: 131,993
Ex-US Non-IND
EUDRACT Number 2016-002481-31
Date: 23-Aug-2016

CLINICAL PROTOCOL IM011011

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

Study Director / Medical Monitor
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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	23-Aug-2016	Not applicable

SYNOPSIS

Clinical Protocol IM011011

Protocol Title: 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

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Subjects will be randomized to 1 of 6 dosing arms: BMS-986165 at 3mg Q2D, 3mg QD, 3mg BID, 6mg BID, 12mg QD or matching placebo capsule taken for the 12 week double-blind period.

Study Phase: II

Research Hypothesis: The proportion of subjects with moderate to severe psoriasis experiencing a 75% reduction in psoriasis area and severity index score (PASI) after 12 weeks of treatment with BMS-986165 will be higher than after 12 weeks of treatment with placebo

Objectives:

The **primary objectives** are as follows:

- To compare the proportion of subjects with moderate to severe psoriasis is experiencing a 75% improvement as measured by reduction in psoriasis area and severity index (PASI-75) score after 12 weeks of treatment between doses of BMS-986165 and placebo.
- To assess the safety and tolerability of multiple oral doses of BMS-986165 in subjects with moderate to severe psoriasis

The **secondary objectives** are as follows:

- To assess that the proportion of subjects experiencing a 75% reduction in psoriasis area and severity index (PASI) score in the most efficacious treatment group
- To compare the proportions of subjects experiencing a 75% reduction in psoriasis area and severity index (PASI) score between treatment groups
- To assess a positive trend between treatment groups of BMS-986165 and proportion of subjects experiencing a 75% reduction in PASI score after 12 weeks of treatment
- To assess clinical efficacy of BMS-986165 as measured by improvement in skin disease area and severity indices PASI 50, 75, 90 and 100 over time in subjects with moderate to severe psoriasis
- To assess a significantly higher proportion of subjects achieving a static physician's global assessment (sPGA) score of "0" ("cleared") or "1" ("minimal") after 12 weeks of treatment with BMS-986165 than after 12 weeks of treatment with placebo
- To assess improvement by BMS-986165 in quality of life assessments (DLQI)
- To assess the trough concentrations of BMS-986165 in subjects with moderate to severe psoriasis

[redacted]

Study Design: This is a 12 week, multi-center, randomized double-blind, placebo-controlled, multiple oral dose study in subjects with psoriasis. Subjects will be randomly assigned to receive BMS-986165 (3mg Q2D, 3mg QD, 3mg BID, 6mg BID, 12mg QD) or placebo. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to administration of study medication.

This will be an outpatient study. Subjects will receive BMS-986165 or placebo capsules to be taken at home. Subjects will be provided by the Investigator Site with enough capsules to cover the treatment interval between study visits beginning on Study Day 1. Additional capsules covering the treatment interval between study visits should be supplied by the Investigator Site during each follow up visit. To facilitate PK analyses, certain doses of BMS-986165 or placebo capsules will be administered in the clinic (See Section 4.5).

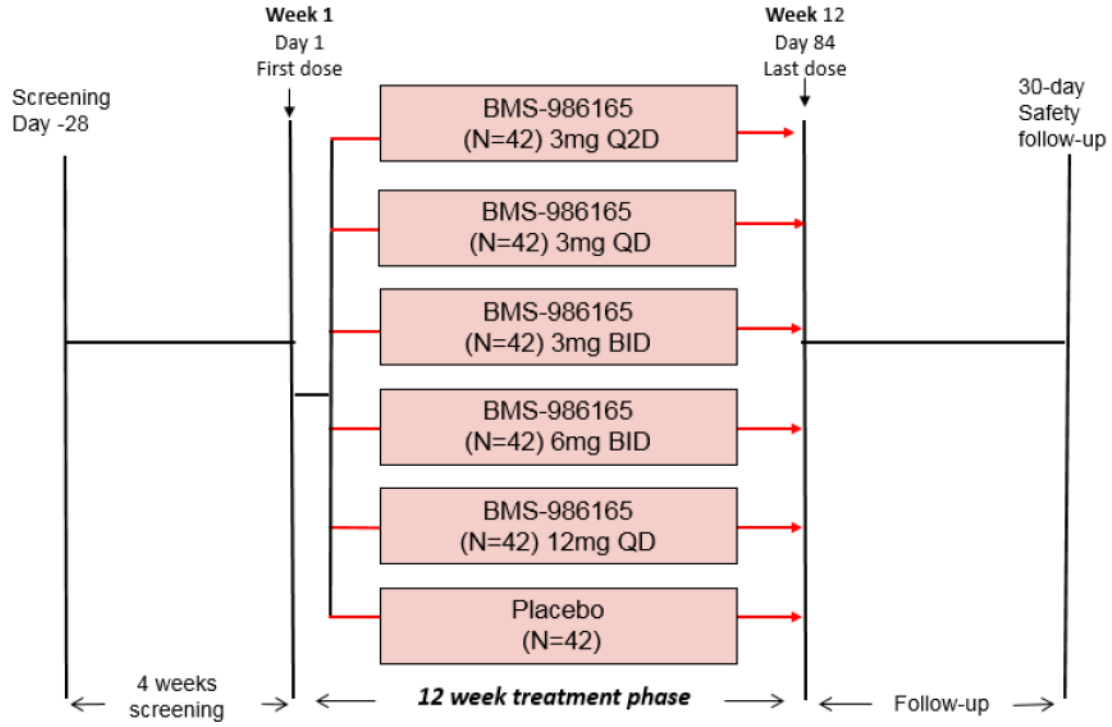
Subjects will be reporting to the clinic for study visits on study Days 1, 8, 15, 29, 57, 85 and on a follow-up Day 115.

Physical examinations, clinical disease activity assessments (Psoriasis Area and Severity Index [PASI], Body Surface Area assessment [BSA], static Physician's Global Assessment sPGA), vital sign measurements, PK evaluations, clinical laboratory evaluations, ECG, skin biopsies, subject reported quality of life measures (DLQI), and PD evaluations will be performed at selected times throughout the dosing interval. Subjects will be closely monitored for adverse events throughout the study. Subjects will be required to return to the clinic for additional (unscheduled) safety follow up visits as deemed necessary by the investigator.

Since BMS-986165 is a novel investigational agent with immunomodulatory effects, immunosuppressant agents will be discontinued prior to dosing in order to maximize subject safety. Further, in order to determine whether BMS-986165 exerts a potent anti-psoriatic effect in the absence of background therapy, participation requires that subjects discontinue therapy (with the exception of topical emollients for symptomatic relief, including topical steroids for sensitive areas like groin etc.) prior to dosing as described in Sections 3.4.1.

The study design schematic is shown in Figure -1 below.

Figure -1: **Study Design Schematic for IM011011**



Q2D=every other day, QD=every day, BID=twice daily

Study Population: Male and female subjects diagnosed with plaque psoriasis vulgaris for ≥ 6 months, eligible for phototherapy or systemic therapy, having plaques covering ≥ 10% BSA and with PASI score of ≥ 12, between 18-70 years of age with a BMI of 18-40 kg/m2, inclusive, will be eligible to participate in the study.

Women of childbearing potential (WOCBP) must not be nursing or pregnant and must be using an acceptable method of contraception. WOCBP must have a negative pregnancy test within 24 hours prior to dosing with study drug.

Key Inclusion Criteria

- Men and women age 18-70, inclusive
- Body mass index (BMI) 18-40 kg/m^2 and total body weight > 50 kg (110 lb)
- Diagnosis of plaque psoriasis for ≥ 6 months
- Deemed by Investigator to be eligible for phototherapy or systemic therapy
- Plaques covering ≥ 10% of Body Surface Area (BSA)
- Psoriasis Area and Severity Index (PASI) score ≥ 12 and sPGA ≥ 3
- Women must not be pregnant, lactating, or planning pregnancy during the study period
- WOCBP and men who are sexually active with WOCBP must follow instructions on birth control
- Willing to discontinue topical and/or systemic therapies, with the exception of topical emollients and low potency topical steroids (rescue) prior to dosing

Key Exclusion Criteria

- Diagnosis of non-plaque psoriasis (guttate, inverse, pustular, erythrodermic)
- History of lack of response to ustekinumab, secukinumab or ixikizumab (any therapeutic agent targeted to IL-12, IL-17 or IL-23) at approved doses after at least 3 months of therapy

