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|---|---|
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# Clinical Protocol IM011046

A Multi-Center, Randomized, Double-Blind, Placebo- and Active Comparator-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis

**Short Title**: Efficacy and Safety of BMS-986165 versus Placebo and Active Comparator in Subjects with Psoriasis

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## DOCUMENT HISTORY

| Document | Date of Issue | Approver(s) | Summary of Change |
|---|---|---|---|
| Original Protocol | 18-May-2018 | [redacted] | Not applicable |
| Amendment 01 | 15-Jun-2018 | | Clarified that Psoriasis Symptoms and Signs Diary (PSSD) daily data collection will begin at the Screening Visit and, for randomized subjects, will continue daily through Week 52. |
| Amendment 02 | 17-Jul-2018 | | Japan-Specific Amendment |
| Amendment 03 | 03-Oct-2018 | | China-Specific Amendment |

| | | | |
|---|---|---|---|
| | | [redacted] | |
| Amendment 04 | 20-Nov-2018 | | Updated the Sponsor's contact information, made typographic corrections to the protocol, clarified certain procedures, updated wording in Appendix 3 to be consistent across studies of BMS-986165, described treatment assignment details, and revised certain exclusion criteria to be consistent with certain elements of the Phase 2 study of BMS-986165 in psoriasis as well as other Phase 3 studies in psoriasis |
| Amendment 05 | 12-Dec-2018 | | German-Specific Amendment |
| Amendment 06 | 14-May-2019 | | As this is designed to be a global study across multiple countries, randomization in each country will be targeted to approximately 35% or less of the total sample size. This change is being implemented to achieve geographical representation across countries and to minimize the potential for any single country to have a disproportionate impact on the overall efficacy and/or safety profile.<br>Other changes include: |

| | | | |
|---|---|---|---|
| | | | -Updated text in the definition of sPGA in Section 8.1.1.1 to be consistent with the description in Appendix 5. [redacted] |
| Amendment 07 | 06-June-2019 | [redacted] | Revised the testing order (hierarchy) of key secondary endpoints [redacted] revised the text in the synopsis, Table 4 and in Sections 9.3.2.1 and 9.3.2.2 accordingly as follows:<br>• Removed endpoints containing 'PSSD sign score.' The reason for this change is that PSSD sign score is redundant with components assessed by PASI and sPGA which are already in the hierarchy.<br>• Removed 'change from baseline in DLQI score.' The reason for this change is that DLQI endpoint 'DLQI 0/1 among subjects with baseline DLQI score ≥2' is clinically meaningful and is already in the hierarchy.<br>• Changed the comparisons to apremilast from 'sPGA 0/1 at Week 52', 'PASI 75 at Week 52', and 'PASI 90 at Week 52' to 'sPGA 0/1 at Week 52 and Week 24', 'PASI 75 at Week 52 and Week 24', and 'PASI 90 at Week 52 and Week 24'. The reason for these changes is to assess maintenance of effect. |

| | | | |
|---|---|---|---|
| Amendment 08 | 24-Jun-2019 | [redacted] | China-Specific Amendment |
| Amendment 09 | 12-Jul-2019 | | Germany-Specific Amendment – Included changes listed above for Global Amendments 04, 06 and 07 |
| Global Revised Protocol 10 | 17-Dec-2019 | | Made the following updates:<br>• provided clarifications in the protocol to aid sites and subjects in the conduct of the study.<br>• added and updated relevant protocol deviation criteria for the Per Protocol Set<br>• corrected typographical errors<br>• added a new analysis for systemic treatment-naïve subjects to the set of subgroup analysis for the coprimary efficacy endpoints |

## SUMMARY OF CHANGES

**Rationale:**

The primary purpose of this global revised protocol is to provide clarifications in the protocol to aid sites and subjects in the conduct of the study.

Key modifications and clarifications are summarized as follows:

- Add clarifying detail to several items in the protocol
- [redacted]
- Added and updated relevant protocol deviation criteria for the Per Protocol Set
- Added a new analysis for systemic treatment-naïve subjects to the set of subgroup analysis for the coprimary efficacy endpoints

Substantive changes made to the previous version of the global protocol and the rationale for these changes are noted below in the summary of key changes table. All changes applied to the protocol body were applied to the synopsis, as necessary; synopsis changes are not included in the summary of key changes table. Only major additions and deletions are provided in this summary document; all minor grammatical, formatting, stylistic changes, or clarifications as well as organizational changes are not included.

| Protocol Section | Revised Protocol Text | Rationale for Change |
|---|---|---|
| Schedule of Assessments Table 3 | Removed Targeted PE from the Week 52 visit | There is already a scheduled Full PE for the Week 52 visit. |

| Protocol Section | Revised Protocol Text | Rationale for Change |
|---|---|---|
| 4.1.6.2 Infection Adjudication Committee<br><br>4.1.6.3 CV Committee<br><br>4.1.6.4 Suicidal Ideation and Behavior Adjudication Committee | Updated text to:<br>An independent Infection Adjudication Committee, composed of individuals with relevant expertise, will **blindly** review and adjudicate infection AEs, such as opportunistic infections, influenza, herpes zoster, and TB, reported in the study **per criteria specified in a separate charter.**<br><br>An independent Cardiovascular (CV) Adjudication Committee, composed of individuals with relevant expertise, will **blindly** review and adjudicate cardiovascular and cerebrovascular AEs such as, but not limited to, Major Adverse Cardiovascular Events (MACE) that include death, non-fatal myocardial infarction, non-fatal stroke; revascularization procedures; heart failure; dysrhythmias; heart blocks; and thrombotic events reported in the study **per criteria specified in a separate charter.**<br><br>An independent Suicidal Ideation and Behavior Adjudication Committee, composed of individuals with relevant expertise, will **blindly** review and adjudicate suicidal ideation/behavior reported in the study **per criteria specified in a separate charter.** | To clarify that the data will be reviewed in a blinded manner by the study's Adjudication committees. |
| 5.3 Lifestyle Restrictions | Updated text:<br>General skin care measures (with above restrictions for topical treatments) that are standard for patients with plaque psoriasis **are permitted**. | To clarify general skin care measures used in the trial. |
| [redacted] | | |

| Protocol Section | Revised Protocol Text | Rationale for Change |
|---|---|---|
| 6.7.1 Prohibited and/or Restricted Treatments | Updated or added text:<br>7) Any use of oral psoriasis medications (eg, methotrexate, cyclosporine, retinoids, fumaric acid derivatives) **for any indication**<br>8) Any use of oral **or injectable** corticosteroids (prednisone, methylprednisolone, etc.), unless it is considered necessary for the subject's welfare and/or treatment of an AE/SAE<br>**Note: otic, ophthalmic, nasal, or inhaled corticosteroids within recommended doses and with no systemic effects are permitted**<br>9) Any topical medications/treatments, **which are used for any indication,** that could affect psoriasis evaluation (including, but not limited to, high potency corticosteroids (**WHO** Classes I-V), >3% salicylic acid, urea, alpha- or beta-hydroxyl acids, anthralin, calcipotriene, vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, and tacrolimus)<br>Exception: The following topical treatments may be initiated only at Week 24 per investigator's discretion in subjects who have sPGA scores ≥ 3 (See Section 4.1.4):<br>• High potency corticosteroids (**WHO** Classes I-V), >3% salicylic acid, urea, alpha- or beta hydroxyl acids, anthralin, calcipotriene, vitamin D derivatives, retinoids, tazarotene<br>**Note: Low potency topical steroids (WHO Classes VI and VII) are permitted on the palms, soles, face, and intertriginous areas but should not be used within 24 hours prior to any study visit. Bland emollients (defined as emollients without urea or alpha or beta-hydroxy acids or other ingredients which are pharmaceutically active) are allowed on all body regions but should not be used within 24 hours prior to any study visit.** | Added clarifying detail around these prohibited medications |
| 6.7.2 Permitted Concomitant Medications | Note: Low potency topical steroids **(WHO Classes VI and VII)** are permitted on the palms, soles, face, and intertriginous areas **but should not be used within 24 hours prior to any study visit. Bland emollients (defined** as emollients without urea or alpha or beta hydroxy acids **or other ingredients which are pharmaceutically active) are allowed on all body regions but** should not be used within 24 hours prior to any study visit. | Added clarifying detail around these medications |
| 8.4.7 Suicidal Ideation and Behavior Monitoring | Subjects who answer yes to Questions 4 or 5 **which indicates a** suicidal ideation **severity level of 4 or 5** or document suicidal behavior or suicidal attempts on the eC-SSRS will have their treatments discontinued and be immediately referred to a mental health professional for further evaluation**.** | Clarified to sites to what levels of suicidal ideation Questions 4 and 5 refer. |

| Protocol Section | Revised Protocol Text | Rationale for Change |
|---|---|---|
| [redacted] | | |

| Protocol Section | Revised Protocol Text | Rationale for Change |
|---|---|---|
| 9.2 Populations for Analyses | Changed to:<br>Full Analysis Set (FAS): All subjects who **were randomized to receive assigned** study **treatment.** Following the intent-to-treat principle, subjects will be analyzed according to the treatment **group** assigned at randomization. The FAS will be the primary efficacy analysis population.<br>Per Protocol Set (PPS): A subset of the FAS who are compliant with study treatment and who do not have any **relevant** protocol deviations that may impact the coprimary efficacy endpoint assessments **(Section 9.6.3). The PPS will be analyzed for the coprimary endpoint comparison according to the treatment assigned at randomization.**<br>As-treated **Population**: All randomized subjects who take at least one dose of study treatment. Subjects will be analyzed according to treatment received. **The As-treated population will be for safety analyses.**<br>[redacted] | To align populations for testing coprimary efficacy endpoints in order and to clarify that Per Protocol set will be a subset of FAS to assess the sensitivity of coprimary endpoints results based on FAS with respect to data irregularity and deviations |
| 9.4.1.4 Subgroup Analyses for the Coprimary Endpoints | Added: Prior systemic treatment of psoriasis (yes/no) | To determine whether treatment effect sizes of BMS-986165 compared to placebo are similar or how much different with respect to prior use of systemic treatment affects |

| Protocol Section | Revised Protocol Text | Rationale for Change |
|---|---|---|
| 9.6.3 Relevant Protocol Deviations | Changed to:<br>**Relevant protocol deviations are deviations that can have an impact on the primary efficacy endpoints.** The impact of **relevant** protocol deviations on the **primary** efficacy results will be assessed by excluding subjects from the **FAS to define the** PPS in supportive analyses of the primary efficacy endpoints. **Relevant** protocol deviations to be considered regarding exclusion of subjects from the **FAS will** include the following:<br>Subject **randomized but** did not take any study **treatment**<br>Subject failed to meet study inclusion criteria but was **randomized to receive** study **treatment**<br>Subject met **a** study exclusion criterion **which may have an impact on the coprimary efficacy endpoints** but was **randomized to receive** study **treatment**<br>Subject non-compliant with study **treatment within the first 16 weeks of treatment; defined as <80% compliant with study treatment**<br>Subject took prohibited concomitant medication **prior to Week 16**<br>**Subject received treatment different to intended treatment at any visit prior to Week 16**<br><br>**All subjects with relevant protocol deviations will be identified prior to database lock. Relevant protocol deviations will be summarized by treatment group and deviation category for the FAS population.** | To clarify and document the final list of relevant protocol deviations for Per Protocol Analysis. |

## TABLE OF CONTENTS

## LIST OF TABLES



[redacted]

## LIST OF FIGURES

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:** A Multi-Center, Randomized, Double-Blind, Placebo- and Active Comparator-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis

**Short Title:** Efficacy and Safety of BMS-986165 versus Placebo and Active Comparator in Subjects with Psoriasis

**Study Phase:** 3

**Rationale:**

BMS-986165 is being evaluated as a therapeutic option for the treatment of subjects with moderate-to-severe plaque psoriasis based on results of a recently completed 12-week, randomized, Phase 2, placebo-controlled, parallel-group study (Study IM011011). The Phase 2 study was conducted with the following 5 different BMS-986165 treatment arms: 3 mg every other day (QOD); 3 mg once daily (QD); 3 mg twice daily (BID); 6 mg BID; and 12 mg QD. Overall, 267 subjects were randomized (44 to 45 subjects per treatment arm) in the Phase 2 study. All BMS-986165 treatment groups, except 3 mg QOD, achieved the primary endpoint of superiority compared with placebo in the proportion of subjects experiencing at least a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) after 12 weeks of treatment. Compared with the placebo treatment group (6.7%), 38.6% ($p = 0.0003$), 68.9% ($p < 0.0001$), 66.7% ($p < 0.0001$) and 75% ($p < 0.0001$) of the subjects treated with BMS-986165 at 3 mg QD, 3 mg BID, 6 mg BID and 12 mg QD doses achieved a PASI 75 response, respectively. The PASI 75 responses appear to plateau at the dose of 3 mg BID. The current Phase 3 study is designed to confirm the efficacy and safety of BMS-986165 6 mg QD which is expected to have equivalent efficacy as the 3 mg BID dose in Phase 2, in a larger global population of subjects with stable moderate-to-severe plaque psoriasis.

**Study Population:**

Men and women ≥18 years of age diagnosed with stable (defined as no morphology changes or significant flares of disease activity in the opinion of the investigator) plaque psoriasis for ≥6 months and with moderate-to-severe disease by involvement of ≥10% of body surface area (BSA), static Physician's Global Assessment (sPGA) ≥3, PASI score ≥12, and candidates for phototherapy or systemic therapy will be eligible to participate in the study.

**Objectives and Endpoints:**

| Objective | Endpoint |
|---|---|
| **Primary** | |
| • Assess whether BMS-986165 is superior to placebo at Week 16 in the treatment of subjects with moderate-to-severe plaque psoriasis | • sPGA 0/1<br>• PASI 75 |
| **Selected Secondary Endpoints** | |
| • Assess whether BMS-986165 is superior to apremilast at Week 16 | • sPGA 0/1<br>• PASI 75<br>• PASI 90<br>• sPGA 0<br>• PASI 100 |
| • Assess whether BMS-986165 is superior to apremilast at Week 52 | • sPGA 0/1<br>• PASI 75<br>• PASI 90<br>• sPGA 0<br>• PASI 100 |
| • Assess whether BMS-986165 is superior to placebo over the first 16 weeks of treatment | • sPGA 0/1<br>• PASI 75<br>• PASI 90<br>• sPGA 0<br>• PASI 100 |
| • Assess whether BMS-986165 is superior to apremilast over 52 weeks of treatment | • sPGA 0/1<br>• PASI 75<br>• PASI 90<br>• sPGA 0<br>• PASI 100 |
| • Evaluate improvement in patient-reported outcomes for BMS-986165 compared with placebo through Week 16<br>• Evaluate improvement in patient-reported outcomes for BMS-986165 compared with apremilast through Week 24 | • Change from baseline in Psoriasis Symptoms and Signs Diary (PSSD) symptom score, sign score, and total score<br>• Change from baseline in Dermatology Life Quality Index (DLQI) score |

| Objective | Endpoint |
|---|---|
| [redacted] | |

**Overall Design:**

This will be a 52-week, multi-center, randomized, double-blind, double-dummy, placebo- and active comparator-controlled study in subjects with stable moderate-to-severe plaque psoriasis. Subjects will undergo screening evaluations within 28 days prior to administration of study medication to determine eligibility. Following the screening process, approximately 600 qualified subjects will be randomized in a 2:1:1 ratio to one of the following 3 treatment groups:

- BMS-986165 6 mg QD
- Placebo
- Apremilast 30 mg BID (with initial titration per label) as active comparator

Randomization should not occur until at least 8 days after the Screening Visit to allow collection of PSSD data during screening in order to calculate a baseline PSSD score. Randomization will be stratified by geographic region (U.S., Japan [body weight stratum will not be applied in Japan], China [body weight stratum will not be applied in China], and Rest of World), previous biologic use (for psoriasis, psoriatic arthritis or other inflammatory diseases only; yes/no), and body weight (≥90 kg and <90 kg). If subjects from China are not enrolled in the study, then the stratification level for China will not be utilized. As this is designed to be a global study across multiple countries, randomization in each country will be targeted to approximately 35% or less of the total sample size. This change is being implemented to achieve geographical representation across countries and to minimize the potential for any single country to have a disproportionate impact on the overall efficacy and/or safety profile.