- Has received ustekinumab, secukinumab or ixikizumab (any therapeutic agent targeted to IL-12, IL-17 or IL-23) within 6 months of first administration of study medication
- Has received anti-TNFα inhibitor(s) within 2 months of first administration of study medication
- Has received natalizumab, efalizumab, or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, alefacept, or visilizumab) within 3 months of first administration of study medication
- Has received Rituximab within 6 months of first administration of study medication
- Has received any systemic immunosuppressants (eg, MTX, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus) or anakinra within 4 weeks of the first administration of study medication
- Has received phototherapy or any systemic medications/treatments that could affect psoriasis or PGA evaluation (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, or fumaric acid derivatives) within 4 weeks of the first administration of study medication
- Has used topical medications/treatments that could affect psoriasis or PGA evaluation (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, picrolimus, aprimilast and tacrolimus) within 2 weeks of the first administration of study medication
- Is currently receiving lithium, antimalarials, leflunomide, or IM gold, or have received lithium, antimalarials, IM gold within 4 weeks or leflunomide within 12 weeks of the first administration of any study medication
- Has received an experimental antibody or biologic therapy within the previous 6 months, or received any other experimental therapy or new investigational agent within 30 days or 5 half-lives (whichever is longer) of any study agent administration or is currently enrolled in an investigational study
- History or evidence of active infection and/or febrile illness within 7 days; or serious infections that led to hospitalization and IV antibiotic treatment within 90 days; or serious infection requiring antibiotic treatment within 30 days
- Active herpes infection, including herpes simplex 1 and 2 and herpes zoster identified on examination and/or medical history within 2 months of administration of study medication
- Hepatitis C virus (HCV): subjects known to be positive for anti-HCV antibody or for HCV RNA detectable by polymerase chain reaction (PCR)
- Hepatitis B virus (HBV): subjects known to be positive for hepatitis B surface antigen or for HBV DNA detectable by PCR
- Human Immunodeficiency Virus (HIV) infection: subjects known to be HIV positive
- History of active or inadequately treated latent TB
- Known or suspected systemic or skin autoimmune disorder other than psoriasis and psoriatic arthritis
- Any major illness or evidence of unstable condition of major organ systems including psychiatric
- Cancer or history of lymphoproliferative disease within last 5 years; exception is resected cutaneous basal cell or squamous cell carcinoma that has been treated without recurrence
- Class III or IV congestive heart failure by New York Heart Association Criteria
- Unstable cardiovascular disease, defined as a recent clinical deterioration (e.g., unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months
- Major surgery within the last 4 weeks
- Live vaccines within the last 60 days
- Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, chest x-ray or clinical laboratory determinations beyond what is consistent with the target population
- Leukopenia (absolute WBC count < 3000/mm3); Lymphopenia (ALC < 500/mm3); Neutropenia (ANC < 1000/mm3)
- Thrombocytopenia (platelet count < 100,000/mm3; Anemia (hemoglobin <9.0 g/dL)

- ALT/AST > 3 X ULN and/or Total, unconjugated, and/or conjugated bilirubin > 2 X ULN within 28 days of dosing

Study Drug: includes both investigational [medicinal] products (IP/IMP) and non-investigational [medicinal] products (Non-IP/Non-IMP) as listed:

Study Drug for IM011011

Medication	Potency	IP/Non-IP
BMS-986165-02 Capsules	3 mg (as the free base)	IP

Study Assessments:

- Efficacy Measures: Efficacy will be assessed using the PASI scores, as well as sPGA and DLQI as listed under the objectives and endpoints.
- Safety Outcome Measures: Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance.
- Pharmacokinetic Measures: Pharmacokinetic parameters Ctrough, plasma concentration versus time data

Statistical Considerations:

Sample Size: The sample size calculation is driven by several considerations.

The first consideration is to compare the response rate in PASI-75, the proportion of subjects with moderate to severe psoriasis experiencing a 75% improvement reduction in psoriasis area and severity index (PASI) score after 12 weeks, between BMS-986165 and placebo arms. With a one-sided, two-sample Fisher's exact test at significant level 0.05, a sample size of 42 per arm will provide at least 99% power to detect 50% increase in the PASI-75 response rate in an active arm (i.e., 60% response rate) compared to the placebo assuming the response rate is 10% in the placebo arm.

The second consideration is to assess the response rate in PASI-75 in active dose arms. Data from 42 treated subjects per arm will produce a two-sided 95% confidence interval with a margin of error at most 15.1% (half width) using normal approximation.

The third consideration is to compare the response rates in PASI-75 in two active arms. With one-sided, two-sample Fisher's exact test at significant level 0.05, 42 subjects per arm will provide at least 82% power to detect at least 30% difference in the response rate in PASI-75 between any two active dose arms.

The proposed sample size is mainly driven by the third consideration. In addition, administration of BMS-986165 to 42 subjects in each active treatment group provides 34%, 88%, and 99% probability of observing at least one occurrence of any adverse event that would occur with 1%, 5%, or 10% incidence rate respectively.

Endpoints: Primary Endpoint

The primary endpoint is the response rate in PASI-75: the proportion of subjects with moderate to severe psoriasis experiencing a 75% improvement reduction in psoriasis area and severity index (PASI) score after 12 weeks.

Secondary Endpoints

The secondary endpoints include efficacy endpoints (PASI-50, PASI-75, PASI-90, PASI-100, sPGA score, DLQI, etc) after week 12 of treatment and PK parameter, Ctrough.

The secondary endpoints to assess the safety and tolerability of BMS-986195 are the incidence, potential significance, and clinical importance of adverse events measured during multiple doses of BMS-986195 and up to 30 days after the last dose, as determined by medical review of adverse event reports, vital sign measurements, electrocardiograms (ECGs), and results of physical examination and laboratory tests.

[redacted]

Analyses:
Demographics and Baseline Characteristics
Demographics and baseline characteristics including baseline disease activities will be tabulated by treatments using descriptive statistics.

Efficacy Analyses
Primary Efficacy Analyses
The primary endpoint, the proportion of subjects with moderate to severe psoriasis experiencing a 75% improvement reduction in PASI score after 12 weeks, will be analyzed by two-sample Fisher's exact test or Chi-square test to compare the response rates in each treatment group and placebo. Cochran–Mantel–Haenszel Chi-square test, stratified according to previous treatment with a biologic and/or region (Japanese vs rest of world), will be performed. The odds ratio (odd in a treatment group/odd in placebo) in the response rates and its corresponding two-sided 90% confidence interval (CI) will be provided when using Fisher's exact test or Cochran-Matel-Haenszel Chi-square test. If Chi-square test is performed, the difference in the response rates and its corresponding two-sided 90% confidence interval (CI) will be provided.

In addition, point estimate and 90% asymptotic and exact two-sided confidence intervals will be provided for the proportion of subjects in PASI-75 in each group. A logistic regression model may be performed to incorporate some of the covariates if these covariate are assumed to impact the response rates. Details of the tests and models will be given in the statistical analysis plan.

Secondary Efficacy Analyses
Similar analyses as in primary efficacy analyses will be performed to compare any two active arms.

A logistic model will be conducted to detect a positive trend between treatment groups of BMS-986165.

The response rate in PASI-50, PASI-75, PASI-90, and PASI-100 will be summarized by treatment and time and will be analyzed using a repeated measure model when applicable. The same analyses will be conducted stratified by previous biologic treatment and/or region. The proportion of subjects with a sPGA score of "0" or "1" will be analyzed similarly to the primary analyses. sPGA, and DLQI Score from psoriasis subjects will be tabulated by treatment and time; the corresponding changes from baseline and percent change from baseline will be calculated and summarized.

For continuous secondary endpoints (e.g. PASI, etc), point estimates and two-sided 90% confidence intervals for mean change from baseline within each treatment group will be provided. For binary endpoints (response rate in

PASI, sPGA, etc.), point estimates of the response rate and two-sided 90% confidence intervals will be provided using normal approximation within each treatment group.

In addition, a two-sided 90% confidence interval will be provided for the difference in the secondary efficacy endpoints between each active arm and the placebo arm at each visit. More analyses, such as analysis of covariance models with treatment group, use of previous biologic treatment, and baseline value included as covariates, may be performed on endpoints such as PASI score, sPGA score, DLQI, etc.

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 to be nominal and may be provided if applicable.

[redacted]

Safety Analyses
All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

Pharmacokinetic Analyses
Summary statistics will be tabulated for Ctrough. Additional details will be provided in the statistical analysis plan (SAP) as necessary.

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1.2 Research Hypothesis

The proportion of subjects with moderate to severe psoriasis experiencing a 75% reduction in psoriasis area and severity index score (PASI) after 12 weeks of treatment with BMS-986165 will be higher than after 12 weeks of treatment with placebo

1.3 Objectives(s)

1.3.1 Primary Objectives

- To compare the proportion of subjects with moderate to severe psoriasis is experiencing a 75% improvement as measured by reduction in psoriasis area and severity index (PASI-75) score after 12 weeks of treatment between doses of BMS-986165 and placebo
- To assess the safety and tolerability of multiple oral doses of BMS-986165 in subjects with moderate to severe psoriasis

1.3.2 Secondary Objectives

- To assess that the proportion of subjects experiencing a 75% reduction in psoriasis area and severity index (PASI) score in the most efficacious treatment group
- To compare the proportion of subjects experiencing a 75% reduction in psoriasis area and severity index (PASI) score between treatment groups
- To assess a positive trend between treatment groups of BMS-986165 and proportion of subjects experiencing a 75% reduction in PASI score after 12 weeks of treatment
- To assess clinical efficacy of BMS-986165 as measured by improvement in skin disease area and severity indices PASI 50, 75, 90 and 100 over time in subjects with moderate to severe psoriasis
- To assess a significantly higher proportion of subjects achieving a static physician global assessment (sPGA) score of "0" ("cleared") or "1" (" minimal") after 12 weeks of treatment with BMS-986165 than after 12 weeks of treatment with placebo
- To assess improvement by BMS-986165 in quality of life assessments (DLQI)
- To assess the trough concentrations of BMS-986165 in subjects with moderate to severe psoriasis

[redacted]

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

- Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form(s) and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a 12 week, multi-center, randomized double-blind, placebo-controlled, parallel-group multiple oral dose study in subjects with moderate to severe psoriasis. Subjects will be randomly assigned to receive BMS-986165 (3mg Q2D, 3mg QD, 3mg BID, 6mg BID, 12mg QD) or placebo. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to administration of study medication.

This will be an outpatient study. Subjects will receive BMS-986165 or placebo capsules to be taken at home. Subjects will be provided by the Investigator Site with enough capsules to cover the treatment interval between study visits beginning on Study Day 1. Additional capsules covering the treatment interval between study visits should be supplied by the Investigator Site during each follow up visit. To facilitate PK analyses, certain doses of BMS-986165 or placebo capsules will be administered in the clinic (see Section 4.5).

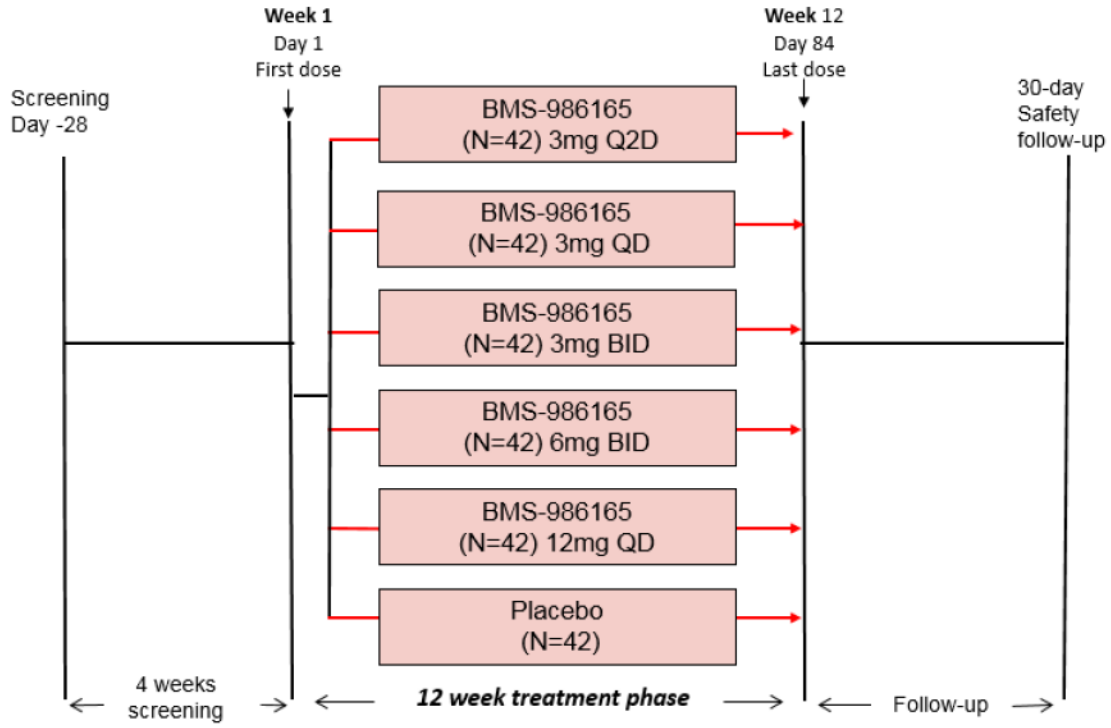
Subjects will be reporting to the clinic for study visits on study Days 1, 8, 15, 29, 57, 85 and 115.

Physical examinations, clinical disease activity assessments (Psoriasis Area and Severity Index [PASI], Body Surface Area assessment [BSA], static Physician's Global Assessment sPGA), vital sign measurements, PK evaluations, clinical laboratory evaluations, ECG, skin biopsies, subject reported quality of life measures (DLQI), and PD evaluations will be performed at selected times throughout the dosing interval. Adverse events will be recorded and assessed by the Investigator (or designee as documented in the DOA) at study visits and throughout the study period. Subjects will be required to return to the clinic for additional (unscheduled) safety follow up visits as deemed necessary by the investigator.

Since BMS-986165 is a novel investigational agent with immunomodulatory effects, immunosuppressant agents will be discontinued prior to dosing in order to maximize subject safety. Further, in order to determine whether BMS-986165 exerts a potent anti-psoriatic effect in the absence of background therapy, participation requires that subjects discontinue therapy (with the exception of topical emollients for symptomatic relief) prior to dosing as described in Sections 3.4.1.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



Q2D=every other day, QD=every day, BID=twice daily

The approximate duration of the study is 20 weeks (143 days), this includes, a 4-week screening period (28 days), a 12-week treatment period (85 days) and 4 weeks of follow-up period (30 days).

The start of the trial is defined as the date of the first Screening Visit (date of signing the informed consent) for the first subject screened. End of trial is defined as the last visit or scheduled procedure shown in the Time & Events schedule for the last subject. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to provide BMS supplied study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects is willing to participate in the study and has signed the informed consent

2. Target Population

a) Male and female subjects with a diagnosis of plaque psoriasis for ≥ 6 months

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

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

d) Psoriatic plaques must cover ≥ 10% of body surface area (BSA)

e) Psoriasis Area and Severity Index (PASI) score ≥ 12 and sPGA ≥ 3

3. Age and Reproductive Status

a) Males and Females, ages 18 or age of majority to 70 years, inclusive

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

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

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) BMS-986165 plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 33 days post-treatment completion

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) BMS-986165 plus 5 half-lives of the study drug plus 90 days (duration of sperm turnover) for a total of 93 days post-treatment completion. In addition, male subjects must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 1) which have a failure rate of < 1% when used consistently and correctly.

3.3.2 Exclusion Criteria

4. Target Disease Exceptions

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

b) Diagnosis of psoriatic arthritis, uveitis, inflammatory bowel disease, or other immune-mediated conditions that are commonly associated with psoriasis for which a subject requires current systemic (oral, SC, or IV) (including corticosteroids, immunosuppressants, biologics) immunosuppressant medical treatment. Certain therapies such as NSAIDs may be permitted, but should be discussed with the BMS Medical Monitor prior to determination of subject eligibility.

5. Infectious/Immune-related Exclusions

a) History or evidence of active infection and/or febrile illness within 7 days of Study Day 1 (e.g., bronchopulmonary, urinary, gastrointestinal, etc.)

b) History of serious bacterial, fungal, or viral infections that let 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 1

c) Live vaccines within 60 days of first dose of study medication

d) 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

e) Active herpes infection, including herpes simplex 1 and 2 and herpes zoster (demonstrated on physical examination and/or medical history within 2 months of administration of study medication)

f) Positive hepatitis-B (HBV) surface antigen or HBV DNA by Polymerase Chain Reaction (PCR)

g) Positive hepatitis-C (HCV) antibody with positive Recombinant ImmunoBlot Assay (RIBA) or HCV RNA by or Polymerase Chain Reaction (PCR)

3. Subjects with any history or risk for tuberculosis (TB), specifically subjects with:

a) Current clinical radiographic or laboratory evidence of active TB

b) History of active TB within the last 3 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 QFG or other diagnostic test in the absence of clinical manifestations, unless subject has received at least 1 month treatment with Isoniazid, or other agents recommended by local Health Authority guidelines, and an interferon gamma release assay (IGRA) test, eg, QFG or T-Spot, is negative before Day 1

d) Any history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the subject's immune status (e.g., history of splenectomy, primary immunodeficiency, HIV infection, etc.)

6. Medical History and Concurrent Diseases

a) Any significant acute or chronic medical illness

b) Any major surgery within 4 weeks of study drug administration

c) Blood transfusion within 4 weeks of study drug administration

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

e) Any major illness/condition or evidence of an unstable clinical condition (e.g., 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 subject if he or she participates in the study

f) Has unstable cardiovascular disease, defined as a recent clinical deterioration (e.g., 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 ($\leq$ 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

l) Any other sound medical, psychiatric and/or social reason as determined by the Investigator

m) History of lack of response to ustekinumab, secukinumab or ixikizumab (any therapeutic agent targeted to IL-12, IL-17 or IL-23) at approved doses after at least 3 months of therapy

n) Has received ustekinumab, secukinumab or ixikizumab (any therapeutic agent targeted to IL-12, IL-17 or IL-23) within 6 months of first administration of study medication

o) Has received anti-TNFα inhibitor(s) within 2 months of first administration of study medication

p) Has received natalizumab, efalizumab, or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, alefacept, or visilizumab) within 3 months of first administration of study medication

q) Has received Rituximab within 6 months of first administration of study medication.