At Week 16, subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD. Subjects who are randomized to BMS-986165 6 mg QD or apremilast 30 mg BID will continue their current dose through Week 52.

At Week 24, subjects originally randomized to apremilast 30 mg BID who do not achieve PASI 50 response will be switched in a blinded manner to BMS-986165 6 mg QD; those who achieve PASI 50 response will continue to receive their current regimen through Week 52. A subject with sPGA ≥3 at Week 24 may be treated with restricted topical medications, such as topical high

potency corticosteroids (WHO Classes I-V), only at this time point at the discretion of the investigator.

Subjects who discontinue study treatment early should remain in the study for protocol-specified procedures (Please refer to Section 7.1 for more details). Those completing 52 weeks of treatment will be offered the opportunity to roll over to a separate long-term extension study (≥2 years) and be treated with open-label BMS-986165 6 mg QD.

**Treatment Arms and Duration:**

**Study treatment:** Subjects in all treatment groups will take oral doses of the investigational product (IP) for 52 weeks during treatment as follows: BMS-986165 6 mg QD, apremilast 30 mg BID (titrated as per label), or placebo QD.

| **Study Treatment for IM011046** | | |
|---|---|---|
| **Medication** | **Potency** | **IP/Non-IP** |
| BMS-986165 tablet | 6 mg | IP |
| apremilast tablet | 10 mg* | IP |
| apremilast tablet | 20 mg† | IP |
| apremilast tablet | 30 mg‡ | IP |
| placebo tablet | n/a | IP |

IP = investigational product; n/a = not applicable
*Used for titration Day 1 through Day 3 morning dose
†Used for titration Day 3 evening dose through Day 5 morning dose.
‡From Day 5 evening dose onwards

**Statistical Methods**

General Methodology

The primary efficacy analysis population will be the Full Analysis Set (FAS). The FAS will include all randomized subjects who are dispensed study drug.

The analysis model for the coprimary efficacy endpoints and secondary binary endpoints will use stratified Cochran-Mantel-Haenszel (CMH) tests stratified by the factors used for randomization (see Sec. 4.1.2) to compare the response rates of BMS-986165 6 mg QD to placebo or apremilast as applicable. If expected cell counts are not sufficient for each strata level, then strata levels will be combined for the analysis. Nonresponder imputation will be used for binary endpoints for subjects who discontinue study or treatment of study prior to Week 16, start a protocol prohibited medication/therapy that could improve psoriasis during the first 16 weeks of treatment, or who have otherwise missing endpoint data at the specified timepoint.

The analysis model for continuous secondary endpoints will use analysis of covariance (ANCOVA) with treatment and the factors used for randomization as fixed effects. The baseline value will be added into the model as a covariate. Treatment differences based on least-squares (LS) means and the corresponding 2-sided 95% confidence intervals (CIs) will be provided for the difference between BMS-986165 6 mg QD and placebo or apremilast depending on the endpoint being assessed.

Testing Strategy for Efficacy Endpoints

The primary family of coprimary endpoints will each be tested at a Type I error=0.05 first, and if significant for both endpoints, testing will proceed for the secondary family of key secondary endpoints [redacted]. The primary family of coprimary endpoints will be the serial gatekeeper for proceeding with testing of the secondary family of key secondary efficacy endpoints.

Primary Family – Coprimary endpoints compared with placebo; both must be significant at a Type I error=0.05 in order to proceed with the secondary family tests for the key secondary endpoints:

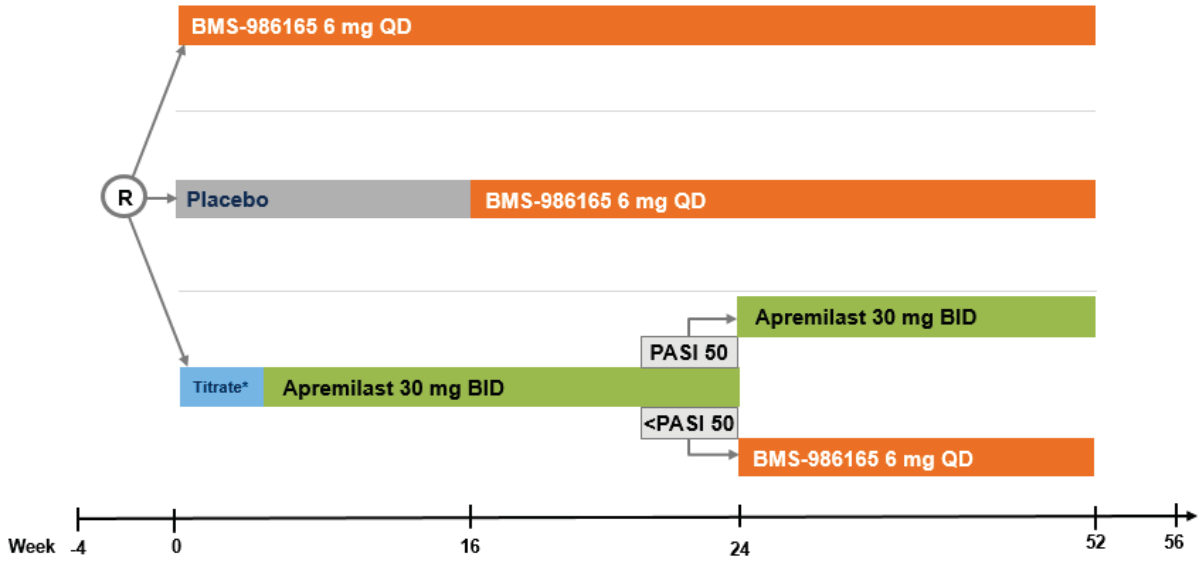
- Primary 1: Proportion of subjects who achieve sPGA 0/1 at Week 16
- Primary 2: Proportion of subjects who achieve PASI 75 at Week 16

In order to control for Type I error rate inflation within the secondary family of key secondary endpoints, separate testing branches with a 2-sided Type I error=0.025 will be used for comparisons of BMS-986165 6 mg QD compared to placebo and BMS-986165 6 mg QD compared to apremilast. A hierarchical testing method within each testing branch will be implemented for the key secondary endpoints. The hierarchical test may only proceed to the next key secondary endpoint within each testing branch if the null hypothesis is rejected a Type I error=0.025. If an endpoint fails at any step, then all subsequent p-values will be considered descriptive.

Safety Analysis

Safety data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency distributions (counts and percentages) for categorical variables.

## 1.2 Schema




*Apremilast is titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing
Abbreviations: BID = twice daily; QD = once daily; R = randomize

The coprimary endpoints will be evaluated at Week 16. The duration of the study for each subject will be up to 52 weeks on treatment and 4 additional weeks for safety follow-up.

## 1.3 Schedule of Activities (SOA)

The schedules of assessments and procedures are documented in Table 1 for screening, Table 2 for baseline through Week 20, and Table 3 for Week 24 through Week 52.

**Table 1: Screening Procedural Outline (IM011046)**

| Procedure | Screening V1 | Notes |
|---|---|---|
| **Eligibility Assessments** | | |
| Informed Consent | X | A subject is considered enrolled only when a protocol-specific informed consent is signed |
| Enroll Subject | X | Obtain number from IRT |
| Inclusion/Exclusion Criteria | X | Includes duration of plaque psoriasis and documentation of presence of plaque psoriasis by the investigator |
| Medical History | X | See Section 5.2 for complete eligibility criteria associated with medical history. Of note, subjects need to be screened for any current uncontrolled neuropsychiatric illness or history of suicidality; any history of TB; any congenital or acquired immunodeficiency; any significant drug allergy such as anaphylaxis; any cancer currently or in the previous 5 years. Investigators are encouraged to check whether subjects have had preventive health measures such as cancer screening (e.g. Pap smear, colonoscopy, mammograms) that is up to date according to local guidelines |
| History of Tobacco Use | X | Include description of current tobacco use |
| Psoriasis-related History | X | Includes scalp symptoms, PsA/joint pain, nail involvement, palmoplantar involvement, genital involvement, history of other forms of psoriasis |
| Psoriasis-related Systemic Treatment | X | History of: conventional systemic (eg, methotrexate), biologic, and/or phototherapy. For each therapy, include length of time on treatment and reason(s) for discontinuation (eg, lack of efficacy, intolerance, side effects, loss of access to treatment) if applicable. |
| Other Prior and Concomitant Treatments | X | Includes topical treatments and shampoos for psoriasis and all medications for other conditions such as cardiovascular and mood disorders |
| **Safety Assessments** | | |
| Physical Examination | X | Complete PE |

**Table 1: Screening Procedural Outline (IM011046)**

| Procedure | Screening V1 | Notes |
|---|---|---|
| Physical Measurements | X | Includes height and weight |
| 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 | X | ECGs should be recorded after the subject has been supine for at least 5 minutes |
| Chest Imaging (eg, Chest x-ray) | X | Chest imaging is required if not performed within 6 months of Screening Visit, copy of radiology report must be on file and reviewed by the investigator. Section 8.4.4 |
| Neuropsychiatric Illness Assessment | X | Based on subject/family response, medical history/medical records, investigator judgment |
| PHQ-8 | X | For establishing baseline depression severity |
| Suicidal Ideation and Behavior Assessment | X | Based on subject/family response, medical history/medical records, investigator judgment |
| eC-SSRS | X | eC-SSRS Assessment: Response of "Actual Suicide Attempt-Lifetime" or suicidal ideation (Severity of 4 or 5) or suicidal behavior will be exclusionary. Rescreening will not be allowed. Section 8.4.7 |
| Monitor for SAEs | X | All SAEs must be collected from the date of subject's written consent until 30 days post discontinuation of dosing or subject's participation in the study. |
| **Laboratory Tests** | | |
| Hematology | X | Complete Blood Count (CBC) with differential |
| Chemistry Panel | X | |
| Lipid Panel | X | |
| Urinalysis | X | |
| Hemoglobin A1C | X | |

**Table 1: Screening Procedural Outline (IM011046)**

| Procedure | Screening V1 | Notes |
|---|---|---|
| TSH | X | If TSH above normal reference range, test free T4; if TSH below normal range, test free T4 & T3 |
| hs-CRP | X | |
| Serology | X | Includes HCV antibody, HBsAg, HBsAb, HBcAb, HBV DNA, and HIV antibodies |
| TB Test | X | In accordance with QuantiFERON-TB Gold. (details described in Section 8.4.4). |
| Pregnancy Test (serum) | X | For WOCBP only |
| FSH | X | To confirm menopausal status (see APPENDIX 4) |
| **Clinical Efficacy/Health Outcomes** | | |
| sPGA | X | |
| PASI | X | |
| BSA | X | |
| PASE Questionnaire | X | For subjects with peripheral joint complaints to screen for presence of psoriatic arthritis |
| PSSD | X | All consented subjects will be given a diary device at the Screening Visit and will begin recording psoriasis signs and symptoms on a daily basis in the diary device. Subjects who are not randomized will stop recording and return their diary device to the site. Subjects who are randomized will continue recording their psoriasis signs and symptoms on a daily basis in the diary device through Week 52. |

BSA = body surface area; CBC = complete blood count; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; IRT = interactive response technology; PASE = psoriatic arthritis screening and evaluation; PASI = Psoriasis Area and Severity Index; PE = physical examination; PHQ-8 = eight-item Patient Health Questionnaire; PsA = psoriatic arthritis; PSSD = Psoriasis Symptoms and Signs Diary; SAE = serious adverse events; sPGA = static Physician Global Assessment; T3 = triiodothyronine; T4 = thyroxine; TB = tuberculosis TSH = thyroid-stimulating hormone; V = visit; WOCBP = women of childbearing potential



Approved v2.0 [redacted]

**Table 2: On Treatment Procedural Outline (IM011046): Week 0 through Week 20**

| Procedure | Week 0 Baseline/D1 V2 | Week 1 D8 (±3 d) V3 | Week 2 D15 (±3 d) V4 | Week 4 D29 (±3 d) V5 | Week 8 D57 (±3 d) V6 | Week 12 D85 (±3 d) V7 | Week 16 D113 (±3 d) V8 | Week 20 D141 (±3 d) V9 | Notes |
|---|---|---|---|---|---|---|---|---|---|
| **Clinical Efficacy/Health Outcomes** | | | | | | | | | |
| DLQI | X | X | X | X | X | X | X | [redacted] | |
| [redacted] | | | | | | | | | |
| sPGA | X | X | X | X | X | X | X | X | |
| PASI | X | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | |
| ss-PGA[a] | X | X | X | X | X | X | X | [redacted] | |

**Table 2: On Treatment Procedural Outline (IM011046): Week 0 through Week 20**

| Procedure | Week 0 Baseline/D1 V2 | Week 1 D8 (±3 d) V3 | Week 2 D15 (±3 d) V4 | Week 4 D29 (±3 d) V5 | Week 8 D57 (±3 d) V6 | Week 12 D85 (±3 d) V7 | Week 16 D113 (±3 d) V8 | Week 20 D141 (±3 d) V9 | Notes |
|---|---|---|---|---|---|---|---|---|---|
| [redacted] | | | | | | | | | |
| PGA-F[b] | X | | | X | X | X | X | | |
| [redacted] | | | | | | | | | |
| Palmoplantar PGA[c] | X | X | X | X | X | X | X | | |
| [redacted] | | | | | | | | | |
| PSSD | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | |
| Complete PE | X | | | | | | X | | |
| Targeted PE | | X | X | X | X | X | | X | See Section 8.4.1 |
| Body Weight | X | | | | X | | X | | |
| Vital Signs | X | X | X | X | X | X | X | X | |
| ECG | X | | | | | | X | | |
| PHQ-8 | X | | | | X | | X | | See Section 8.4.6.1 |
| eC-SSRS Assessment | X | | | | X | | X | | Suicidal Ideation and Behavior since last visit |
| Adverse Event (AE) Assessment | X | X | X | X | X | X | X | X | |
| Concomitant Medication Use | X | X | X | X | X | X | X | X | |
| **Laboratory Tests** | | | | | | | | | |

**Table 2: On Treatment Procedural Outline (IM011046): Week 0 through Week 20**

| Procedure | Week 0 Baseline/D1 V2 | Week 1 D8 (±3 d) V3 | Week 2 D15 (±3 d) V4 | Week 4 D29 (±3 d) V5 | Week 8 D57 (±3 d) V6 | Week 12 D85 (±3 d) V7 | Week 16 D113 (±3 d) V8 | Week 20 D141 (±3 d) V9 | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Hematology | X | X | X | X | X | X | X | X | |
| Lymphocyte Subsets (TBNK) | X | | | | X | | X | | |
| Chemistry Panel | X | X | X | X | X | X | X | X | If CK >2.5 × ULN, reflex testing is required (see Section 8.4.5) |
| Hemoglobin A1C | X | | | | | | X | | |
| hs-CRP | X | X | X | X | X | | X | X | |
| Fasting Lipid Panel | X | | | | X | | X | | |
| Fasting Plasma Glucose | X | | | | X | | X | | |
| Urinalysis | X | | | | | | X | | |
| Serum Immunoglobulin Levels (IgM, IgG, IgA, IgE) | X | | | | X | | X | | |
| Pregnancy Test (Urine) | X | | | X | X | X | X | X | WOCBP only |
| **Study Treatment** | | | | | | | | | |
| Randomize | X | | | | | | | | |
| Dispense Study Treatment | X | | X | X | X | X | X | X | |
| Study Treatment Compliance | | X | X | X | X | X | X | X | See Section 6.6 |
| [redacted] | | | | | | | | | |



Approved v2.0 [redacted]

**Table 2: On Treatment Procedural Outline (IM011046): Week 0 through Week 20**

| Procedure | Week 0 Baseline/D1 V2 | Week 1 D8 (±3 d) V3 | Week 2 D15 (±3 d) V4 | Week 4 D29 (±3 d) V5 | Week 8 D57 (±3 d) V6 | Week 12 D85 (±3 d) V7 | Week 16 D113 (±3 d) V8 | Week 20 D141 (±3 d) V9 | Notes |
|---|---|---|---|---|---|---|---|---|---|
| [redacted] | | | | | | | | | |

[redacted] eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; CK = creatine kinase; [redacted] D = Day; d = days; DLQI = Dermatology Life Quality Index; [redacted]; ECG = electrocardiogram; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; [redacted] hs-CRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; [redacted] PASI = Psoriasis Area and Severity Index; PE = physical examination; PGA = Physician Global Assessment; PGA-F = Physician Global Assessment-Fingernails; [redacted] PHQ-8 = eight-item Patient Health Questionnaire; [redacted] PSSD = Psoriasis Symptoms and Signs Diary; [redacted] sPGA = static Physician Global Assessment; ss-PGA = scalp specific Physician's Global Assessment; TBNK = T cells, B cells, and natural killer cells; ULN = upper limit of normal; V = visit; [redacted] Wk = Week; [redacted] WOCBP = women of childbearing potential

[redacted]

[b] In subjects with nail psoriasis at baseline
[c] In subjects with palmoplantar psoriasis at baseline
[d] If sample is missed, it may be taken at any visit once informed consent is obtained.