r) Has received any systemic immunosuppressants (eg, MTX, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus) or anakinra within 4 weeks of the first administration of study medication

s) Has received phototherapy or any systemic medications/treatments that could affect psoriasis or PGA evaluation (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens,

sulfasalazine, hydroxyurea, or fumaric acid derivatives) within 4 weeks of the first administration of any study medication

t) Has used topical medications/treatments that could affect psoriasis or PGA evaluation (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, picrolimus, and tacrolimus) within 2 weeks of the first administration of any study medication

u) Is currently receiving lithium, antimalarials, or IM gold, or have received lithium, antimalarials, or IM gold within 4 weeks of the first administration of any study medication

v) Has received an experimental antibody or biologic therapy within the previous 6 months, or received any other experimental therapy or new investigational agent within 30 days or 5 half-lives (whichever is longer) of any study medication administration or is currently enrolled in an investigational study

7. Physical and Laboratory Test Findings

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

b) Urinalysis findings suspicious of infection (e.g. pyuria, bacteriuria) in a non-contaminated sample collected at screening. Subjects 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. Subjects may be rescreened if deemed eligible may be randomized within 28 days of completing an appropriate course of antibiotic treatment for pulmonary infection.

d) Leukopenia defined as absolute WBC count < 3000/mm3 within 28 days of dosing with study drug on Day 1

e) Lymphopenia defined as absolute lymphocyte count < 500/mm3 within 28 days of dosing with study drug on Day 1

f) Neutropenia defined as absolute neutrophil count < 1000/mm3 within 28 days of dosing with study drug on Day 1

g) Moderate to severe thrombocytopenia defined as platelet count < 100,000/mm3 within 28 days of dosing with study drug on Day 1

h) Moderate to severe anemia defined as hemoglobin < 9 g/dL within 28 days of dosing with study drug on Day 1

i) ALT and/or AST > 3X ULN within 28 days of dosing with study drug on Day 1

j) Total, unconjugated, and/or conjugated bilirubin > 2X ULN within 28 days of dosing with study drug on Day 1

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

8. Allergies and Adverse Drug Reaction

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

9. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required.

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4

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

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a documented serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

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

- 1 week minimum for vaginal hormonal products (e.g., 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.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below in Table 3.4.1-1. Medications taken within 4 weeks prior to study drug administration must be recorded on the CRF.

Table 3.4.1-1: Prohibited and or Restricted Treatments

Prohibited Treatments	Washout Period (before randomization)
Ustekinumab, secukinumab or ixikizumab (any therapeutic agent targeted to IL-12, IL-17, or IL-23)	6 months
TNFα inhibitors	2 months
Natalizumab, efalizumab, or agents that modulate B cells or T cells (e.g. alemtuzumab, abatacept, alefacept, visilizumab)	3 months
Rituximab	6 months
Systemic immunosuppressants (e.g. MTX, Azahiopine, cyclosporine, 6-thiouganine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus) or anakinara	4 weeks
Phototherapy	4 weeks
Systemic medications/treatments (including but not limited to oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, fumaric acid derivative)	4 weeks
Topical Treatments (e.g. corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, picrolimus, tacrolimus)	2 weeks
Lithium, antimalarias, IM gold	4 weeks
Any biological therapy	6 months
Any experimental therapy or new investigational agent or participation in any other experimental/investigational trial	30 days or 5 half-life (whichever is longer)

3.4.2 Other Prohibited and/or Restricted Concomitant Medications:

- Due to potential pharmacokinetic interactions with the transporters BCRP (as inhibitor) and P-gp (as substrate), the following medications that are restricted or prohibited:
  - Breast cancer resistance protein (BRCP) substrates, such as rosuvastatin should be used with caution. If a subject is taking rosuvastatin during the study duration, the following guidelines should be used :
  - Monitor of LFTs & CPK for duration of study:
    - If 2x baseline and <3 ULN increase, consider lowering statin dose by ½
    - If > 3 ULN, stop statin for duration of study
    - If > 5 ULN, stop statin and discontinue study medication
    - If myopathy and CPK<10 ULN are observed consider lowering statin dose by ½
    - If CPK ≥10 ULN or rhabdomyolysis, stop statin and discontinue study medication

– Strong inhibitors of P-gp such as quinidine, cyclosporine, cobicistat, conivaptan, indinavir, itraconazole, ketoconazole, nefazodone, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole are prohibited for the duration of the study.

Additional references[24,25] and individual drug labels should be referred to for further information on pharmacokinetic DDIs

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

3.4.3 Other Restrictions and Precautions

- Subjects 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 medication until the safety follow-up visit.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment and/or participation in the study
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Inability to comply with protocol
- Discretion of the investigator

In the case of pregnancy, the investigator must immediately notify the Sponsor or designate of this event. In the event a normal healthy female subject becomes pregnant during a clinical trial, the study drug must be discontinued immediately. In most cases, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Please contact the Sponsor or designate within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designate must occur.

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Follow up

In this study, PASI-75 is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug 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 subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, if possible. 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 drug 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 subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, texts, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both investigational [medicinal] product (IP/IMP) and non-investigational [medicinal] product (Non-IP/Non-IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection

Table 4-1: Study Drugs for IM011011

Product Description Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
BMS-986165 capsule	3 mg (as the free base)	IP	Blinded	Blister Card containing 48 active (3mg) and/or placebo capsules to equal required subject daily dosing/ Size #1 hard gelatin capsule	Store 2 to 8°C ; Protected from light
Placebo Matching BMS-986165 capsule	N/A	IP	Blinded	Blister Card containing 48 active (3mg) and/or placebo capsules to equal required subject daily dosing/ Size #1 hard gelatin capsule	Store 2 to 8°C ; Protected from light

4.1 Investigational Product

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

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

4.2 Non-investigational Product

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 as non-investigational products. Not applicable for this study.

4.3 Storage of Study Drug

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS (see Table 4-1). If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Please refer to Section 9.2.2 for guidance on IP records and documentation.

4.4 Method of Assigning Subject Identification

Within each panel, subjects will be randomized to receive either BMS-986165 at one of the doses being evaluated (3mg every other day, 3mg every day, 3 mg twice daily, 6mg twice daily, 12mg every day) or placebo according to a computer-generated randomization scheme prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research and Development. Randomization will be stratified by previous treatment with a biologic and region (Japanese vs rest of world).

Enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, (e.g., 00001, 00002, 00003.... 00010). Sequential numbering may restart at 00001 for each participating site as the distinct patient identification number (PID) will ultimately be comprised of the site number and subject number, (e.g., 0002 00001). Those enrolled subjects meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing.

During the screening visit, the investigative site will call into the enrollment option of the Interactive Web Response System (IWRS) designated by BMS for assignment of a 5-digit subject number that will be unique across all sites. Enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, (e.g., 00001, 00002, 00003....

00010). The patient identification number (PID) will ultimately be comprised of the site number and subject number. For example, the first subject screened (i.e., enrolled) at site number 1, will have a PID of 0001 00001. Once it is determined that the subject meets the eligibility criteria following the screening visit, the investigative site will call the IWRS to randomize the subject.

4.5 Selection and Timing of Dose for Each Subject

The BMS-986165 capsules (active or placebo) are provided in blister card kits which contain 48 capsules and will treat the patients for 8 days. The capsules will be arranged in 8 rows each containing four capsules to be taken each morning and two capsules to be taken at night, approximately 12 hours after the morning dose and will contain the appropriate combination of active and placebo to provide the subjects required daily dose (3mg every other day, 3mg every day, 3 mg twice daily, 6 mg twice daily, 12 mg every day, or placebo). It is essential that all patients finish all 8 days of treatment prior to starting a new blister card kit to ensure appropriate doses as identified above. If the subject forgets to take the dose, but remembers within 4 hours of the scheduled dose, then they should take it. If it is past 4 hours, they should miss that dose and take the next scheduled dose. Fasting is not required for drug administration, except on the days scheduled for blood collection under fasting conditions (Days 1, 8, 15, 29, 57 and 85). On these days, the morning dose should be administered at the investigator's site.

4.6 Blinding/Unblinding

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

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the medical monitor, but the investigatory always has ultimate authority for the decision to unblind. The principal investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

In cases of accidental unblinding, contact the medical monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a subject for non-emergency purposes should be discussed with the medical monitor.

In case of an emergency, the investigator(s) has unrestricted access to randomization information via the IWRS and is capable of breaking the blind through the IWRS system without prior approval from sponsor. Following the unblinding the Investigator shall notify the medical monitor and/or study director.

4.7 Treatment Compliance

At each study visit compliance with study drug will be reinforced. Subject diaries will be used to assist subjects in maintaining an accurate assessment of daily pill intake. Subject diaries and study blister pack will be required to be returned at every visit throughout the study.

4.8 Destruction or Return of Investigational Product

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

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

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

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

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

If conditions for destruction cannot be met the responsible BMS study monitor will make arrangements for return of IP provided by BMS (or its vendors). Destruction of non-IP sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designate.

Please refer to Section 9.2.2 for additional guidance on IP records and documentation

4.9 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1 and Table 5.1-2.