When multiple assessments are conducted at a single visit, the following is the order in which they should be done:
1) Health outcomes assessments
2) Safety assessments (eg, vitals, AEs)
3) Clinical efficacy assessments
4) Laboratory tests (eg, safety laboratory tests, [redacted])

On fasting days, safety assessments can be done first followed by blood draws, and then health outcomes and finally efficacy assessments.
The dose of the drug on a visit day is to be taken after blood draws.



Approved v2.0 [redacted]

**Table 3: On Treatment Procedural Outline (IM011046): Week 24 through Week 52**

| Procedure | Week 24 D169 (±3 d) V10 | Week 28 D197 (±3 d) V11 | Week 32 D225 (±3 d) V12 | Week 36 D253 (±3 d) V13 | Week 40 D281 (±3 d) V14 | Week 44 D309 (±3 d) V15 | Week 48 D337 (±3 d) V16 | Week 52[a] (or early DC) D365 (±3 d) V17 | Safety Follow-Up[b] (Week 56) D393 (±3 d) V18 | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| **Clinical Efficacy/Health Outcomes** | | | | | | | | | | |
| [redacted] | | | | | | | | | | |
| sPGA | X | X | X | X | X | X | X | X | | |
| PASI | X | X | X | X | X | X | X | X | | |
| [redacted] | | | | | | | | | | |

**Table 3: On Treatment Procedural Outline (IM011046): Week 24 through Week 52**

| Procedure | Week 24 D169 (±3 d) V10 | Week 28 D197 (±3 d) V11 | Week 32 D225 (±3 d) V12 | Week 36 D253 (±3 d) V13 | Week 40 D281 (±3 d) V14 | Week 44 D309 (±3 d) V15 | Week 48 D337 (±3 d) V16 | Week 52[a] (or early DC) D365 (±3 d) V17 | Safety Follow-Up[b] (Week 56) D393 (±3 d) V18 | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | |
| Full PE | X | | | | | | | X | X | |
| Targeted Physical Examination | | X | X | X | X | X | X | | | |
| Body Weight | X | | | X | | | | X | X | |
| Vital Signs | X | X | X | X | X | X | X | X | X | |
| ECG | X | | | | | | | X | | |
| PHQ-8 | | X | | | X | | | X | | See Section 8.4.6.1 |
| eC-SSRS | | X | | | X | | | X | | Suicidal Ideation and Behavior since last visit |
| AE Assessment | X | X | X | X | X | X | X | X | X | |
| Concomitant Medication Use | X | X | X | X | X | X | X | X | X | |
| **Laboratory Tests** | | | | | | | | | | |
| Hematology | X | X | X | X | X | X | X | X | X | |
| Lymphocyte Subsets (TBNK) | | | | X | | | | X | | |

**Table 3: On Treatment Procedural Outline (IM011046): Week 24 through Week 52**

| Procedure | Week 24 D169 (±3 d) V10 | Week 28 D197 (±3 d) V11 | Week 32 D225 (±3 d) V12 | Week 36 D253 (±3 d) V13 | Week 40 D281 (±3 d) V14 | Week 44 D309 (±3 d) V15 | Week 48 D337 (±3 d) V16 | Week 52[a] (or early DC) D365 (±3 d) V17 | Safety Follow-Up[b] (Week 56) D393 (±3 d) V18 | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| Chemistry Panel | X | X | X | X | X | X | X | X | X | If CK >2.5 × ULN, reflex testing is required (see Section 8.4.5) |
| Fasting Lipid Panel | X | | | | | | | X | | Subjects are required to fast for at least 10 hours prior to collection |
| Fasting Plasma Glucose | X | | | | | | | X | | |
| hs-CRP | X | | | X | | | | X | | |
| Hemoglobin A1C | | | | X | | | | X | | |
| Urinalysis | | | | X | | | | X | X | |
| Serum Immunoglobulin Levels (IgM, IgG, IgA, IgE) | | | | X | | | | X | | |
| Pregnancy Test (Urine) | X | X | X | X | X | X | X | X | X | WOCBP Only |
| [redacted] | | | | | | | | | | |

**Table 3: On Treatment Procedural Outline (IM011046): Week 24 through Week 52**

| Procedure | Week 24 D169 (±3 d) V10 | Week 28 D197 (±3 d) V11 | Week 32 D225 (±3 d) V12 | Week 36 D253 (±3 d) V13 | Week 40 D281 (±3 d) V14 | Week 44 D309 (±3 d) V15 | Week 48 D337 (±3 d) V16 | Week 52[a] (or early DC) D365 (±3 d) V17 | Safety Follow-Up[b] (Week 56) D393 (±3 d) V18 | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study Treatment** | | | | | | | | | | |
| Blinded PASI Response Transferred Electronically to IRT | X | | | | | | | | | To determine PASI 50 response at Week 24 |
| Dispense Study Treatment | X | X | X | X | X | X | X | | | |
| Study Treatment Compliance | X | X | X | X | X | X | X | X | | |

BMI = body mass index; [redacted] eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; CK = creatine kinase; [redacted] hs-CRP = High-sensitivity C-reactive protein; IRT = interactive response technology; PASI = Psoriasis Area and Severity Index; [redacted] PHQ-8 = eight-item Patient Health Questionnaire; [redacted] sPGA = static Physician Global Assessment; [redacted] TBNK = T cells, B cells, and natural killer cells; ULN = upper limit of normal; Wk = Week; [redacted] WOCP = women of childbearing potential

[a]For subjects who discontinue study treatment prior to Week 52, please refer to Section 7.1 for more details.
[b]For subjects who do not continue in a long-term extension study

[redacted]

When multiple assessments are conducted at a single visit, the following is the order in which they should be done:
1) Health outcomes assessments
2) Safety assessments (eg, vitals, AEs)
3) Clinical efficacy assessments
4) Laboratory tests (eg, safety laboratory tests, [redacted])

On fasting days, safety assessments can be done first followed by blood draws, and then health outcomes and finally efficacy assessments.
The dose of the drug on a visit day is to be taken after blood draws.

## STUDY ACKNOWLEDGMENT/DISCLOSURE

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

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

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

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

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

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

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

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

Original Protocol ☐ Revised Protocol ☒

Protocol Number: IM011046_____ Site Number: _____

Date of Protocol or Revised Protocol: 17 Dec 2019

IND Number: 131,993 EUDRACT Number: 2018-001926-25

Investigator _____ Date_____
(signature)

_____
(printed name*)

# 2 INTRODUCTION

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

Treatments include topical preparations, eg, corticosteroids, vitamin D analogues, calcineurin inhibitors, and salicylic acid; phototherapy modalities, including PUVA (psoralens with UVA) and narrow band UVB; and systemic therapies. In moderate-to-severe disease, systemic treatments are usually needed and may include oral agents (retinoids, methotrexate, cyclosporine, and apremilast) or injectables (eg, biologics such as tumor necrosis factor (TNF) inhibitors etanercept, infliximab, and adalimumab) anti-IL-12/23p40 antibody (ustekinumab), IL-17 antagonists (secukinumab, ixekizumab, and brodalumab), and anti-IL-23p19 antibody (guselkumab). Many of these treatments are associated with increased risk of adverse events (AEs) such as hepatotoxicity and neutropenia (methotrexate);[10] nephrotoxicity (cyclosporine);[11] depression and weight loss (apremilast);[12] serious infections (cytokine inhibitors);[13,14,15,16] candidiasis and Crohn's disease (IL-17 antagonists).[16, 17, 18]

Although effective therapeutic options are available, under-treatment or nontreatment of psoriasis has been reported in up to half of surveyed patients (based on absence of treatment and/or dissatisfaction with treatment).[19] Many patients with severe disease are still being managed with only topicals,[4,8] and many patients consider their psoriasis treatment to be inadequate. Accordingly, there remains a need for more effective oral options, when compared with currently available agents, that would improve efficacy responses and increase adherence to treatment.

## 2.1 Study Rationale

BMS-986165 could be a therapeutic option for the treatment of subjects with moderate-to-severe plaque psoriasis based on results of a recently completed 12-week, randomized, Phase 2, placebo-controlled, parallel-group study with 5 different BMS-986165 treatment arms: 3 mg every other

day (QOD); 3 mg once daily (QD); 3 mg twice daily (BID); 6 mg BID; and 12 mg QD (Study IM011011). Overall, 267 subjects were randomized (44 to 45 subjects per treatment arm) in the Phase 2 study. All BMS-986165 treatment groups, except 3 mg QOD, achieved the primary endpoint of superiority compared with placebo in the proportion of subjects achieving PASI 75 after 12 weeks of treatment. Compared with placebo treatment group, in which 6.7% of the subjects achieved PASI 75 response, 38.6% ($P = 0.0003$), 68.9% ($P < 0.0001$), 66.7% ($P < 0.0001$) and 75% ($P < 0.0001$) of subjects treated with 3 mg QD, 3 mg BID, 6 mg BID, and 12 mg QD achieved PASI 75, respectively. The PASI 75 responses plateaued at a dose of 3 mg BID. Also, there was a clinically significant proportion of subjects treated with BMS-986165 achieving an sPGA score of 0 or 1 compared with placebo at Week 12. Compared with the placebo treatment group in which 6.7% of the subjects achieved an sPGA score of 0 or 1, 41.5%, 75.6%, 65.9%, and 75% of the subjects treated with 3 mg QD, 3 mg BID, 6 mg BID, and 12 mg QD achieved an sPGA score of 0 or 1, respectively with responses again plateauing at dose of 3 mg BID. The Phase 3 dose selected (6 mg QD) is expected to demonstrate equivalent efficacy to the 3 mg BID dose. Please refer to [redacted]

This Phase 3 study is designed to confirm the efficacy and safety of BMS-986165 6 mg QD and demonstrate its superiority to a widely used oral agent, apremilast, in a larger global population of subjects with moderate-to-severe plaque psoriasis.

## 2.2 Background

Tyrosine kinase 2 (TYK2) is a nonreceptor tyrosine kinase associated with receptors for the p40-containing cytokines IL-12 and IL-23, as well as the Type I interferon (IFN) receptor, and is required for the activation of their downstream signaling pathways. TYK2 catalyzes the phosphorylation of the intracellular receptor domains and signal transducer and activator of transcription (STAT) proteins resulting in the activation of STAT-dependent transcription and functional responses specific for these cytokines.[20,21,22] Because TYK2-dependent cytokines (eg, Type I IFNs, IL-12, IL-23) are distinct from those dependent on closely related Janus kinase (JAK) family members JAK1/JAK3 (eg, IL-2, IL-15, IL-7) or JAK2 (eg, erythropoietin, thrombopoietin, GM-CSF), a TYK2 inhibitor would be expected to have a highly differentiated profile from inhibitors of other JAK family kinases. TYK2-dependent pathways and the cytokine networks they modulate (eg, IL-23/IL-17, IFNα) have been implicated in the pathophysiology of multiple immune-mediated diseases, including psoriasis, lupus, spondyloarthritides, and Crohn's disease.

BMS-986165 is a potent, highly-selective, oral, small molecule inhibitor of TYK2. A comprehensive in vitro and in vivo characterization of BMS-986165 has been established and supports the development of this compound in humans. Inhibition of TYK2 is expected to provide therapeutic benefit for subjects with psoriasis for multiple reasons: 1) Many of the pathways in the TYK2 signaling cascade (IL-23 and the downstream mediators IL-17 and IL-22; IFNα) have been implicated in pathogenesis of psoriasis.[8] 2) Biologic agents targeting the IL-17, IL-23p19, and IL-12/23 p40 pathways have been approved for and are highly efficacious in the treatment of psoriasis.

[redacted]

[redacted]

### 2.2.1 Early Clinical Development

The clinical data available to date supporting the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of BMS-986165 are from 5 completed Phase 1 studies in healthy subjects (IM011002, IM011015, IM011016, IM011031, and IM011039) and 1 completed Phase 2 study in adult subjects with moderate-to-severe plaque psoriasis (IM011011).

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

[redacted]

[redacted]

# 3 OBJECTIVES AND ENDPOINTS

**Table 4: Objectives and Endpoints**

| Objective | Endpoint |
|---|---|
| **Primary** | |
| • Assess whether BMS-986165 is superior to placebo at Week 16 in the treatment of subjects with moderate-to-severe plaque psoriasis | • static Physician Global Assessment (sPGA) 0/1 response<br>• Psoriasis Area and Severity Index (PASI) 75 response (defined as a 75% improvement in PASI score from baseline) |
| **Secondary** [redacted] | |
| • Assess whether BMS-986165 is superior to apremilast at Week 16 | • sPGA 0/1 response<br>• PASI 75 response<br>• PASI 90 response<br>• sPGA 0 response<br>• PASI 100 response |
| • Assess whether BMS-986165 is superior to apremilast at Week 52 | • sPGA 0/1 response<br>• PASI 75 response<br>• PASI 90 response<br>• sPGA 0 response<br>• PASI 100 response |
| • Assess whether BMS-986165 is superior to placebo over the first 16 weeks of treatment | • sPGA 0/1 response<br>• PASI 75 response<br>• PASI 90 response<br>• sPGA 0 response<br>• PASI 100 response<br>[redacted] |
| • Assess whether BMS-986165 is superior to apremilast over 52 weeks of treatment | • sPGA 0/1 response<br>• PASI 75 response |

**Table 4: Objectives and Endpoints**

| Objective | Endpoint |
|---|---|
| | • PASI 90 response<br>• sPGA 0 response<br>• PASI 100 response<br>[redacted] |
| • Assess whether BMS-986165 is superior to placebo in scalp psoriasis through Week 16 in those subjects who have baseline scalp severity Physician's Global Assessment (ss-PGA) score ≥3<br>[redacted] | • ss-PGA 0/1 response<br>[redacted] |
| • Assess whether BMS-986165 is superior to placebo in nail psoriasis through Week 16 in those subjects who have baseline Physician's Global Assessment-Fingernail (PGA-F) psoriasis score ≥3<br>[redacted] | • PGA-F 0/1 response<br>[redacted] |
| • Assess whether BMS-986165 is superior to placebo in palmoplantar psoriasis through Week 16 in those subjects who have baseline palmoplantar Physician's Global Assessment (pp-PGA) score ≥3 | • pp-PGA 0/1 response<br>[redacted] |
| • Evaluate improvement in patient-reported outcomes for BMS-986165 compared with placebo through Week 16<br>• Evaluate improvement in patient-reported outcomes for BMS-986165 compared with apremilast through Week 52 | • Change from baseline in Psoriasis Symptoms and Signs Diary (PSSD) symptom score, sign score, and total score<br>[redacted]<br>• Change from baseline in Dermatology Life Quality Index (DLQI) score |

**Table 4: Objectives and Endpoints**

| Objective | Endpoint |
|---|---|
| | • DLQI 0/1 (among subjects with a baseline DLQI score ≥2) |

# 4 STUDY DESIGN

## 4.1 Overall Design

This will be a 52-week, multi-center, randomized, double-blind, double-dummy, placebo- and active comparator-controlled study to evaluate the safety and efficacy of BMS-986165 vs placebo and apremilast. A total of 600 qualified subjects with moderate-to-severe plaque psoriasis will be enrolled.

The duration of study participation is approximately 60 weeks and will be divided into the following periods: screening (up to 4 weeks), treatment (52 weeks), and follow-up (4 weeks).

Physical exams, 12-lead ECGs, clinical laboratory evaluations, and other assessments will be done at select visits during the study. Subjects in this study will be monitored for AEs.

### *4.1.1 Screening Period*

Subjects will be evaluated during the screening period to ensure they meet eligibility criteria. A detailed medical history will be done at this time, as well as a complete physical exam. Psoriasis-related history, which will include length of diagnosis, body involvement, and history of systemic treatment, will be assessed here. Depression and suicidality assessments will also be performed. An evaluation for tuberculosis will be done based on medical history, recent chest imaging, and a QuantiFERON-TB Gold test.

### *4.1.2 Treatment Period*

Qualified subjects who have completed the screening procedures and have met the inclusion/exclusion criteria will be randomized on Day 1 in a 2:1:1 ratio, respectively to one of the following 3 treatment groups:

- BMS-986165 6 mg QD
- Placebo
- Apremilast titrated to 30 mg BID as follows:
    - Day 1: 10 mg tablet in the morning
    - Day 2: 10 mg tablet in the morning and evening
    - Day 3: 10 mg tablet in the morning and 20 mg tablet in the evening
    - Day 4: 20 mg tablet in the morning and the evening
    - Day 5: 20 mg tablet in the morning and 30 mg tablet in the evening
    - Day 6 and thereafter: 30 mg tablet in the morning and the evening

Dummy tablets (placebo to the BMS-985165 6 mg tablet, placebo to apremilast 30 mg tablet BID, and placebo to apremilast 10 mg, 20 mg, and 30 mg during titration) will be administered to the subjects to maintain blinding. Additional details are provided in Section 6.1. Note that apremilast will not be used as a treatment arm in China.

Randomization should not occur until at least 8 days after the Screening Visit to allow collection of PSSD data during screening in order to calculate a baseline PSSD score. Randomization will be stratified by geographic region (U.S., Japan [body weight stratum will not be applied in Japan], China [body weight stratum will not be applied in China], and Rest of World), previous biologic use (for psoriasis, psoriatic arthritis or other inflammatory diseases only; yes/no), and body weight (≥90 kg and <90 kg). If subjects from China are not enrolled in the study, then the stratification level for China will not be utilized. As this is designed to be a global study across multiple countries, randomization in each country will be targeted to approximately 35% or less of the total sample size. This change is being implemented to achieve geographical representation across countries and to minimize the potential for any single country to have a disproportionate impact on the overall efficacy and/or safety profile.

### 4.1.3 Week 16

The coprimary endpoints (sPGA 0/1 and PASI 75) will be assessed at Week 16. Subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD at Week 16. Subjects who are randomized to BMS-986165 6 mg QD or apremilast 30 mg BID will continue their treatment regimen.

### 4.1.4 Week 24

At Week 24, subjects originally randomized to apremilast 30 mg BID who do not achieve PASI 50 response will be switched in a blinded manner to BMS-986165 6 mg QD. Subjects in the apremilast treatment arm who achieve PASI 50 response at Week 24 will continue to receive apremilast 30 mg BID in a blinded manner through Week 52.

During the Week 24 assessment, a subject who has an sPGA ≥3 [redacted] may be treated with restricted topicals/shampoos as described in Section 6.7.1 at the investigator's discretion. These treatments may be only initiated at Week 24, and not at subsequent time points. A subject who is initiated on these treatments at Week 24 may use them as needed per the investigator's judgment through Week 52.

### 4.1.5 Week 52 and Follow-up Period

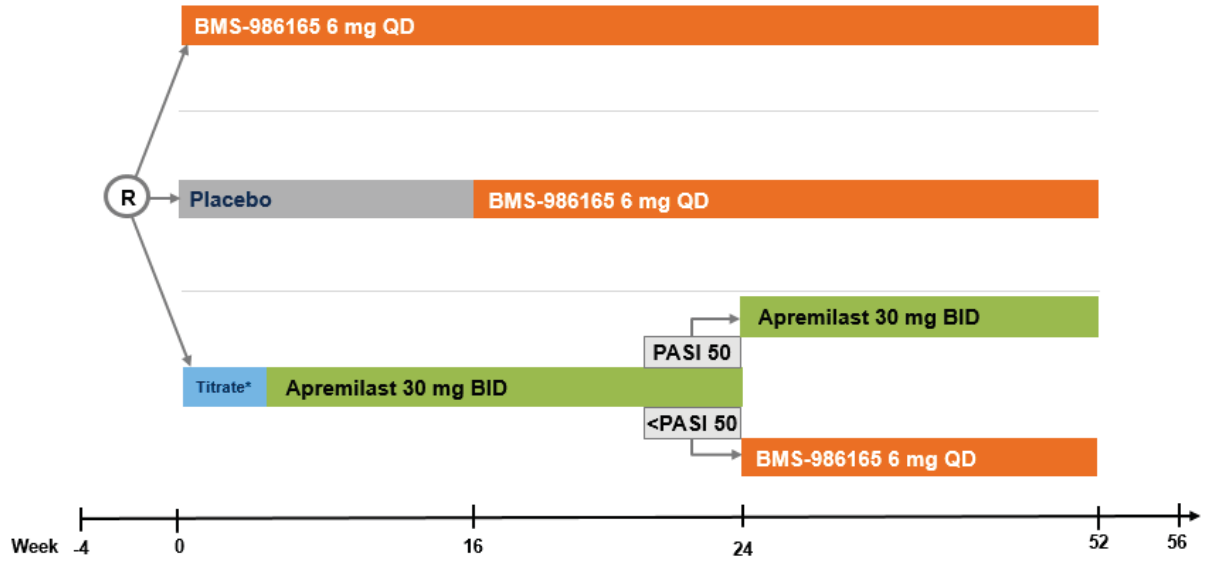
The follow-up period is a 4-week window after the Week 52 visit, unless the subject rolls over into the long-term extension. The subject will be encouraged to report any SAEs or AEs experienced during this time.

Subjects who discontinue study treatment early should remain in the study for protocol-specified procedures (please refer to Section 7.1 for more details).

Subjects completing 52 weeks of treatment will be offered the opportunity to roll over to a separate long-term extension study (≥2 years) where they will be treated with BMS-986165 6 mg QD.

The study design schematic is presented in Figure 1.

**Figure 1: Study Design Schematic**




*Apremilast is titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing as described in Section 4.1.2
Abbreviations: BID = twice daily; QD = once daily; R = randomize

The coprimary endpoints will be evaluated at Week 16.

### 4.1.6 Data Monitoring Committee and Other External Committees

#### 4.1.6.1 Data Monitoring Committee

An external data monitoring committee (DMC) with multi-disciplinary representation will be established to evaluate on a periodic basis; AEs, laboratory measurements, and safety assessments to ensure the ongoing safety of study subjects. An independent reporting statistician not involved in the conduct of the study will be designated by [redacted] to provide the DMC with essential safety data during the study.

The DMC responsibilities, authorities, and procedures will be documented and followed according to the DMC charter.

#### 4.1.6.2 Infection Adjudication Committee

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

#### 4.1.6.3 CV Adjudication Committee

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

#### 4.1.6.4 Suicidal Ideation and Behavior Adjudication Committee

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

### 4.2 Number of Subjects

Approximately 600 qualified subjects will be randomized in a 2:1:1 ratio to BMS-986165 6 mg QD, apremilast 30 mg BID, and placebo, respectively. [redacted]

### 4.3 End of Study Definition

The duration of study participation for individual subjects is expected to be up to 60 weeks (420 days), which includes screening (up to 4 weeks), treatment (52 weeks) and follow-up (up to 4 weeks) periods.

The start of the study is defined as first visit for first subject screened. The end of the study is defined as the last visit or scheduled procedure shown in the Schedule of Activities (Section 1.3) for the last subject. Study completion is defined as the final date on which data was or is expected to be collected (Week 56 for collection of potential SAEs).

### 4.4 Scientific Rationale for Study Design

This Phase 3 study will be conducted in a population of subjects with stable moderate-to-severe plaque psoriasis who are candidates for systemic psoriasis therapy. The study is designed to confirm the efficacy and safety of BMS-986165 compared with placebo and apremilast in achieving sPGA of 0/1 and PASI 75 at Week 16. The sPGA and PASI 75 are standard measures in clinical trials of demonstrating efficacy of systemic psoriasis treatments. A placebo arm is

included in this study for a short duration of 16 weeks to provide a control for the natural fluctuation of psoriasis activity that may occur and to provide a safety standard for comparison. Subjects in the placebo arm will be switched to BMS-986165 at Week 16 to provide them psoriasis treatment after the endpoints are collected. Apremilast is included as the active control in this study as it is an approved, widely used, oral, daily medication for psoriasis. Week 16 was chosen as it would allow enough time for BMS-986165 as well as apremilast to treat psoriasis. In addition, prior apremilast registrational trials had reported psoriasis-related outcomes at Week 16 as their primary endpoints. Subjects in the apremilast arm who do not achieve PASI 50 at Week 24 will be switched in a blinded fashion to BMS-986165. This will allow subjects who are not responding to apremilast to receive an alternate study treatment. PASI 50 is used to justify the switch because achieving PASI 50 has been shown to have a meaningful impact on quality of life in people with psoriasis.[24]

# 5 STUDY POPULATION

Eligibility criteria for this study have been carefully considered to ensure: 1) selection of appropriate subjects with psoriasis, 2) safety of the study subjects and 3) the results of the study can be used for regulatory filing and other purposes. It is imperative that subjects fully meet all eligibility criteria.

All screening and randomization evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

## 5.1 Inclusion Criteria

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

**1) Signed Written Informed Consent**

a) Subjects must be willing to participate in the study and sign the informed consent form (ICF)

**2) Type of Subject and Target Disease Characteristics**

a) Men and women diagnosed with stable plaque psoriasis for 6 months or more. Stable psoriasis is defined as no morphology changes or significant flares of disease activity in the opinion of the investigator

b) Deemed by the investigator to be a candidate for phototherapy or systemic therapy

c) ≥10% of BSA involvement at Screening Visit and Day 1

d) Psoriasis Area and Severity Index (PASI) score ≥12 and static Physician's Global Assessment (sPGA) ≥3 at Screening Visit and Day 1

**3) Age and Reproductive Status**

a) Men and women aged ≥18 years at the time of Screening Visit

b) Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at Screening Visit, and a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [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 must agree to use correctly a highly effective method(s) of contraception for the duration of treatment (52 weeks) with study drug(s) BMS-986165 plus 5 half-lives of study drug (3 days) plus 30 days (duration of ovulatory cycle) for a total of 33 days post-treatment completion (total of 33 days after last dose of study drug). WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, but must still undergo pregnancy testing as described in this protocol

e) Male subjects who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (APPENDIX 4) for the duration of treatment with study treatment(s) plus 5 half-lives of the study treatment (3 days) for a total of 3 days post-treatment completion. In addition, male subjects must be willing to refrain from sperm donation during this time

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 4) which, have a failure rate of <1% when used consistently and correctly.

## 5.2 Exclusion Criteria

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

**1) Target Disease Exceptions**

a) Has nonplaque psoriasis (ie, guttate, inverse, pustular, erythrodermic, or drug-induced psoriasis) at Screening or Day 1

**2) Infectious/Immune-related Exclusions**

a) History or evidence of outpatient active infection and/or febrile illness within 7 days prior to Day 1

b) History of serious bacterial, fungal, or viral infection requiring hospitalization and intravenous (IV) antimicrobial treatment within 60 days prior to Day 1

c) Any untreated bacterial infection within 60 days prior to Day 1

d) Any ongoing evidence of chronic, bacterial infection (eg chronic pyelonephritis, chronic osteomyelitis, chronic bronchiectasis)

e) Any history of proven infection of a joint prosthesis in which the prosthesis was not removed or replaced, or received antibiotics for suspected infection of a joint prosthesis in which the prosthesis was not removed or replaced

f) Received live vaccines within 60 days prior to Day 1, or plans to receive a live vaccine during the study, or within 60 days after completing study treatment

g) Presence of herpes zoster lesions at Screening or Day 1

h) History of serious herpes zoster or serious herpes simplex infection which includes, but is not limited to, any episode of disseminated herpes simplex, multidermatomal herpes zoster, herpes encephalitis, ophthalmic herpes, or recurrent herpes zoster (recurrent is defined as 2 episodes within 2 years)

i) Evidence of, or test positive for, hepatitis B virus (HBV) at Screening. Positive hepatitis B lab testing is defined as: 1) Positive hepatitis B surface antigen (HBsAg+) **OR** 2) Presence of hepatitis B virus deoxyribonucleic acid (DNA) **OR** 3) Positive anti-hepatitis B core antibody without concurrent positive hepatitis B surface antibody (HBcAb+ and HBsAb-)

j) Evidence of, or test positive for, hepatitis C virus (HCV) at Screening. A positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti-HCV Ab) **AND** 2) positive via a confirmatory test for HCV (eg, HCV polymerase chain reaction)

k) Positive for human immunodeficiency virus by antibody testing (HIV-1 and -2 Ab) at Screening

l) Any history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the subject's immune status (eg, history of opportunistic infections [eg, *Pneumocystis jirovecii* pneumonia, histoplasmosis, or coccidioidomycosis], history of splenectomy, primary immunodeficiency)

**3) Any of the following TB criteria:**

a) History of active TB prior to Screening Visit, regardless of completion of adequate treatment

b) Signs or symptoms of active TB (eg, fever, cough, night sweats, and weight loss) during screening as judged by the investigator

c) Any imaging of the chest (eg, chest x-ray, chest computed tomography [CT] scan) obtained during the screening period or anytime within 6 months prior to Screening with documentation, showing evidence of current active or history of active pulmonary TB

d) Latent TB infection (LTBI) defined as positive IFN gamma release assay (IGRA), by QuantiFERON-TB Gold testing at Screening, in the absence of clinical manifestations

Note: Subject is eligible if (i) there are no current signs or symptoms of active TB **AND** (ii) subject has received adequate documented treatment for LTBI within 5 years of Screening **OR** has initiated prophylactic treatment for LTBI per local guidelines and is rescreened after 1 month of treatment. To continue in the study, subject must agree to complete a locally-recommended course of treatment for LTBI. Use of rifampin, however, is not recommended as it can reduce efficacy of apremilast used as a comparator in this trial.