Table 5.1-1: Screening Procedural Outline (IM011011)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	A subject is considered enrolled only when a protocol specific informed consent is signed.
Inclusion/Exclusion Criteria	X	
Medical History	X	Include any toxicities or allergy related to previous treatments.
Safety Assessments		
Physical Examination (PE)	X	
Physical Measurements	X	Includes height, weight, and BMI.
Vital Signs	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 subject has been resting quietly for at least 5 minutes.
Electrocardiogram (ECGs)	X	ECGs should be recorded after the subject has been supine for at least 5 minutes. See Section 5.3.5
Chest X-ray	X	Chest x-ray is required if not performed within 6 months of Screening visit, documentation must be on file. See Section 5.3.4
Laboratory Tests		
Urinalysis	X	Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests. See Section 5.3.2
Hematology	X	Complete Blood Count (CBC) with differential Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests. See Section 5.3.2
Chemistry Panel	X	Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests. See Section 5.3.2
Serology	X	Includes Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B core antibody, and HIV-1 and HIV-2 antibodies. See Section 5.3.2
Tuberculosis Test	X	In accordance with BMS standard testing. See Section 5.3.4 of the protocol for more details.
Pregnancy Test (urine)	X	For WOCBP only.

Table 5.1-1: Screening Procedural Outline (IM011011)

Procedure	Screening Visit	Notes
Follicle Stimulating Hormone (FSH)	X	Women only, Refer to Section 3.3.3.
Study Procedures		
PASI Score Assessment	X	See Section 5.4
BSA Assessment	X	See Section 5.4
Adverse Event Reporting		
Monitor for Serious Adverse Events	X	All SAEs must be collected from the date of subject's written consent until 28 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time.

Table 5.1-2: On Treatment Procedural Outline for IM011011

Procedure	D1	D8 ±3 day	D15 ±3 day	D29 ±3 day	D57 ±3 day	D85 ±7 days[a]	Follow-Up visit D115	Notes
Safety Assessments								
Full Physical Examination (PE)	X			X	X	X	X	See Section 5.3.3
Targeted Physical Examination		X	X					See Section 5.3.3
Physical Measurements	X			X	X		X	Weight only
Vital Signs	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 subject has been resting quietly for at least 5 minutes.
Electrocardiograms (ECGs)	X	X	X	X	X	X	X	See Section 5.3.5
Laboratory Tests								
Hematology	X*	X	X	X	X	X	X	Including CBC with differential See Section 5.3.2 *predose (Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests Day 1)
Chemistry Panel	X*	X	X	X	X	X	X	See Section 5.3.2 *predose (Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests Day 1)
High sensitivity CRP	X*			X	X	X		See Section 5.3.2

Table 5.1-2: On Treatment Procedural Outline for IM011011

Procedure	D1	D8 ±3 day	D15 ±3 day	D29 ±3 day	D57 ±3 day	D85 ±7 days[a]	Follow-Up visit D115	Notes
(hsCRP)								*predose
Fasting Lipid Panel	X*					X		Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests See Section 5.3.2 *predose
Fasting Plasma Glucose	X*					X		Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests See Section 5.3.2 *predose
Fasting C-peptide	X*					X		Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests See Section 5.3.2 *predose
Urinalysis	X*	X	X	X	X	X	X	See Section 5.3.2 *predose (Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests on Day 1)
Serum Immunoglobulin Levels (IgM, IgG, IgA, IgE)	X*			X	X	X		See Section 5.3.2. *predose
Pregnancy Test (Urine)	X*			X	X	X	X	Female subjects only. *All women must have a negative pregnancy prior to dosing on Day 1.
Adverse Event Reporting								

Table 5.1-2: On Treatment Procedural Outline for IM011011

Procedure	D1	D8 ±3 day	D15 ±3 day	D29 ±3 day	D57 ±3 day	D85 ±7 days[a]	Follow-Up visit D115	Notes
Monitor for non-Serious Adverse Events	X	X	X	X	X	X	X	See Section 6.2 .
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	See Section 6.1
Pharmacokinetic (PK) Assessments								
Blood PK Sampling	X*	X	X	X	X	X		*Pre and post-dose. See Section 5.5 and
Study Procedure								
PASI Score Assessment	X	X	X	X	X	X	X	See Section 5.4
BSA Assessment	X	X	X	X	X	X	X	See Section 5.4
sPGA	X	X	X	X	X	X	X	See Section 5.4
Subject Global Assessment of Pain VAS	X	X	X	X	X	X	X	See Section 5.4
Medical Photography (skin)	X			X		X		At selected sites only. See Section 5.3.6
Skin Biopsy	X		X			X		See Section 5.3.7
Biomarker Assessments								
Target Engagement	X	X	X					See Section 5.6 (TE samples will be collected in the 1st 100 dosed subjects)
Blood PD Sampling	X	X	X	X	X	X	X	See Section 5.6
TBNK	X			X		X		See Section 5.6
Blood PaxGene RNA	X			X	X	X	X	See Section 5.6
CV/Metabolic blood sample (Serum)	X			X		X		See Section 5.6

Table 5.1-2: On Treatment Procedural Outline for IM011011

Procedure	D1	D8 ±3 day	D15 ±3 day	D29 ±3 day	D57 ±3 day	D85 ±7 days[a]	Follow-Up visit D115	Notes
CV/Metabolic blood sample (Plasma)	X			X		X		See Section 5.6
Other Assessments								
DLQI	X			X	X	X	X	See Section 5.4
Clinical Drug Supplies								
Dispense Study Drug	X	X	X	X	X			Subjects will be supplied with enough oral study drug (or placebo) to cover the intervals between study visits. See Section 4

[a] Evaluations performed prior to study discharge, or for subjects who are prematurely discontinued. In addition for subjects who are prematurely discontinued, the following should also be performed prior to study discharge: D85 procedure

Abbreviations: D = Day

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (i.e., the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the medical monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

The site will provide all required materials for the tests performed locally (i.e., relevant clinical laboratory tests and urine drug screens). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked basic cardiac life support (BCLS)] cart will be immediately available on the premises. The site will have urine collection containers, a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-20°C or below), as well as containers and dry ice for shipment and storage of blood and urine samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study.

Subjects will be provided with cooler bags and gel packs for transporting BMS-986165/matched placebo as it needs to be kept refrigerated,

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), and investigator brochure. Case report forms (electronic or hard copy) will be provided by BMS. The Central Laboratory will provide labels and tubes for the collection of blood samples forPK and biomarker samples.

Study supplies and documents (eg, electronic Case Reports Forms, patient drug logs, etc.) will be provided to the study center by BMS. Subject dosing diaries will be provided for each subject for completion throughout the study. IVRS/IWRS worksheets and instruction manuals will be provided by the IVRS/IWRS vendor.

5.3 Safety Assessments

On Day 1, the results of all assessments must be reviewed to assure that eligibility requirements are met before contacting the Central Randomization System for the subject's randomization assignment.

Subjects who terminate early will complete the Day 85/Early Termination (ET) Visit assessments. The Early Termination Visit should be as soon as possible after the last dose of

study medication (investigational product) and prior to the subject receiving a prohibited concomitant medication.

All assessments should be performed or administered prior to study drug administration unless otherwise indicated.

Every effort must be made to ensure the same evaluator will complete the assessments for each subject at all visits.

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of your institutional or medical practice standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested from the sponsor.

5.3.1 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment.

5.3.2 Laboratory Test Assessments

All laboratory assessments will be analyzed centrally with exception of pregnancy test.

The following clinical laboratory tests will be performed:

Hematology	
Hemoglobin Hematocrit Total leukocyte count, including differential Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) Uric acid Fasting glucose (Day 1 and Day 85 only) Fasting C-peptide (Day 1 and Day 85 only)	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase Creatinine clearance (CLcr)- 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 subject should be fasting at least 10 hours.

Urinalysis

Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick

Serology
Serum for hepatitis C antibody, hepatitis B surface antigen, Hepatitis B core antibody, HIV-1 and -2 antibody (screening only)

Other Analyses

Confirmatory Hepatitis B, C virus testing if positive serology: quantitative Hepatitis B viral load by PCR, quantitative Hepatitis C viral load by PCR (screening only)

TBNK flow cytometry panel - abnormalities in T, B, and NK cell subsets present at baseline do not necessarily warrant subject exclusion.

High sensitivity CRP (hsCRP) - abnormalities in hsCRP levels present at baseline do not necessarily warrant subject exclusion. Please discuss with the Medical Monitor.

Serum immunoglobulin levels: Total, IgA, IgE, IgG, IgM levels - abnormalities in serum immunoglobulin levels present at baseline do not necessarily warrant subject exclusion.

Tuberculosis test (at screening only)

Pregnancy test - WOCBP only: Urine pregnancy test
Follicle stimulating hormone (FSH) (screening only for women only)

Specialized Liver Laboratory Panel -(should only be done for elevated liver enzymes (see Appendix 6)

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (e.g., provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3).

5.3.3 Physical Exams

A complete physical examination will be obtained at specified timepoints as outlined in Table 5.1-1 and Table 5.1-2. The complete physical examination will consist of evaluation of the following systems: general, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, psychiatric, skin, and musculoskeletal. A targeted physical examination will be performed at other study visits. The targeted physical exam will consist of evaluation of the following systems: general, eyes, throat, cardiovascular, lungs, abdominal, extremities, and skin, musculoskeletal. Complete and targeted physical examinations may be performed by a Doctor of Medicine (MD), Doctor of Osteopathy (DO), Physician's Assistant (PA), or a Nurse Practitioner (NP). A targeted physical examination may note any changes in the subject's condition since the last assessment and does not preclude examination of any of the body systems as clinically indicated

5.3.4 Tuberculosis Screening and Chest X-Ray

A chest x-ray (CXR) and physical examination (PE) are considered part of the process to assess a subject's eligibility as outlined in Section 3.3.2. CXR 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 physical examination and medical history to evaluate exposure to tuberculosis, all subjects will have a screening test, an interferon gamma release assay [(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 study medical monitor.

Subjects with a positive screening test will not be eligible for the study unless they have completed at least four (4) weeks of treatment for latent TB prior to dosing of study drug, and the subject 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 1.

5.3.5 ECG

12-lead ECGs should be collected at times specified in Table 5.1-1 and Table 5.1-2. All scheduled ECGs should be performed after the subject 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.

5.3.6 Medical Photography (Optional)

Standard medical dermatology photographs of the affected areas of psoriasis will be taken at selected sites. BMS will host a training session prior to study initiation to demonstrate proper photographic technique of subjects with psoriasis. Subjects can request to have sensitive areas covered. Detailed instructions on the collection and transmission of digital images will be provided to the Investigator in a separate manual at or before the time of study initiation

5.3.7 Skin Biopsy

Skin biopsy is a standard diagnostic test performed for skin diseases, and has been used to characterize responses to therapeutic agents in patients diagnosed with psoriasis. Skin biopsy will be performed at 3 timepoints: Study Days 1 (for baseline evaluation), 15 and 85. The skin biopsies are voluntary, but subjects should be encouraged to participate. Four 4 mm punch skin biopsies will be collected prior to dosing at the baseline study visit (Day 1). Two skin biopsies will obtain involved skin tissue at approximately 3 mm from the edge of an active psoriatic plaque (lesional skin biopsy), and two biopsies will obtain uninvolved skin tissue (non-lesional skin biopsy). One of each type of skin biopsy, will be used for histolopathology analyses and the other will be used for RNA analyses. On Days 15 and 85 two 4mm punch biopsies will be obtained from the same skin plaque as the original lesional skin biopsies, and utilized for RNA and histopathologic analyses. The serial biopsies should avoid the scar tissue at the same location where previous biopsies have been taken. One of the biopsies should be placed in formalin as described in the study manual and the other half should be stored in RNA Later as described in the laboratory manual and shipped to the central laboratory. Complete details for the collection, processing, storage, shipment and analysis of samples will be provided in a separate Laboratory Manual. Skin biopsies should be performed by a qualified health care provider who has experience in biopsying psoriatic skin lesions.

5.4 Efficacy Assessments

5.4.1 Primary Efficacy Assessment

5.4.1.1 Psoriasis Area and Severity Index (PASI)

The PASI is a measure of the average redness, thickness, and scaliness of psoriatic skin lesions (each graded on a 0–4 scale), weighted by the area of involvement (head, arms, trunk to groin, and legs to top of buttocks).[26] The PASI produces a numeric score that can range from 0 to 72, with higher PASI scores denoting more severe disease activity. PASI can also be used to assess response to treatment. The PASI-50 is the proportion of subjects who experience at least a 50% improvement in PASI score as compared with 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 psoriasis patients (see Appendix 2).

5.4.2 Secondary Efficacy Assessments

5.4.2.1 Body Surface Area (BSA)

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

5.4.2.2 static Physician Global Assessment (sPGA)

The sPGA[30] is an average assessment of all psoriatic lesions based on erythema, scale, and induration. The static PGA determines psoriasis severity at a single point in time, without taking the baseline disease condition into clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5). PGA assessments should be performed by a dermatologist or appropriately trained investigator who is experienced in the assessment of psoriasis patients. Every effort should be made to ensure that the physician or designee who performed the sPGA evaluations for a subject at randomization performs the sPGA for that subject at all subsequent visits (see Appendix 3).

5.4.2.3 Dermatology Life Quality Index (DLQI)

The DLQI[31] is a subject reported quality of life index which consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work, school, personal relationships, and treatment during the last week. Each question is scored on a scale of 0 to 3 by a tick box: "not at all", "a little", "a lot", or "very much". The scores are summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment) (see Appendix 4).

[redacted]

5.5 Pharmacokinetic Assessments

Pharmacokinetics of BMS-986165 will be derived from plasma concentration versus time data. The pharmacokinetic parameters to be assessed include:

Ctrough	Trough observed plasma concentration

5.5.1 Pharmacokinetics: Collection and Processing

Table 5.5.1-1 lists the sampling schedule to be followed for the assessment of pharmacokinetics. Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 5.5.1-1: Pharmacokinetics Sampling Schedule

Study Day of Sample Collection	Event	Time (Relative To BMS-986165 Dose) Hour: Min	BMS-986165 Blood Sample for PK	Notes
1	predose[a]	00:00	X	
1		00:30	X	
1		01:00	X	
8	Predose[a]	00:00	X	
15	Predose[a]	00:00	X	
15*		00:30	X	*These post-dose samples maybe drawn at any scheduled visit day after Day 15 (i.e On Day 29, 57 or 85)
15*		01:00	X	
15*		04:00	X	
15*		06:00	X	
29	Predose[a]	00:00	X	
57	predose[a]	00:00	X	
85	predose[a]	00:00	X	

[a] predose samples must be drawn before the morning dose on the Visit Day

5.5.2 Pharmacokinetic Sampling Window

It is expected that every effort is made to collect PK samples at the times indicated. However for flexibility in PK sampling, the following windows serve as a guideline for PK sample collection:

Pre-dose samples must be drawn before the morning dose on the Visit Day

For other samples:

- +/- 1 hour for the samples within the first two hours of dosing
- +/- 3 hours for the 4 and 6 hour sample.

The samples should be collected using the time point labels provided even if outside suggested window. Any missed PK sample collections should be noted in the source documents.

5.5.3 Pharmacokinetic Sample Analyses

The plasma samples will be analyzed for BMS-986165 by a validated LC/MS/MS assay. Pharmacokinetic samples collected from a subject who received placebo will not be analyzed.

In addition, plasma samples will be archived for potential metabolite analysis, if the need arises and to the extent possible.

5.5.4 Labeling and Shipping of Biological Samples

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

[redacted]

5.7 Outcomes Research Assessments

Not applicable.

5.8 Other Assessments

Not applicable.

5.9 Additional Research Collection

This protocol will include residual sample storage for additional research (AR). This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc. All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development to ensure the research supports appropriate and well-defined scientific research activities.

Residual serum, plasma, RNA and skin biopsy samples from skin biopsy, skin biopsy RNA, blood for PD assessments and blood RNA collections (see Table 5.9-1) will also be retained by the BMS Biorepository in Hopewell, NJ or at a BMS approved third party storage management facility for additional research purposes. Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections.

Table 5.9-1: Residual Sample Retention for Additional Research Schedule

Sample	Timepoints for which residual samples will be retained
Blood for PD	All
Skin Biopsy histology	All
Skin Biopsy RNA	All
Blood RNA	All
CV/Metabolic (Plasma)	All
CV/Metabolic (Serum)	All

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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

Sponsor or designate will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- 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 result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an SAE (see Section 6.1.1 for reporting details.

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., 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)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing.

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

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to Sponsor or designate within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

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

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

All SAEs must be followed to resolution or stabilization.

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

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious adverse event.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the Sponsor or designate of this event and complete and forward a Pregnancy Surveillance Form to the BMS designate within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Please call the Sponsor or designate within 24 hours of awareness of the pregnancy.

The investigator must immediately notify the Sponsor or designate of this event and complete and forward a Pregnancy Surveillance Form to Sponsor or designate within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designate. In order for BMS to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event (see Appendix 6 flow chart for sustained elevated liver safety abnormalities). All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. Aminotransaminases (AT) (ALT or AST) elevation > 3 times upper limit of normal (ULN)

   AND

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

   AND

3. No other immediately apparent possible causes of AT 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.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, or any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

An Independent Data Monitoring Committee (IDMC) will be established to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study, to ensure the integrity of the blinded nature of the study, and to oversee the planned interim analyses. An IDMC charter will be developed which 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 patients and their study partners.

Data summaries and listings will be provided to the IDMC to facilitate their safety assessment at the regularly scheduled times on an ad hoc basis if needed. The safety review includes serious adverse events 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 Charter of that Committee along with the processes and procedures the committee will follow.

8 STATISTICAL CONSIDERATIONS

8.1 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 subjects with moderate to severe psoriasis experiencing a 75% improvement reduction in psoriasis area and severity index (PASI) score after 12 weeks, between BMS-986165 and placebo arms. With a one-sided, two-sample Fisher's exact test at significant level 0.05, a sample size of 42 per arm will provide at least 99% power to detect 50% increase in the PASI-75 response rate in an active

arm (i.e., 60% response rate) compared to the placebo assuming the response rate is 10% in the placebo arm.