Note: An IGRA test that is indeterminate with no signs or symptoms of active TB must be retested for confirmation. If the second test is again indeterminate, the subject will be excluded from the study. If the retest is positive, the subject should be treated as having LTBI. If the retest is negative, subject may be eligible provided no other exclusion criteria for TB are met.

**4) Medical History and Concurrent Diseases**

a) Any major surgery within 8 weeks prior to Day 1, or any planned surgery for the first 52 weeks of the study

b) Has donated blood >500 mL within 4 weeks prior to Day 1, or plans to donate blood during the course of the study

c) Drug or alcohol abuse, as determined by the investigator, within 6 months prior to Day 1

d) Medical marijuana or prescription marijuana taken for medicinal reasons

e) Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, psychiatric, neurologic, immunologic, or local active infection/infectious illness) that, in the investigator's judgment or after consultation with the Medical Monitor, will substantially increase the risk to the subject if he or she participates in the study

f) Unstable cardiovascular disease, defined as a recent clinical cardiovascular event (eg, unstable angina, myocardial infarction, stroke, rapid atrial fibrillation) in the last 3 months prior to Screening, or a cardiac hospitalization (eg, revascularization procedure, pacemaker implantation) within 3 months prior to Screening

g) Has uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) >160 mm Hg or diastolic BP >100 mm Hg

Note: Determined by 2 consecutive elevated readings. If an initial BP reading exceeds this limit, the BP may be repeated once after the subject has rested sitting for ≥10 minutes. If the repeat value is less than the criterion limits, the second value may be accepted

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

i) Has cancer or 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, or carcinoma of cervix in situ that has been treated with no evidence of recurrence)

j) Any significant/uncontrolled neuropsychiatric illness judged as clinically significant by the investigator during Screening or at Day 1

**OR**

Any lifetime history of suicidal ideation, suicidal behavior, or suicidal attempts by medical history or by electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) documentation, or by answering "yes" to Question 4 or 5 for suicidal ideation on the eC-SSRS at Screening or at Day 1, or is clinically deemed to have a suicide risk by the investigator

k) Prior exposure to investigational product (ie, BMS-986165 or apremilast)

l) If the subject has received biologics previously, the following exclusion criteria for washout will apply:

i) Antibodies to IL-12, IL-17, or IL-23 (eg, ustekinumab, secukinumab, tildrakizumab, ixekizumab, or guselkumab) within 6 months of Day 1

ii) TNF inhibitor(s) (eg, etanercept, adalimumab, infliximab, certolizumab) within 2 months of Day 1

iii) Agents that modulate integrin pathways to impact lymphocyte trafficking (eg natalizumab), or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, or visilizumab) within 3 months of Day 1

iv) Rituximab within 6 months of Day 1

m) Has received systemic nonbiologic psoriasis medications and/or any systemic immunosuppressants (including, but not limited to, methotrexate, azathioprine, cyclosporine, JAK inhibitors, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, or fumaric acid derivatives) within 4 weeks prior to Day 1

n) Has used leflunomide within 6 months prior to Day 1

o) Has used opioid analgesics within 4 weeks prior to Day 1

p) Has received lithium, antimalarials, or intramuscular (IM) gold within 4 weeks of the first administration of any study medication

q) Has used any strong CYP450 inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin) within 4 weeks prior to Day 1

r) Has received phototherapy (including either oral and topical PUVA light therapy, ultraviolet B [UVB] or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to Day 1

s) Has used topical medications/treatments that could affect psoriasis evaluation (including, but not limited to, high potency corticosteroids [WHO Classes I-V], >3% salicylic acid, urea, alpha- or beta-hydroxy acids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, and tacrolimus) within 2 weeks prior to Day 1

Note: Low potency topical steroids (WHO Class VI and VII) are permitted on the palms, soles, face, and intertriginous areas but should not be used within 24 hours prior to any study visit. Bland emollients (defined as emollients without urea or alpha or beta-hydroxy acids or other ingredients which are pharmaceutically active) are allowed on all body regions but should not be used within 24 hours prior to any study visit.

t) Use of shampoos that contain corticosteroids, coal tar, >3% salicylic acid, or vitamin D3 analogues within 2 weeks prior to Day 1

u) Has received an experimental antibody or experimental 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) prior to Day 1 **OR** is currently enrolled in an investigational study

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

**5) Physical and Laboratory Evaluations**

a) At Screening

i) Absolute WBC count <3000/$mm^3$

ii) Absolute lymphocyte count <500/$mm^3$

iii) Absolute neutrophil count <1000/$mm^3$

iv) Platelet count <100,000/$mm^3$

v) Hemoglobin <9 g/dL

vi) ALT and/or AST >3 × upper limit of normal (ULN)

vii) Total unconjugated and/or conjugated bilirubin >2 × ULN

viii) Thyroid-stimulating hormone (TSH) outside the normal reference range

**AND**

Free T4 (thyroxine) or T3 (triiodothyronine) outside the normal reference range

b) ECG abnormalities that are considered clinically significant and would pose an unacceptable risk to the subject if participating in the study

c) Renal impairment based on an estimated glomerular filtration rate (eGFR) <45 mL/min

d) Inability to be venipunctured and/or tolerate venous access

e) Any other significant laboratory abnormalities that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study

**6) Allergies and Adverse Drug Reactions**

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

**7) 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 BMS approval is required).

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

c) Inability to comply with restrictions and prohibited activities/treatments as listed in the study protocol

d) Site personnel or their immediate family

e) Any contraindications listed in the country-specific label for apremilast

## 5.3 Lifestyle Restrictions

General skin care measures (with above restrictions for topical treatments) that are standard for patients with plaque psoriasis are permitted. Subjects should avoid excessive sun exposure and avoid risks that are known to provoke flare of psoriasis.

### *5.3.1 Meals and Dietary Restrictions*

Study treatment may be taken without regard to meals, however, subjects are required to fast for a minimum of 10 hours before visits on which fasting lipid, fasting glucose [redacted] samples will be drawn. [redacted]

### *5.3.2 Caffeine, Alcohol and Tobacco*

No restrictions are required; however, extensive use of caffeine, alcohol and tobacco should be avoided.

### *5.3.3 Activity*

No restrictions are required; however, unusual physical exertion should be avoided during the study.

## 5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized in the study for any reason. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal set of screen failure information includes date of consent, demography, screen failure details (ie, eligibility criteria that the subject did not meet), and any serious AEs during the screening period.

### 5.4.1 Retesting During Screening or Rescreening

For laboratory parameters that initially do not meet eligibility requirements, a single retest within the 28-day screening period is permitted before subject is declared a screen failure. This is 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 would be clinically relevant.

The study permits the rescreening (after the end of the initial 28-day screening period) of a subject who discontinues the study as a pretreatment failure (ie, the subject fails to meet eligibility criteria and has not been treated). The subject must be reconsented, will be assigned a new identification number, and a full Screening Visit must be performed again. A subject can only be rescreened 1 time (ie, if the subject fails 1 rescreening attempt, no additional rescreening is allowed). Depending on the timing of rescreening, repeat chest imaging may not be required. Duration of existing treatments and required discontinuation periods shall be considered relative to the new Screening Visit and/or randomization.

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

## 6 TREATMENT

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

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following: BMS-986165, placebo, and apremilast.

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

Other medications used as support or escape medication for preventive, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IP. Table 5 shows the study treatments for Protocol IM011046.

**Table 5: Study Treatments for IM011046**

| Product Description/Class and Dosage Form | Potency | IP/Non-IMP | Blinded or Open-Label | Packaging / Appearance | Storage Conditions (per label) |
|---|---|---|---|---|---|
| BMS-986165 tablet | 6 mg | IP | Blinded | Bottle | Store at 15 to 25°C; Store in a tightly closed container; Protect from light |
| Placebo tablet to match BMS-986165 6 mg | n/a | IP | Blinded | Bottle | Store at 15 to 25°C; Store in a tightly closed container; Protect from light |
| Apremilast tablet | 10 mg* | IP | Blinded | Blister card | Store tablets below 30°C (86°F). Store in original container |
| Placebo tablet to match apremilast 10 mg | n/a | IP | Blinded | Blister card | Store tablets below 30°C (86°F). Store in original container |
| Apremilast tablet | 20 mg† | IP | Blinded | Blister card | Store tablets below 30°C (86°F). Store in original container |
| Placebo tablet to match apremilast 20 mg | n/a | IP | Blinded | Blister card | Store tablets below 30°C (86°F). Store in original container |
| Apremilast tablet | 30 mg‡ | IP | Blinded | Bottle | Store tablets below 30°C (86°F). Store in original container |
| Placebo tablet to match apremilast 30 mg | n/a | IP | Blinded | Bottle | Store tablets below 30°C (86°F). Store in original container |

IP = investigational product; IMP = investigational medical product; n/a = not applicable

*Used for titration Day 1 through Day 3 morning dose
†Used for titration Day 3 evening dose through Day 5 morning dose
‡From Day 5 evening dose onwards.

## 6.1 Treatments Administered

Study treatment will be administered in a double-blind, double-dummy fashion as described in Section 4.1.2. The selection and timing of dose for each subject is as follows:

**Table 6: Selection and Timing of Dose**

| Study Treatment | Unit dose strength(s)/Dosage level(s) | Dosage formulation Frequency of Administration | Route of Administration |
|---|---|---|---|
| 6 mg QD BMS-986165 | 6 mg | 1 active tablet QD in the morning; 1 placebo titration kit* then 2 apremilast placebo (1 tablet in the morning, 1 tablet in the evening) | oral |
| 30 mg BID apremilast | 30 mg | 1 active titration kit* then 1 active morning and evening and 1 BMS-986165 placebo once daily in the morning | oral |
| Placebo BID | n/a | 1 placebo apremilast titration kit* then 2 apremilast placebo (1 tablet in the morning, 1 tablet in the evening) and 1 BMS-986165 placebo once daily in the morning | oral |

Abbreviations: BID = twice daily; n/a = not applicable; QD = once daily
*Titration kit is described in Section 6.1.1

### *6.1.1 Titration Kit for Active and Placebo Apremilast*

Apremilast will be titrated over 5 days to a maintenance dose of 30 mg BID. To maintain the blind between subjects receiving apremilast and BMS-986165 during the titration period, active apremilast and matching apremilast placebo tablets will be provided. This will be supplied in an 18-day titration kit as follows:

One 10 mg tablet in the morning on Day 1; two 10 mg tablets (one in the morning, one in the evening) on Day 2; one 10 mg tablet in the morning and one 20 mg tablet in the evening on Day 3; two 20 mg tablets (one tablet in the morning, one tablet in the evening) on Day 4; one 20 mg tablet in the morning and one 30 mg tablet in the evening on Day 5; one 30 mg tablet in the morning and one 30 mg tablet in the evening for each Day 6 through Day 18.

## 6.2 Method of Treatment Assignment

Before the study is initiated, each user (at investigative sites) will receive log-in information and directions on how to access the interactive response technology (IRT) system. At the time of the Screening Visit, immediately after informed consent is obtained and before any study-related procedures are performed, the investigative site will access the enrollment option of the IRT system for assignment of a subject number for all subjects, including subjects not subsequently randomized or treated. The subject number is assigned sequentially by the system and will be unique across all sites. All enrolled subjects will be assigned sequential subject numbers. The subject number will not be used for any other subject. If a subject is rescreened, they will be given a new identification number.

At Week 0 (Day 1), subjects who meet all criteria for enrollment at Screening and Day 1 will be centrally randomized in a 2:1:1 ratio to BMS-986165 6 mg QD, placebo, or apremilast 30 mg BID as determined by a computer-generated randomization schedule using IRT. The randomization lists will be generated by the IRT vendor using a permuted block design within each combination of stratum level. The randomization in this study will be stratified by geographic region (U.S., Japan [body weight stratum will not be applied in Japan], China [body weight stratum will not be applied in China], and Rest of World), previous biologic use (for psoriasis, psoriatic arthritis or other inflammatory diseases only; yes/no), and body weight (≥90 kg and <90 kg). As this is designed to be a global study across multiple countries, randomization in each country will be targeted to approximately 35% or less of the total sample size. This change is being implemented to achieve geographical representation across countries and to minimize the potential for any single country to have a disproportionate impact on the overall efficacy and/or safety profile.

After all inclusion/exclusion criteria have been met for a subject, the investigative site will access the IRT on Day 1 for the purposes of randomizing a subject. A treatment group will be assigned by IRT based on the above-described randomization schedule and each subject will be assigned a unique randomization number. In addition, a unique kit number will be assigned to the subject corresponding to the treatment assignment.

A kit will contain adequate study treatment for a 4-week supply. At subsequent visits, when new treatment kits need to be provided, the investigative site will access the IRT to obtain the kit number to assign to the subject. Study treatment will be dispensed at study visits as shown in the Schedule of Activities (Section 1.3).

At Week 16, subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD.

At Week 24, subjects originally randomized to apremilast 30 mg BID who do not achieve PASI 50 response will be switched in a blinded manner to BMS-986165 6 mg QD. Subjects originally randomized to apremilast 30 mg BID who achieve PASI 50 response at Week 24 will continue to receive apremilast 30 mg BID in a blinded manner. The investigative site and other study personnel will not have knowledge of the PASI 50 score at this visit and will therefore remain blinded.

## 6.3 Blinding

### *6.3.1 Maintaining the Blind*

Blinded treatment assignments will be managed using IRT. Throughout the study, subjects will receive matching placebo (for BMS-986165 and/or apremilast) as needed to maintain the treatment blind. IP supply will be controlled by IRT at each visit.

All tablets are identical in appearance and will be supplied in blister cards or bottles with each daily dose made up of the appropriate combination of active and/or placebo tablets to provide the correct treatment, as shown in Table 5. Investigative site staff, Sponsor and designee personnel, and subjects and their families will remain blinded to treatment assignments. [redacted]

[redacted]

### 6.3.2 Circumstances for 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 IP 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, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The principal investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

In case of an emergency, the investigator has unrestricted access to randomization information via IRT and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. After the unblinding, the investigator shall notify the Medical Monitor and/or study director. The method of unblinding for emergency purposes is described in the IRT manual. Subject and unblinded treatment information and the reason for the blind being broken must be recorded on the appropriate study status page of the electronic case report form (eCRF). After unblinding via IRT, the investigator shall notify the Medical Monitor.

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 nonemergency purposes must be discussed with the Medical Monitor prior to unblinding.

If a subject is unblinded for any reason, the subject will be discontinued from treatment.

## 6.4 Dosage Modification

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

## 6.5 Preparation/Handling/Storage/Accountability

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

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

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

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

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

### *6.5.1 Retained Samples for Bioavailability/Bioequivalence*

Not applicable.

## 6.6 Treatment Compliance

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

## 6.7 Concomitant Therapy

### *6.7.1 Prohibited and/or Restricted Treatments*

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

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

**2)** Any concurrent use of strong CYP450 inducers according to the US package insert for apremilast as it may reduce apremilast efficacy. Examples include rifampin, phenobarbital, carbamazepine, and phenytoin, unless it is considered necessary for the subject's welfare and/or treatment of an AE/SAE

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

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

**5)** Phototherapy; use of tanning booths or therapeutic sunbathing

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

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

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

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

**9)** Any topical medications/treatments, which are used for any indication, that could affect psoriasis evaluation (including, but not limited to, high potency corticosteroids [WHO Classes I-V], >3% salicyclic acid, urea, alpha- or beta-hydroxy acids, anthralin, calcipotriene, vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, and tacrolimus)

Exception: The following topical treatments may be initiated only at Week 24 per investigator's discretion in subjects who have sPGA scores ≥3 (See Section 4.1.4):

- High potency corticosteroids (WHO Classes I-V), >3% salicylic acid, urea, alpha- or beta-hydroxy acids, anthralin, calcipotriene, vitamin D derivatives, retinoids, tazarotene

Note: Low potency topical steroids (WHO Classes VI and VII) are permitted on the palms, soles, face, and intertriginous areas but should not be used within 24 hours prior to any study visit. Bland emollients (defined as emollients without urea or alpha or beta hydroxy acids or other ingredients which are pharmaceutically active) are allowed on all body regions but should not be used within 24 hours prior to any study visit

**10)** Any medicated shampoos that contain corticosteroids, coal tar, >3% salicylic acid, or vitamin D3 analogues

Exception: The above shampoos may be initiated only at Week 24 per investigator's discretion in subjects who have [redacted] (See Section 4.1.4).

**11)** Live vaccination

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

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

### *6.7.2 Permitted Concomitant Medications*

Stable doses of concomitant medication for chronic medical conditions are permitted as long as neither the medication nor the medical condition meet exclusion criteria as detailed in Section 5.2. Dose adjustments of these medications should be avoided during the study unless clinically indicated. If a dose adjustment of these medications should occur, they must be recorded on the Concomitant Medications eCRF or the Procedures and Significant Nondrug Therapies eCRF. The investigator should instruct the subject to notify the study site about any new treatments he/she takes after the start of the study treatment. All medications and significant nondrug therapies (including physical therapy and blood transfusions) administered after the subject starts study treatment must be listed on the Concomitant Medications eCRF or the Procedures and Significant Nondrug Therapies eCRF.

Note: Low potency topical steroids (WHO Classes VI and VII) are permitted on the palms, soles, face, and intertriginous areas but should not be used within 24 hours prior to any study visit. Bland emollients (defined as emollients without urea or alpha- or beta-hydroxy acids or other ingredients which are pharmaceutically active) are allowed on all body regions but should not be used within 24 hours prior to any study visit.

### *6.7.3 Rescue Medications*

At Week 24, a subject who has an sPGA ≥3 [redacted] may be treated with restricted topicals or shampoos, respectively, as described in Section 6.7.1 at the investigator's discretion. These treatments may only be initiated at Week 24, and not at subsequent time points. A subject who is initiated on these treatments at Week 24 may use them as needed per the investigator's judgment through Week 52.

## 6.8 Treatment After the End of the Study

At the end of the study, the investigator should ensure that subjects continue to receive appropriate standard of care to treat the condition under study.

In addition, for subjects who continue to demonstrate clinical benefit, BMS may continue to provide study treatment via a rollover extension study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS.

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

# 7 DISCONTINUATION CRITERIA

## 7.1 Discontinuation from Study Treatment

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

- Subject requests to stop study treatment. Subjects who discontinue study treatment early should remain in the study for protocol-specified 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 subject to provide this information.
- Any clinically significant AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject. If treatment is discontinued due to an AE, the AE eCRF must be completed to show that the AE caused discontinuation.
- eGFR <45 mL/min on repeat assessment within 7 days
- Abnormal liver tests suggestive of drug-induced liver injury (DILI), as defined in Section 8.2.8 or if the investigator believes that it is in the best interest of the subject
- Subject reports suicidal ideation, suicidal behavior, or suicide attempts at any time after randomization, or documents suicidal ideation by answering "Yes" to Question 4 or 5 on the eC-SSRS, or documents suicidal behavior on the eC-SSRS at any time during the study. The subject should then be immediately referred to a mental health professional for evaluation of suicide risk.

- The subject develops a malignancy, with the exception of a subject who develops nonmelanoma skin cancer who may continue in the study at the discretion of the investigator
- Pregnancy, positive pregnancy test, or subject expresses an interest in becoming pregnant (refer to Section 8.2.6)
- Subject develops active TB during the study or prematurely discontinues treatment for LTBI, or subject is noncompliant with LTBI therapy (refer to Section 8.4.4)
- Termination of the study or program by BMS
- Unblinding of a subject's treatment assignment for any reason (emergency or nonemergency)
- Inability or failure to comply with protocol requirements in the opinion of the investigator
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All subjects who discontinue BMS-986165 should comply with protocol-specified follow-up procedures as outlined in Section 1.3. 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 (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). Replacement of subjects is not permitted.

If study treatment is discontinued 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 eCRF page.

### 7.1.1 Temporary Discontinuation of Study Medication

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

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

### 7.1.2 Post-Study Treatment Study Follow-Up

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 treatment must continue to be followed for collection of outcomes and/or survival follow-up data as required and in line with Section 4 until death or the conclusion of the study.

Subjects who discontinue study treatment should be encouraged to undergo all study-related visits for the full treatment period in order to support the final efficacy and safety analysis.

## 7.2 Discontinuation from the Study

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures as specified in Section 1.3. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information.

- Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate 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.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

## 7.3 Lost to Follow-Up

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

# 8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 1.3) and described in Section 4.1.
- Protocol waivers or exemptions are not allowed.
- All significant safety concerns must be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.

- Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria before randomization. Randomization should not occur until at least 8 days after the Screening Visit to allow collection of PSSD data during screening in order to calculate a baseline PSSD score. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 1.3).
- For several assessments, appropriate training will be provided to investigators and designated personnel at sites. Only those individuals trained and certified to perform these assessments will be performing them during the study.

## 8.1 Efficacy Assessments

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

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

### *8.1.1 Investigator-Administered Assessments*

#### *8.1.1.1 static Physician's Global Assessment (sPGA)*

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

#### *8.1.1.2 Psoriasis Area and Severity Index (PASI)*

The PASI is a measure of the average redness, thickness, and scaliness of psoriatic skin lesions (each graded on a 0–4 scale), weighted by the area of involvement (head, arms, trunk to groin, and legs to top of buttocks).[26] The PASI produces a numeric score that can range from 0 to 72, with

higher PASI scores denoting more severe disease activity. The PASI can also be used to assess response to treatment. The PASI 50 is the proportion of subjects who experience at least a 50% improvement in PASI score as compared with the baseline value. The PASI 75, PASI 90, and PASI 100 are defined similarly. BMS will host a training session prior to initiation of the study to demonstrate proper PASI scoring. All PASI assessments should be performed by a trained physician (dermatologist) or appropriately trained investigator who is experienced in the assessment of psoriasis patients (see APPENDIX 6).

#### 8.1.1.3 Body Surface Area (BSA)

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

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

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

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

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

[redacted]

#### 8.1.1.6 Physician's Global Assessment-Fingernails (PGA-F)

In this assessment,[32] the overall condition of the fingernails is rated on a 5-point scale:

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

The PGA-F will be performed only in subjects with psoriatic fingernail involvement to assess severity and subsequent improvement. An example is provided in APPENDIX 9. The PGA-F

should be performed by a dermatologist or appropriately trained investigator who is experienced in the assessment of psoriasis patients.

[redacted]

#### 8.1.1.8 Palmoplantar PGA (pp-PGA)

This measure will be used for subjects with palmoplantar involvement at baseline.[34] The pp-PGA uses a 5-point (0-4) scale:

0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe (see APPENDIX 11).

The pp-PGA should be performed by a dermatologist or appropriately trained investigator who is experienced in the assessment of psoriasis patients.

[redacted]

### 8.1.2 Subject-Reported Assessments

#### 8.1.2.1 Psoriasis Symptoms and Signs Diary (PSSD)

The PSSD is an 11-item subject-reported instrument that assesses severity of symptoms and subject-observed signs commonly associated in plaque psoriasis.[36,37] It has been shown to be reliable and valid in measuring symptoms and signs of subjects with moderate-to-severe plaque psoriasis in the clinic and has strong psychometric properties in assessing treatment effects in

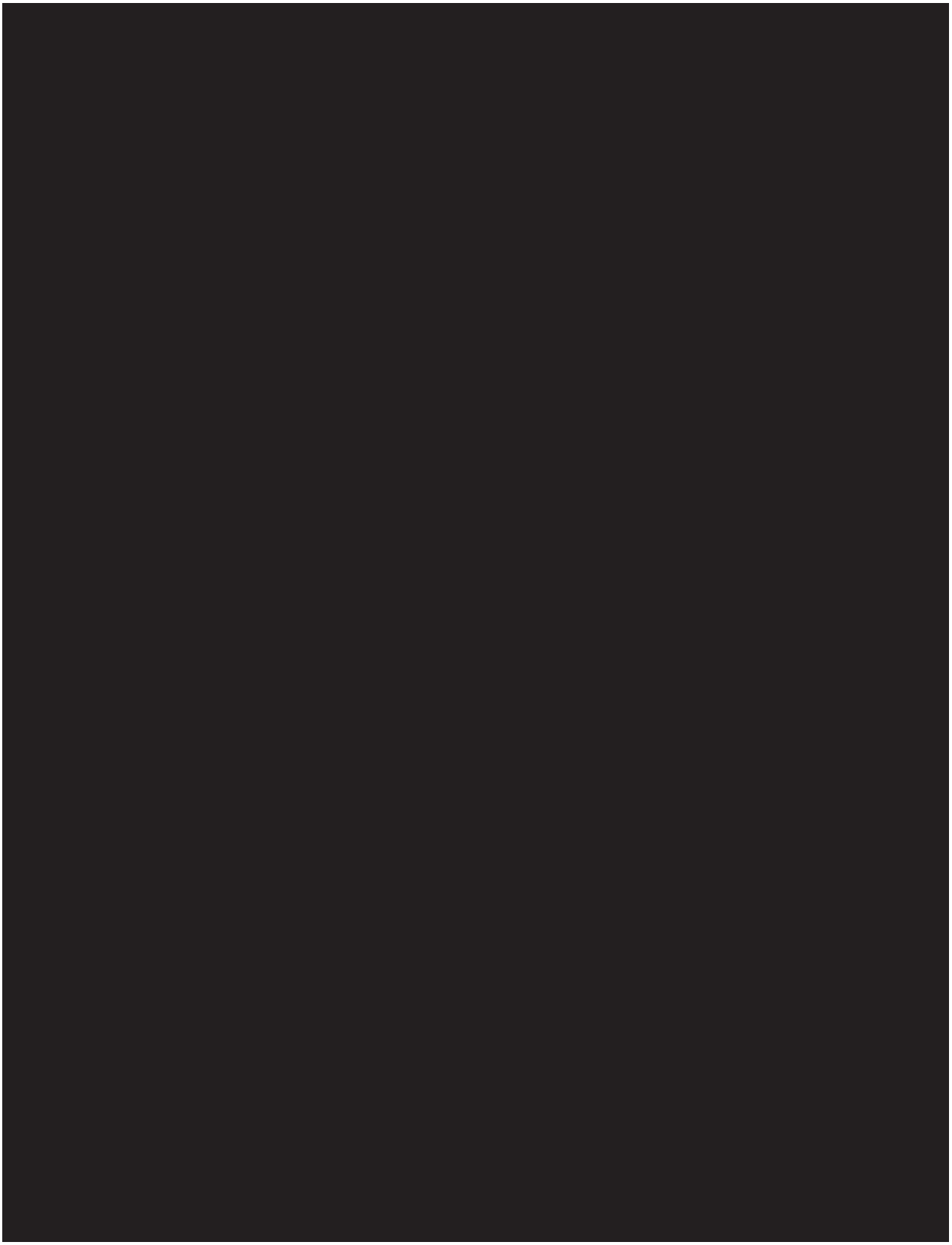
clinical trials.[38] The PSSD assesses severity of 5 symptoms (itch, pain, stinging, burning, skin tightness) and 6 subject-observed signs (skin dryness, cracking, scaling, shedding or flaking, redness, bleeding) using 0–10 numerical ratings. The severity of each item is rated on an 11-point numeric rating scale ranging from 0 (absent) to 10 (worst imaginable). Two versions of the PSSD were developed, one with a 24-hour recall period (PSSD-24h) and one with a 7-day recall period. The PSSD-24h will be administered daily in this trial to avoid recall bias with a longer recall period (see APPENDIX 13).

[redacted]

#### 8.1.2.4 Dermatology Life Quality Index (DLQI)

The DLQI[39] is a subject-reported quality of life index which consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work, school, personal relationships, and treatment during the last week. Each question is scored on a scale of 0 to 3 by a tick box: 0 - "not at all", 1 -- "a little", 2 - "a lot", or 3 - "very much". The scores are summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment) (see APPENDIX 14).

[redacted]



#### 8.1.2.11 Psoriatic Arthritis Screening and Evaluation (PASE) Questionnaire

The PASE questionnaire will be administered at Screening in subjects with peripheral joint complaints. The PASE questionnaire is a self-administered tool that is used to screen for psoriatic arthritis among subjects who have psoriasis. The PASE questionnaire consists of 15 questions subdivided into 7 questions focusing on symptoms of psoriatic arthritis, and 8 questions focusing on the impact of psoriatic arthritis on function. Each question is scored on a 1 to 5 scale, with a maximum score of 75. A score of 47 or above has been shown to distinguish between psoriatic arthritis and non-psoriatic arthritis.[46] This questionnaire is only intended to be a screening tool for psoriatic arthritis and does not replace a comprehensive musculoskeletal exam performed by a rheumatologist. The PASE questionnaire should take 6 to 10 minutes to complete and is only done at Screening (See APPENDIX 21).

## 8.2 Adverse Events

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

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

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

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

### 8.2.1 Adverse Events of Interest

Adverse events of interest (AEIs) are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. Adverse events of interest may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the BMS-986165 clinical development program, certain skin-related AEs (eg, acne), infection AEs, and CK elevation have been identified as potential AEIs; however, there has been no definitive

assessment on the causal relationship between these events and treatment with BMS-986165. Additionally, given a potential association between treatment for autoimmune diseases and increased risk for cancer, malignancy has been identified as a potential AEI. Therefore, additional information about certain skin-related AEs, infection AEs, CK elevation, and malignancy may be collected on the case report form in order to better characterize and understand them.

### 8.2.2 Time Period and Frequency for Collecting AE and SAE Information

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

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

All SAEs must be collected from the date of subject's written consent until 30 days after the final dose of the study drug or subject's participation in the study if the last scheduled visit occurs at a later time. Monitoring for SAEs will occur at every study visit.

- The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure. Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in APPENDIX 3.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.

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

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

### 8.2.3 Method of Detecting AEs and SAEs

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

### 8.2.4 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see APPENDIX 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.

- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF. Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

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

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

### 8.2.5 Regulatory Reporting Requirements for SAEs

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

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

### 8.2.6 Pregnancy

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

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

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

### 8.2.7 Laboratory Test Result Abnormalities

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

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

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

### *8.2.8 Potential Drug-Induced Liver Injury (DILI)*

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

Potential DILI is defined as:

**1)** ALT or AST elevation >3 times ULN

**AND**

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

**AND**

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

### *8.2.9 Other Safety Considerations*

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

## 8.3 Overdose

For this study, taking more than 2 days' worth of study treatment within a 24-hour time period will be considered an overdose.

In the event of an overdose the investigator should:

**1)** Contact the Medical Monitor immediately

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

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

## 8.4 Safety

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

### 8.4.1 Physical Examinations

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

### 8.4.2 Vital Signs

Refer to Schedule of Activities (Section 1.3).

### 8.4.3 Electrocardiograms

A 12-lead ECG will be performed at the visits indicated in the schedule of activity (Section 1.3). The patient will remain supine for 5-10 minutes prior to the ECG and must have their lab work done after the tracing so that the ECG results remain as accurate as possible. The ECG results will be read by the primary study investigator or a designee.

### 8.4.4 Tuberculosis Screening and Chest Imaging

Chest imaging results and PE are part of the process to assess a subject's eligibility, as outlined in Section 1.3 and as defined in exclusion criterion 3.c (Section 5.2). Chest imaging (eg, chest x-ray, chest CT scan) at the Screening Visit is required if not already performed and documented within 6 months of obtaining written informed consent. A subject must not have active signs or symptoms of TB, as judged by the investigator, to be eligible for the study.