The second consideration is to assess the response rate in PASI-75 in active dose arms. Data from 42 treated subjects per arm will produce a two-sided 95% confidence interval with a margin of error at most 15.1% (half width) using normal approximation.

The third consideration is to compare the response rates in PASI-75 in two active arms. With one-sided, two-sample Fisher's exact test at significant level 0.05, 42 subjects per arm will provide at least 82% power to detect at least 30% difference in the response rate in PASI-75 between any two active dose arms.

The proposed sample size is mainly driven by the third consideration. In addition, administration of BMS-986165 to 42 subjects in each active treatment group provides 34%, 88%, and 99% probability of observing at least one occurrence of any adverse event that would occur with 1%, 5%, or 10% incidence rate respectively.

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who sign an informed consent.
- All Randomized Subjects: All subjects who are randomized to a treatment. Subjects will be analyzed as per randomized treatment. All efficacy analyses will be performed using this population.
- All Treated Subjects: All subjects who have received at least one dose of study treatment. This population will be used for safety analyses and will be analyzed as per actual treatment received.
- Biomarker Analysis Population: All subjects that receive any study medication and have at least 1 post-treatment biomarker measurement.
- Pharmacokinetic Population: All subjects who receive any study medication and have any available concentration-time data.

All subjects who receive study drug will be included in the safety data set. All available data from subjects who receive BMS-986165 will be included in the pharmacokinetic data set. All available data from subjects for whom pharmacodynamic measurements are available at baseline and at least one other time will be included in the pharmacodynamic data set.

Summary analyses of safety, pharmacokinetic, pharmacodynamic, biomarker, and efficacy data will be based on all treated subjects. For analyses such as PK parameter estimations, the analyses will be based on all treated subjects with adequate data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary efficacy endpoint is the proportion of subjects in the study experiencing a 75% reduction from baseline in the PASI score after 12 weeks.

The safety and tolerability of BMS-986195 will be assessed by the incidence, potential significance, and clinical importance of adverse events measured during multiple doses of BMS-986195 and up to 30 days after the last dose, as determined by medical review of adverse event reports, vital sign measurements, electrocardiograms (ECGs), and results of physical examination and laboratory tests.

8.3.2 Secondary Endpoint(s)

The secondary efficacy endpoints are

- the proportion of subjects at week 12 with PASI-50, PASI-75, PASI-90, PASI-100
- sPGA score, DLQI score and the proportion of subjects with moderate to severe psoriasis in each category of these endpoints after week 12 of treatment

The secondary endpoint to assess PK is Ctrough.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, height, and Body Mass Index (BMI) will be tabulated. In addition, baseline disease activities will be tabulated by treatments using descriptive statistics.

8.4.2 Efficacy Analyses

Primary Efficacy Analyses

The primary endpoint, the proportion of subjects with moderate to severe psoriasis experiencing a 75% improvement reduction in PASI score after 12 weeks, will be analyzed by two-sample Fisher's exact test or Chi-square test to compare the response rates between each treatment group and placebo. Cochran–Mantel–Haenszel Chi-square test, stratified according to previous treatment with a biologic and/or region (Japanese vs rest of world), will be performed. The odds ratio (odd in a treatment group/odd in placebo) in the response rates and its corresponding two-sided 90% confidence interval (CI) will be provided when using Fisher's exact test or

Cochran-Matel-Haenszel Chi-square test. If Chi-square test is performed, the difference in the response rates and its corresponding two-sided 90% confidence interval (CI) will be provided.

In addition, point estimate and 90% asymptotic and exact two-sided confidence intervals will be provided for the proportion of subjects in PASI-75 in each group. A logistic regression model may be performed to incorporate some of the covariates if these covariate are assumed to impact the response rates. Details of the tests and models will be given in the statistical analysis plan.

Secondary Efficacy Analyses

Similar analyses as in primary efficacy analyses will be performed to compare any two active arms.

A logistic model will be conducted to detect a positive trend between treatment groups of BMS-986165.

The response rate in PASI-50, PASI-75, PASI-90, and PASI-100 will be summarized by treatment and time and will be analyzed using a repeated measure model when applicable. The same analyses will be conducted stratified by previous biologic treatment and/or region. The proportion of subjects with a sPGA score of "0" or "1" will be analyzed similarly to the primary analyses. sPGA, and DLQI Score from psoriasis subjects will be tabulated by treatment and time; the corresponding changes from baseline and percent change from baseline will be calculated and summarized.

For continuous secondary endpoints (e.g. PASI, etc), point estimates and two-sided 90% confidence intervals for mean change from baseline within each treatment group will be provided. For binary endpoints (PASI, sPGA, etc.), point estimates of the response rate and two-sided 90% confidence intervals will be provided using normal approximation within each treatment group.

In addition, a two-sided 90% confidence interval will be provided for the difference in the secondary efficacy endpoints between each active arm and the placebo arm at each visit. More analyses, such as analysis of covariance models with treatment group, use of previous biologic treatment, and baseline value included as covariates, may be performed on endpoints such as PASI score, sPGA score, DLQI, etc.

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 to be nominal and may be provided if applicable.

[redacted]

8.4.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

8.4.4 Pharmacokinetic Analyses

Ctrough will be summarized by time for BMS-986165 in subjects with moderate to severe psoriasis. Additional details will be provided in the statistical analysis plan (SAP) as necessary.

[redacted]

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

8.4.8.1 Population PK and Exposure Response Analysis

Analysis of PK and exposure-response relationships of BMS-986165 will be conducted using a population approach as appropriate and reported separately from the clinical study report.

8.5 Interim Analyses

There are no planned interim analyses for the current study.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

- IRB/IEC

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

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

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

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

9.1.2 Monitoring

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

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

In addition, the study may be evaluated by BMS or designate 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 BMS or designate.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

9.2 Records

9.2.1 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 designate, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS or designate prior to destroying any records associated with the study and BMS or designate will notify the investigator when the study records are no longer needed.

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

9.2.2 Study Drug Records

Records for IP (whether supplied by BMS, its vendors, or the site) must substantiate IP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designate or a Health Authority.

If...	Then...
Supplied by BMS (or its vendors):•	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designate accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

For sites using the Sponsor or designate electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the or electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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

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

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

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

9.3 Clinical Study Report and Publications

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

For this protocol, the signatory investigator will be selected as appropriate based on the following criteria:

External principal investigator designated at protocol development

National coordinating investigator

Study steering committee chair or their designate

Subject recruitment (e.g., among the top quartile of enrollers)

Involvement in trial design

Regional representation (e.g., among top quartile of enrollers from a specified region or country)

Other criteria (as determined by the study team)

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

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.
Additional Research	Those scientific activities which cannot be reasonably anticipated at the time of trial design, for which we would like to collect and/or retain samples from study participants. Examples of additional research include, but are not limited to, new assay development and validation, companion diagnostic development, new hypotheses in the interaction of drug and the human body, and exploration of emerging science in the understanding of disease.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AR	Additional research
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
BA/BE	bioavailability/bioequivalence
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BSA	Body Surface Area

Term	Definition
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride
CLcr	creatinine clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (e.g., concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (e.g., concentration at 24 hours, concentration at 12 hours, etc.)
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DMC	Data monitoring committee
DLQI	Dermatology Quality Life Index
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)

Term	Definition
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
e.g.	exempli gratia (for example)
ESR	Expedited Safety Report
F	bioavailability
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Council on Harmonisation
i.e.	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board

Term	Definition
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	potassium
kg	kilogram
L	liter
LAM	Lactation amenorrhea method
LC	liquid chromatography
LDH	lactate dehydrogenase
ln	natural logarithm
mg	milligram
Mg^{++}	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na^+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time

Term	Definition
Pu	percent of unbound drug
Q2D	Every other day
QC	quality control
QD, qd	quaque die, once daily
R^2	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
sPGA	Static Physician's Global Assessment
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
T-HALFeff_AUC	Effective elimination half life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	Effective elimination half life that explains the degree of Cmax accumulation observed)
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

APPENDIX 1 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 3 days after the end of study treatment, plus 30 days

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. 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.* • 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 5. • Acceptable alternate methods of highly effective contraception must be discussed in the

event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 3 days after the end of treatment plus an additional 90 days.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 3 days after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 3 days after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and until 3 days after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 2 PSORIASIS AREA AND SEVERITY INDEX (PASI)

The PASI is a grading system used for the evaluation of the severity of psoriatic lesions and their response to treatment. The PASI produces a numeric score that can range from 0 to 72. The severity of a subject's disease is calculated as described below:

In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (ux) and lower extremities (lx), which account for 10%, 30%, 20%, and 40% respectively of the total body surface area (BSA). Each of these areas are evaluated for erythema, induration and scaling, which are rated on a scale from 0 to 4.