In addition to a complete PE and medical history to evaluate exposure to TB, all subjects will have a screening test, an IGRA (eg, QuantiFERON®-TB Gold) performed centrally. If unable to obtain central laboratory results, an IGRA test could be obtained locally, after consultation with the [redacted] Medical Monitor. A subject with an indeterminate IGRA test result must be retested for confirmation. If the second result is again indeterminate, the subject will be excluded from the study. If the second result is positive, the subject should be considered as having LTBI provided there are no signs or symptoms of active TB. If the second result is negative, the subject may be eligible provided no other exclusion criterion for TB is met.

### 8.4.5 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

| **Hematology** | |
|---|---|
| Hemoglobin (Hgb)<br>Hematocrit (Hct)<br>White Blood Cell Count, including differential<br>Platelet Count | |
| **Chemistry** | |
| AST<br>ALT<br>Total Bilirubin | Total Protein<br>Albumin<br>Sodium |

| | |
|---|---|
| Direct Bilirubin (if total bilirubin >ULN)<br>Alkaline Phosphatase<br>Lactate Dehydrogenase (LDH)<br>Creatinine<br>Blood Urea Nitrogen (BUN)<br>Uric Acid<br>Glucose (fasting at some visits) | Potassium<br>Chloride<br>Calcium<br>Phosphorus<br>Creatine Kinase (CK)*<br>Estimated Glomerular Filtration Rate (eGFR) |
| **Urinalysis** | |
| Protein<br>Glucose<br>Blood<br>Leukocyte Esterase<br>Specific Gravity<br>pH<br>Microscopic Examination (reflex if abnormal) | |
| **Lipid Panel** | |
| Cholesterol (total)<br>High Density Lipoprotein (HDL)<br>Low Density Lipoprotein (LDL)<br>Triglycerides | |
| **Infectious Serologies** | |
| Hepatitis C Antibody with reflex to Hepatitis C RNA if positive<br>Hepatitis B Surface Antigen (HBsAg)<br>Hepatitis B Surface Antibody (HBsAb)<br>Hepatitis B Core Antibody (HBcAb)<br>Hepatitis B DNA Viral Load (HBV DNA)<br>HIV-1 and -2 antibody | |
| **Other Analyses** | |
| Pregnancy test (WOCBP only: serum hCG test at Screening, followed by urine hCG test every 4 weeks)<br>Follicle-Stimulating Hormone (FSH) (to confirm menopausal status [see APPENDIX 4], at screening)<br>Hemoglobin A1C<br>Thyroid-Stimulating Hormone (TSH)<br>• If TSH above normal reference range, test free T4; if TSH below normal range, test free T4 & T3<br><br>High-Sensitivity C Reactive Protein (hs-CRP)<br><br>Serum Immunoglobulins (IgM, IgG, IgA, IgE) | |

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

#### *8.4.5.1 Estimated Glomerular Filtration Rate (eGFR)*

Glomerular filtration rate will be estimated using the Modification of Diet in Renal Disease (MDRD) equation at screening and during the study at select visits.

The MDRD equation is as follows:[47]

$$eGFR = 175 \times \text{standardized } SCr^{-1.154} \times age^{-0.203} \times 1.212 \text{ [if black] or } 0.742 \text{ [if female]}$$

Note: GFR is expressed as mL/min/1.73 $m^2$ of body surface area and SCr (serum creatinine) is expressed in mg/dL.

Subjects with an eGFR <45 mL/min will be excluded from participation.

### 8.4.6 Depression Monitoring

Depression will be monitored by administration of the eight-item Patient Health Questionnaire (PHQ-8) at Screening and during visits as outlined in Section 1.3.

#### 8.4.6.1 Eight-Item Patient Health Questionnaire (PHQ-8)

The PHQ-8 is established as a valid diagnostic and severity measure for depressive disorders in large clinical studies.[48] Each of the 8 questions is based on a 2-week recall and scored on a scale of 0 to 3 by a tick box as: Not at All, Several Days, More than Half the Days, and Nearly Every Day. A score of ≥10 is suggestive of moderate depressive symptoms (see APPENDIX 22).[49] If a subject scores ≥15 on the PHQ-8 during the study, the investigator will review the situation and refer the subject to a mental health professional if deemed necessary.

### 8.4.7 Suicidal Ideation and Behavior (SIB) Monitoring

Subjects in this clinical trial will be monitored for SIB by the eC-SSRS (Section 8.4.7.1) at the visits outlined in the Schedule of Activities (Section 1.3). Subjects who answer yes to Questions 4 or 5 which indicates a suicidal ideation severity level of 4 or 5 or document suicidal behavior or suicidal attempts on the eC-SSRS will have their treatments discontinued and be immediately referred to a mental health professional for further evaluation. In addition, family members or caregivers of the subjects will be instructed to immediately report any suicidal ideation, suicidal behavior, or suicide attempt to the investigator.

#### 8.4.7.1 electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

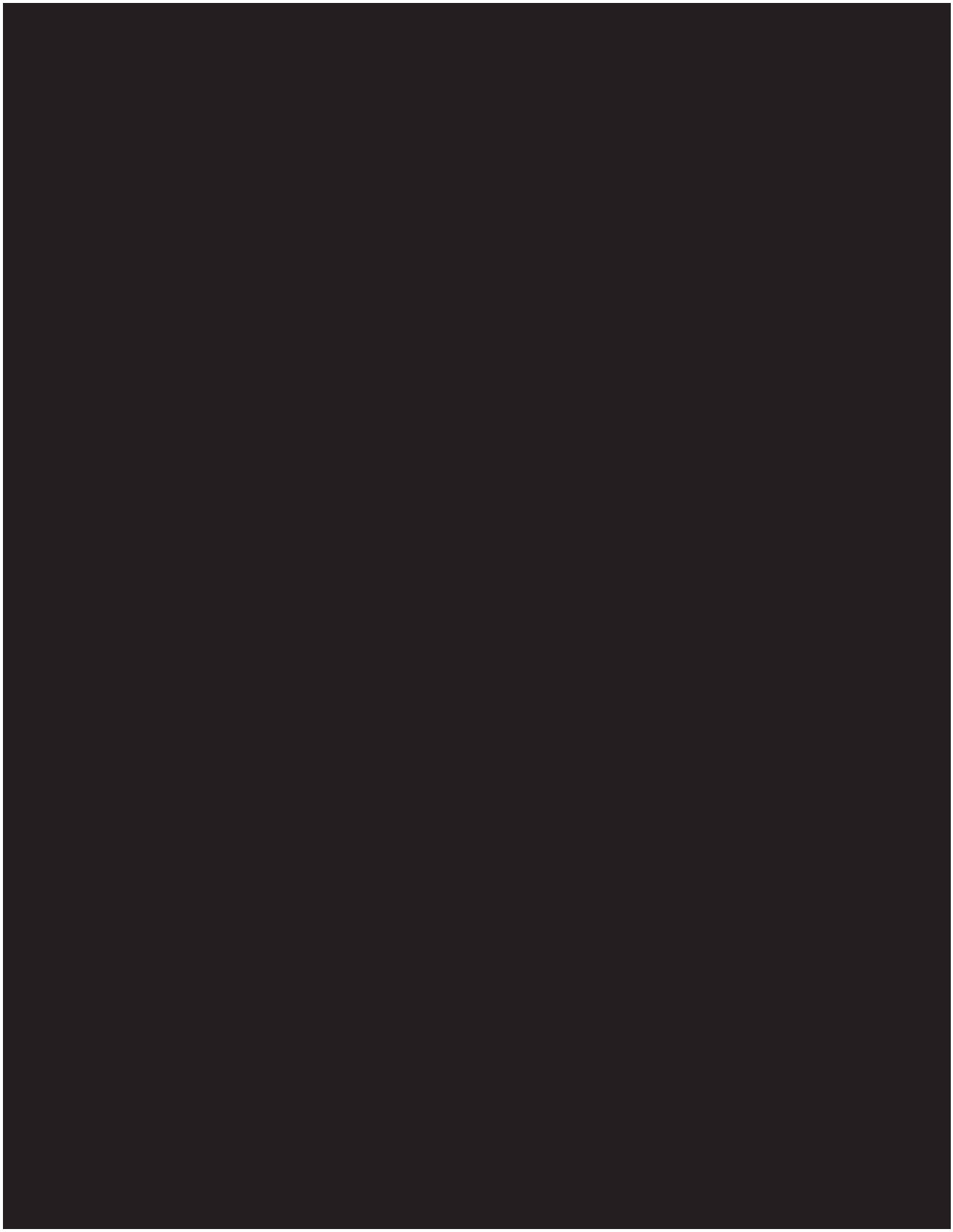
The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) is a computer-automated, patient-reported version of the C-SSRS instrument that defines 11 categories of SIB events.[50,51,52] The categories are as follows:

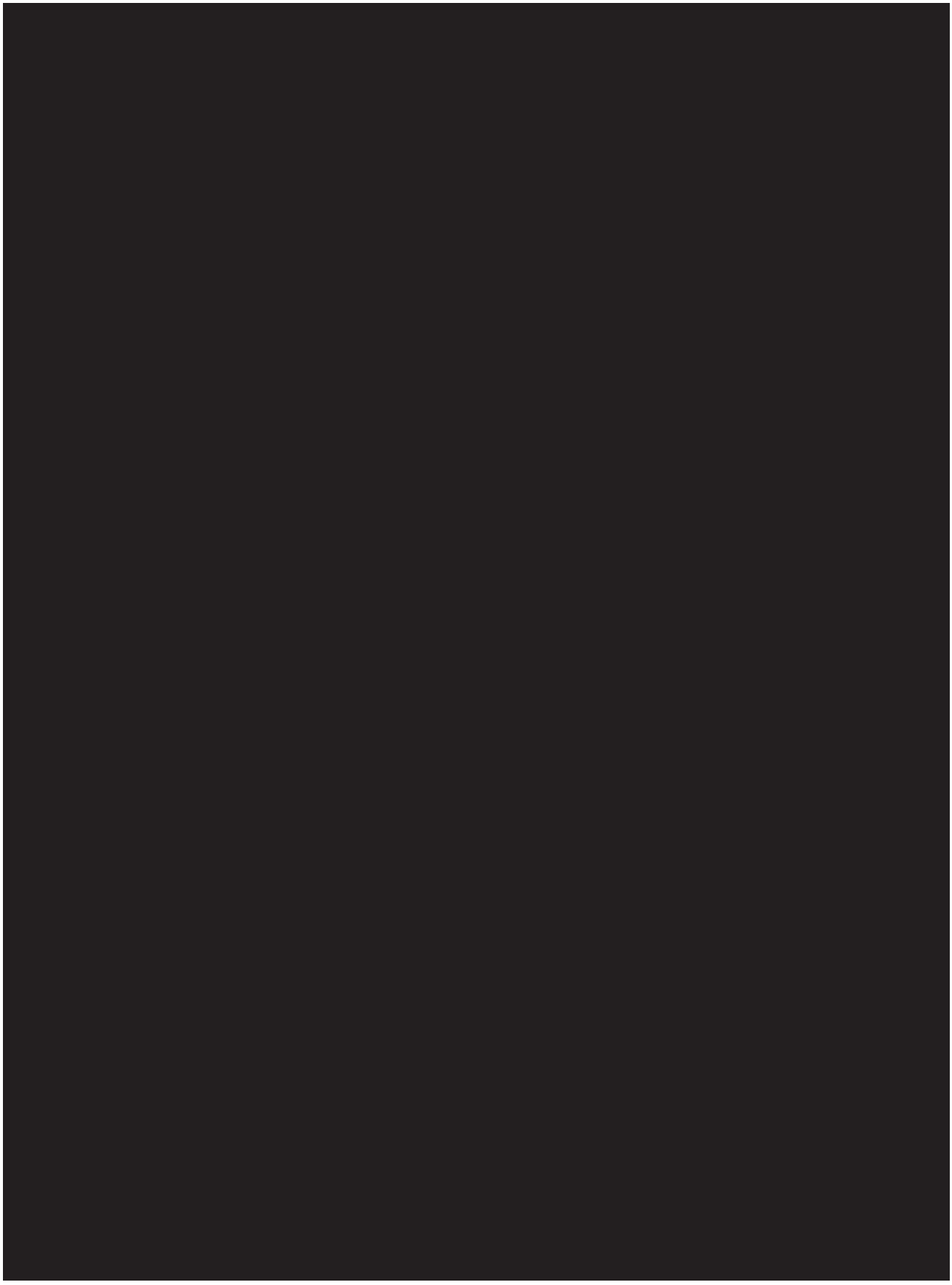
- Suicidal ideation
  1. Passive
  2. Active: Nonspecific (no method, intent, or plan)
  3. Active: Method, but no intent or plan
  4. Active: Method and intent, but no plan
  5. Active: Method, intent, and plan
- Suicidal behavior
  1. Completed suicide
  2. Suicide attempt
  3. Interrupted attempt

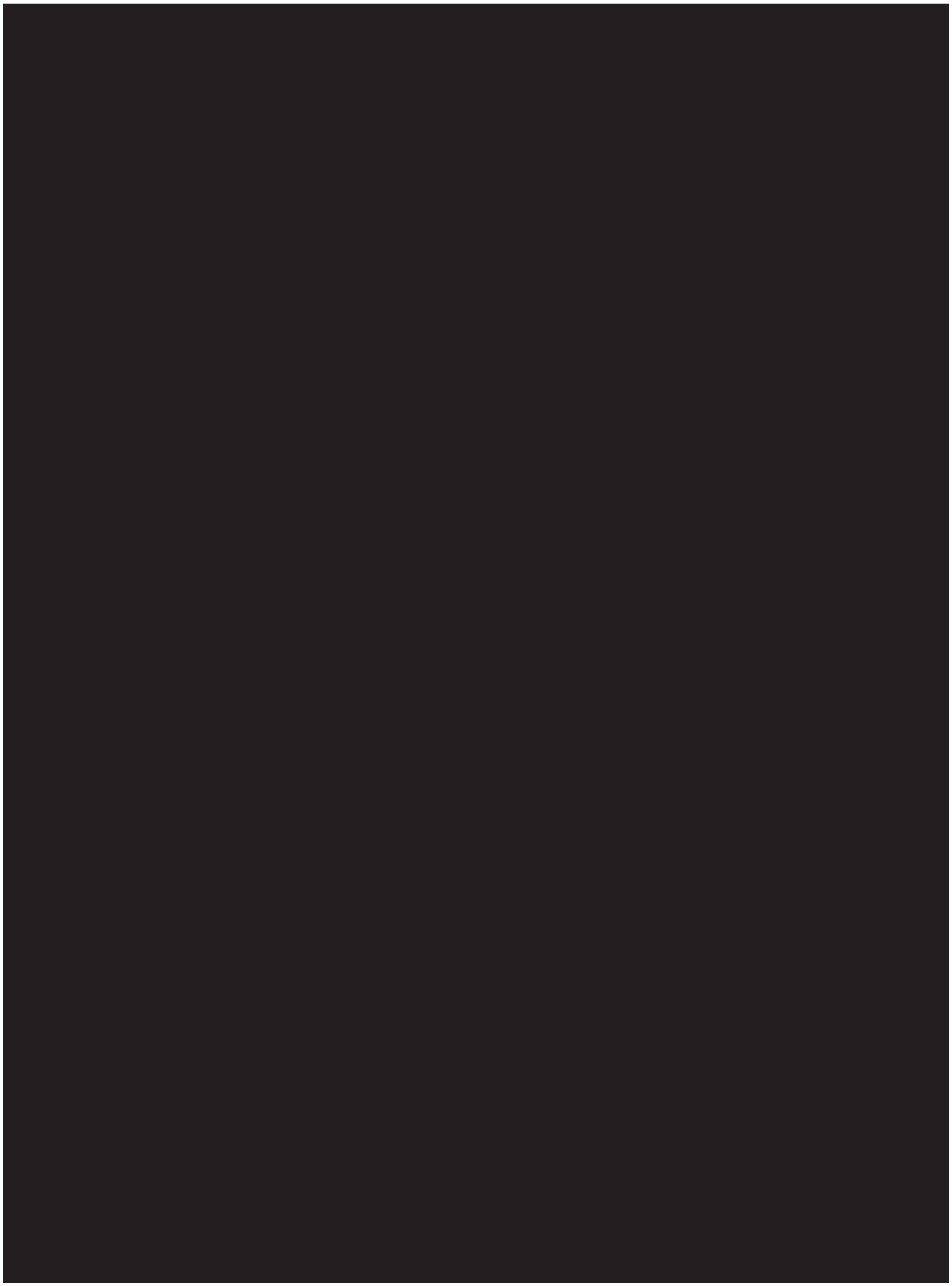
4. Aborted attempt
5. Preparatory actions toward imminent suicidal behaviors

- Self-injurious behavior, no suicidal intent

APPENDIX 23 provides definitions of these categories.[53]







## 8.7 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

[redacted]

## 9.2 Populations for Analyses

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

**Enrolled Population:** All subjects who sign informed consent.

**Full Analysis Set (FAS):** All subjects who were randomized to receive assigned study treatment. Following the intent-to-treat principle, subjects will be analyzed according to the treatment group assigned at randomization. The FAS will be the primary efficacy analysis population.