The scoring system for the signs of disease (erythema, in duration and scaling) is below:

0 = none
1 = slight
2 = moderate
3 = severe
4 = very severe

The scoring system for estimating the area of involvement for psoriatic lesions is outlined below:

0 = no involvement
1 = 1% to 9% involvement
2 = 10% to 29% involvement
3 = 30% to 49% involvement
4 = 50% to 69% involvement
5 = 70% to 89% involvement
6 = 90% to 100% involvement

To aid in the area assessments, the following conventions are followed:

a. the neck is considered part of the head
b. the axilla and groin are considered part of the trunk
c. the buttocks are considered part of the lower extremities

The PASI formula is:

$$PASI = 0.1(E_h + S_h + I_h)A_h + 0.3(E_t + S_t + I_t)At + 0.2(E_{ux} + S_{ux} + I_{ux})A_{ux} + 0.4(E_{lx} + S_{lx} + I_{lx})A_{lx}$$

Clinical assessments of response should be performed by the same assessor(s).

APPENDIX 3 STATIC PHYSICIAN'S GLOBAL ASSESSMENT (SPGA)

The Physician Global Assessment (PGA) is used to determine the subject's psoriasis lesions overall at a given time point. Overall lesions will be graded for induration, erythema, and scaling based on the scales below. The sum of the 3 scales will be divided by 3 to obtain a final PGA score.

Induration (I) (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)

0 = no evidence of plaque elevation

1 = minimal plaque elevation, = 0.25 mm

2 = mild plaque elevation, = 0.5 mm

3 = moderate plaque elevation, = 0.75 mm

4 = marked plaque elevation, = 1 mm

5 = severe plaque elevation, = 1.25 mm or more

Erythema (E) (averaged over all lesions)

0 = no evidence of erythema, hyperpigmentation may be present

1 = faint erythema

2 = light red coloration

3 = moderate red coloration

4 = bright red coloration

5 = dusky to deep red coloration

Scaling (S) (averaged over all lesions)

0 = no evidence of scaling

1 = minimal; occasional fine scale over less than 5% of the lesion

2 = mild; fine scale dominates

3 = moderate; coarse scale predominates

4 = marked; thick, nontenacious scale dominates

5 = severe; very thick tenacious scale predominates

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

Physician's Static Global Assessment based upon above Total Average

0 = Cleared, except for residual discoloration

1 = Minimal - majority of lesions have individual scores for I + E + S / 3 that averages 1

2 = Mild - majority of lesions have individual scores for I + E + S / 3 that averages 2

3 = Moderate - majority of lesions have individual scores for I + E + S / 3 that averages 3

4 = Marked - majority of lesions have individual scores for I + E + S / 3 that averages 4

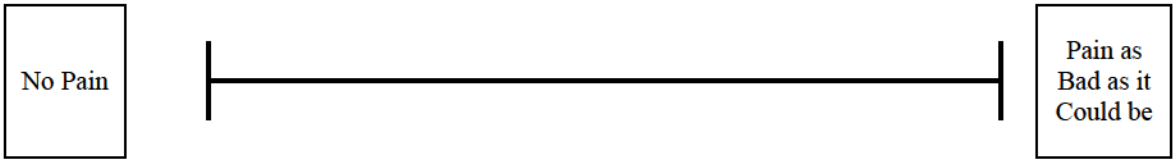
5 = Severe - majority of lesions have individual scores for I + E + S / 3 that averages 5

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

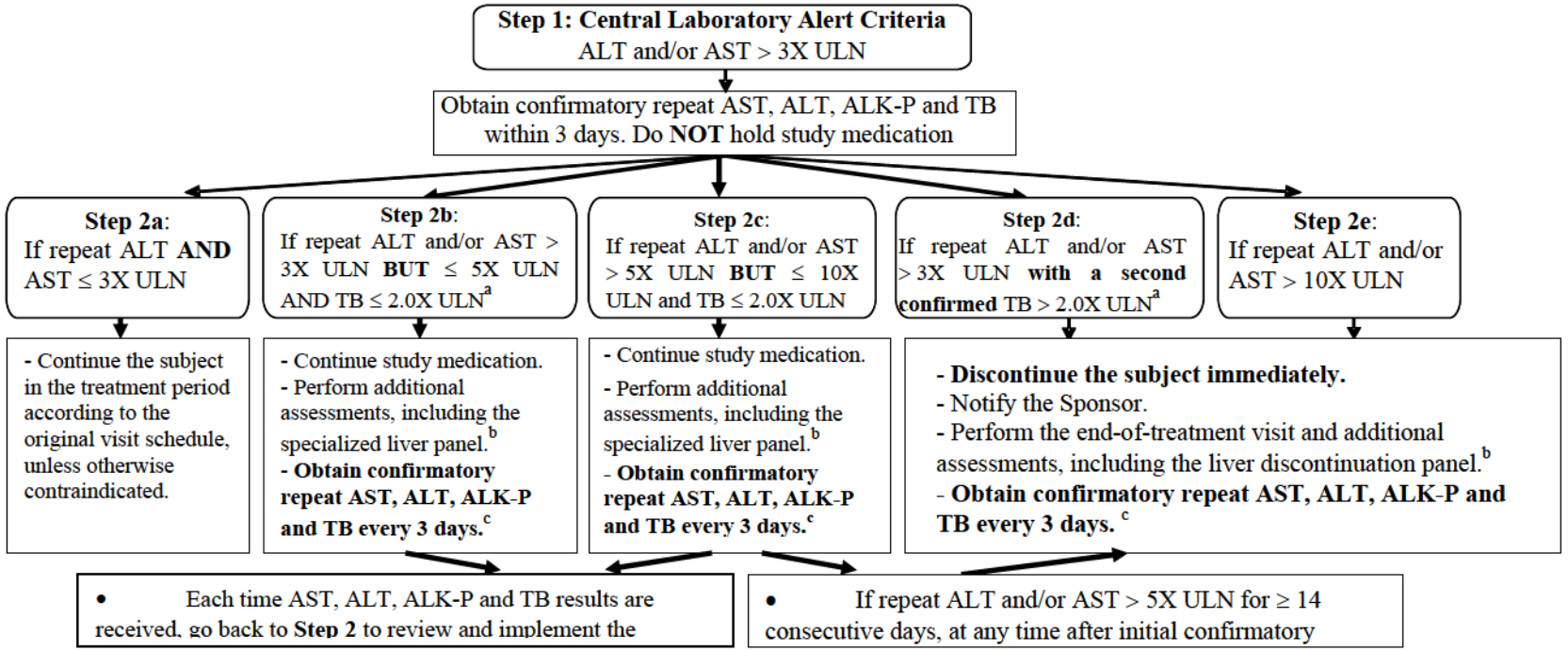
APPENDIX 5 AMERICAN COLLEGE OF RHEUMATOLOGY SUBJECT ASSESSMENT OF PAIN VISUAL ASSESSMENT SCALE

Measure with a metric ruler. Line on Case Report Form is exactly 10 cm long. Scores should be recorded in millimeter format. DO NOT USE THIS APPENDIX AS SOURCE DOCUMENT OR CASE REPORT FORM.

How much pain have you had because of your condition over the past week? Place a mark on the line below to indicate how severely your pain has been:



APPENDIX 6 SUSTAINED ELEVATED LIVER SAFETY ABNORMALITIES FLOW CHART



[a] In subjects with repeat ALT or AST > 3X ULN but ≤ 10X ULN, only subjects with TB ≤ 2.0X ULN at Step 1 should be followed according to Step 2b. Subjects with an initial TB and confirmatory repeat TB > 2.0X ULN should be followed according to Step 2d.

[b] additional assessments to be performed (AE assessment, PE, review of current medical history including focused review of risk factors for liver diseases and collection of blood samples [specialized liver panel or liver discontinuation panel](see below)).

[c] Confirmatory repeat AST, ALT, ALK-P and TB should be obtained every 3 days following receipt of prior laboratory results, until the ALT and AST are ≤ 2X ULN or until ALT and AST are at or below baseline levels. The frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic.

Specialized Liver Panel:

For subjects who are being monitored frequently as a result of confirmed AST and/or ALT > 3X ULN, additional central laboratory tests will be performed within 3 days of receipt of confirmatory results. These laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

- Hepatitis A IgM
- Hepatitis BsAg
- Hepatitis B Core Ab IgM
- Hepatitis C virus RNA or RIBA
- Hepatitis C Ab
- Hepatitis E IgM
- Epstein-Barr Virus (EBV) IgM Ab
- Lactate Dehydrogenase (LDH)
- Gamma-glutamyl-transpeptidase (GGT)
- Carbohydrate deficient transferrin (CDT)
- Prothrombin time (PT/INR)
- Iron Panel - iron, ferritin, total iron binding capacity (TIBC)
- Immunology Panel including Antinuclear Antibody (ANA), Anti-Smooth Muscle Antibody (SMA) and Anti-Liver/Kidney Microsomal Antibody (Anti-LKM)
- Anti-tissue Transglutaminase Antibody

Liver Discontinuation Panel:

For subjects who are discontinued from the study as a result of sustained elevated liver safety abnormalities, additional central laboratory tests will be performed at the time of Early Termination (End-of-Treatment) visit. Similar to the Specialized Liver Panel, these laboratory tests will study the possible causes of the increased ALT and/or AST and/or TB, and may include, but are not limited to, the following tests:

- Cytomegalovirus (CMV) IgM Ab
- Herpes Simplex Virus (HSV) 1 and 2
- Ceruloplasmin
- Toxoplasmosis
- Alpha-1 antitrypsin