**Per Protocol Set (PPS):** A subset of the FAS who are compliant with study treatment and who do not have any relevant protocol deviations that may impact the coprimary efficacy endpoint assessments (Section 9.6.3). The PPS will be analyzed for the coprimary endpoint comparisons according to the treatment assigned at randomization.

**As-treated Population:** All randomized subjects who take at least one dose of study treatment. Subjects will be analyzed according to treatment received. The As-treated population will be for safety analyses.

[redacted]

## 9.3 Endpoints

### *9.3.1 Primary Endpoints*

The coprimary efficacy endpoints for BMS-986165 compared to placebo at Week 16 are defined as:

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

### *9.3.2 Secondary Endpoints*

#### *9.3.2.1 Key Secondary Endpoints for Comparisons to Placebo*

The key secondary endpoints for BMS-986165 compared to placebo at Week 16 are defined as:

- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score
- PASI 100 response assessed as a proportion of subjects who achieve a 100% improvement from baseline in the PASI score
- sPGA 0 response assessed as a proportion of subjects with an sPGA score of 0
- Change from baseline in PSSD symptom score
- PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥1
- ss-PGA 0/1 assessed as a proportion of subjects with a ss-PGA score 0 or 1 among subjects with a baseline ss-PGA score ≥3
- DLQI 0/1 assessed as a proportion of subjects with a DLQI score of 0 or 1 among subjects with a baseline DLQI score ≥2
- PGA-F 0/1 assessed as a proportion of subjects with a PGA-F score of 0 or 1 among subjects with a baseline PGA-F score ≥3
- pp-PGA 0/1 assessed as a proportion of subjects with a pp-PGA score of 0 or 1 among subjects with a baseline pp-PGA score ≥3

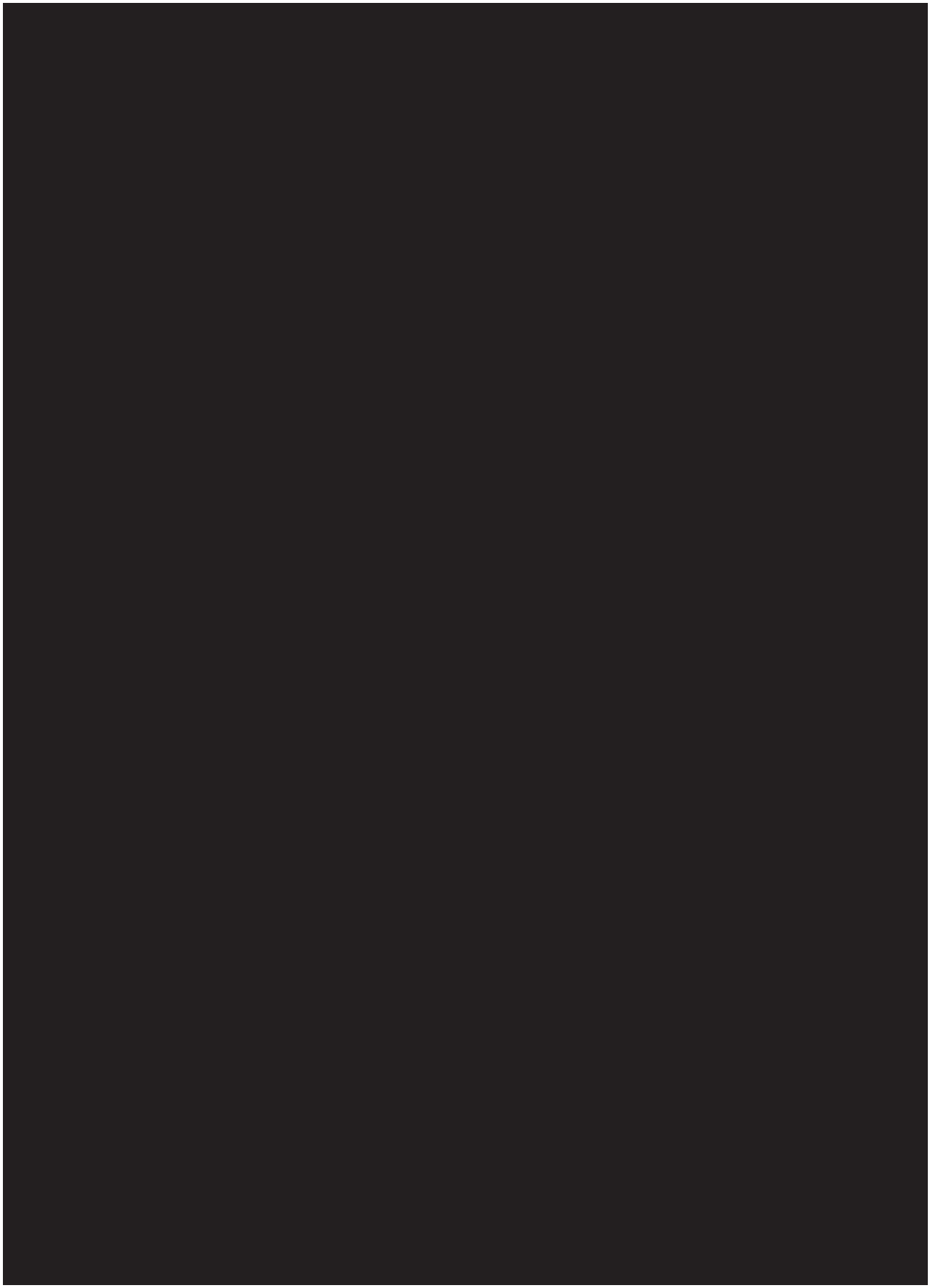
#### 9.3.2.2 Key Secondary Endpoints for Comparisons to Apremilast

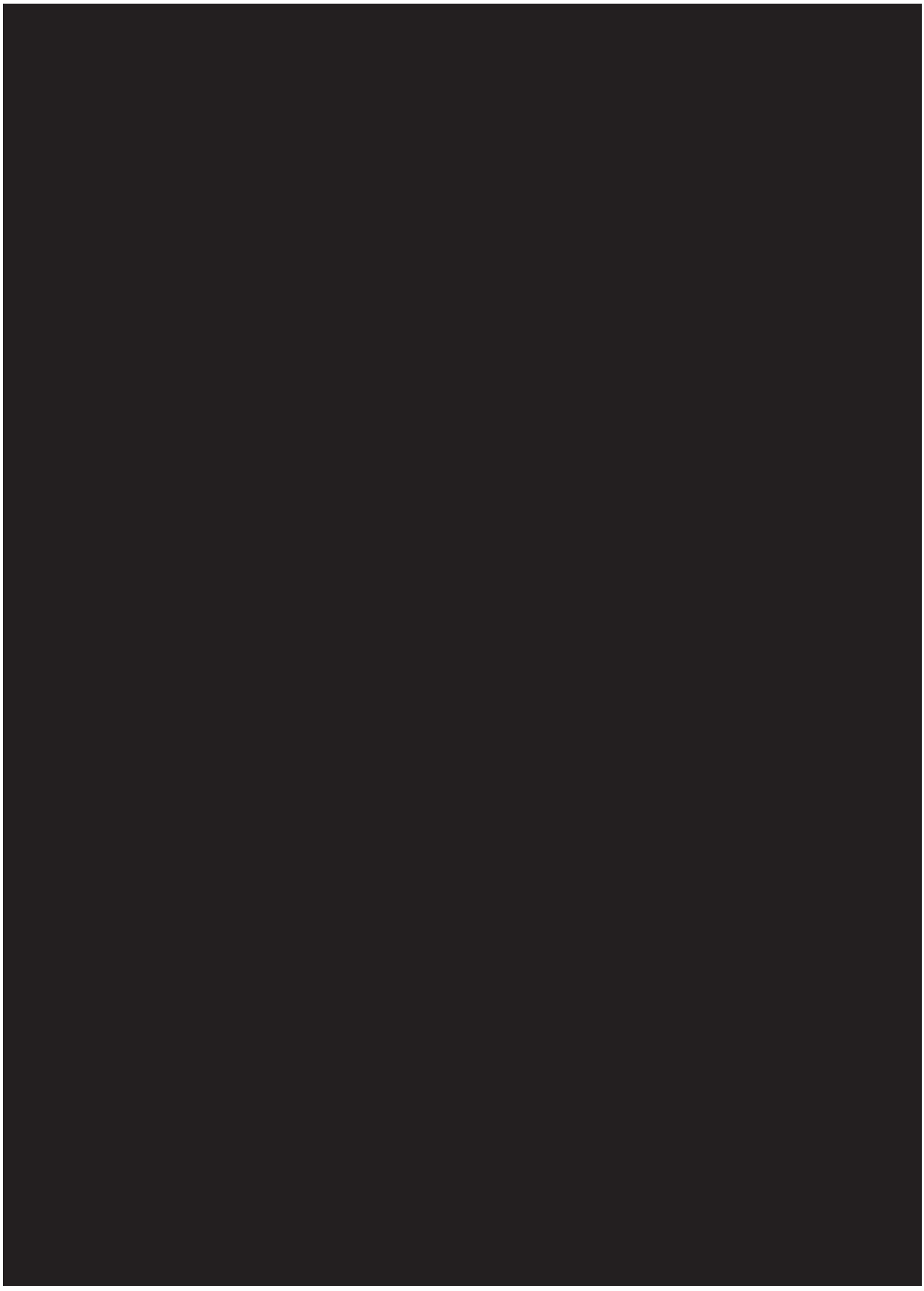
The key secondary endpoints for BMS-986165 compared to apremilast at Week 16 are defined as:

- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score
- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score
- PASI 100 response assessed as a proportion of subjects who achieve a 100% improvement from baseline in the PASI score
- sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1
- sPGA 0 response assessed as a proportion of subjects with an sPGA score of 0
- Change from baseline in PSSD symptom score
- PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥1
- ss-PGA 0/1 assessed as a proportion of subjects with a ss-PGA score 0 or 1 among subjects with a baseline ss-PGA score ≥3

The key secondary endpoints for BMS-986165 compared to apremilast both at Week 52 and Week 24 are defined as:

- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score
- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score
- sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1





## 9.4 Efficacy Analyses

Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified. Efficacy variables will be summarized for all visits in which the variable is assessed. Complete details of the planned analyses will be documented in the statistical analysis plan and finalized before database lock.

During the first 16 weeks of treatment, data will be presented for the following treatments:

- BMS-986165 6 mg QD
- Apremilast 30 mg BID
- Placebo

After Week 16, data will be presented for the following treatments:

- BMS-986165 6 mg QD
- Apremilast 30 mg BID
- Placebo→BMS-986165 6 mg QD (starting from Week 16 through Week 52)
- All BMS-986165 6 mg QD (all subjects exposed to BMS-986165 6 mg QD; includes subjects on placebo and apremilast 30 mg BID that switched to BMS-986165 6 mg QD)

### 9.4.1 Coprimary Endpoint Analyses

The analysis model for the coprimary efficacy endpoints, sPGA 0/1 and PASI 75 (responder/nonresponder) at Week 16, will use stratified Cochran-Mantel-Haenszel (CMH) tests stratified by the stratification factors used for randomization (see Section 4.1.2) to compare the response rates of BMS-986165 6 mg QD to placebo using the Week 16 data of the FAS. If expected cell counts are not sufficient for each strata level, then strata levels will be combined for the analysis. The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the odds in placebo group) and the corresponding 2-sided 95% confidence interval (CI) will be provided. Estimates of proportions and their 2-sided 95% CIs will be provided.

#### 9.4.1.1 Imputation Methods for Coprimary Endpoints

Nonresponder imputation (NRI) will be used for coprimary efficacy endpoints for subjects who discontinue study or treatment of study prior to Week 16, start a protocol prohibited medication/therapy that could improve psoriasis during the first 16 weeks of treatment, or who have otherwise missing endpoint data at the specified timepoint. The NRI will the primary method of imputation for the coprimary efficacy endpoints.

#### 9.4.1.2 Sensitivity Analyses for the Coprimary Endpoints

The following imputation methods will be used in sensitivity analyses of the coprimary efficacy endpoints:

- Last observation carried forward (LOCF) for subjects with missing values at Week 16
- For subjects with missing values at Week 16, LOCF will be used for placebo subjects and NRI will be used for BMS-986165 6 mg QD subjects. This will include subjects who discontinue early, start a protocol prohibited medication/therapy prior to Week 16 that could improve psoriasis, or who have otherwise missing endpoint data at Week 16

#### 9.4.1.3 Supportive Analyses for the Coprimary Endpoints

The coprimary efficacy endpoints will also be analyzed using the Week 16 data of the PPS using the analysis described in Section 9.4.1 and the imputation methods described in Section 9.4.1.1.

Additionally, the coprimary efficacy endpoints for the FAS will be analyzed with a logistic regression model with treatment and the stratification factors used for randomization as covariates.

#### 9.4.1.4 Subgroup Analyses for the Coprimary Endpoints

Subgroup analyses will be conducted for the coprimary efficacy endpoints for the FAS using the analysis described in Section 9.4.1 and the imputation methods described in Section 9.4.1.2. Subgroups to be evaluated will include the following:

- Gender
- Age categories (<65; ≥65)
- Race

- Body weight categories (<90 kg; ≥90 kg)
- Prior biologic use (yes/no)
- Prior systemic treatment of psoriasis (yes/no)
- Geographic region

In addition, additional subgroups defined for descriptive summaries will be specified in the statistical analysis plan.

### 9.4.2 Secondary Endpoint Analyses

The analysis model for the binary secondary endpoints will use stratified CMH tests stratified by the stratification factors used for randomization (see Section 4.1.2) to compare the response rates of BMS-986165 6 mg QD to placebo or apremilast for the FAS. If expected cell counts are not sufficient for each strata level, then strata levels will be combined for the analysis. The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the/odds in placebo group or active comparator group), and the corresponding 2-sided 95% CI will be provided.

The analysis model for continuous secondary endpoints will use analysis of covariance (ANCOVA) [redacted], with treatment and stratification factors used for randomization as fixed effects. The baseline value will be added into the model as a covariate. Treatment differences based on least-squares (LS) means and the corresponding 2-sided 95% CIs will be provided for the difference between BMS-986165 6 mg QD and placebo or active comparator depending on the endpoint being assessed.

#### 9.4.2.1 Imputation Methods for Secondary Endpoints

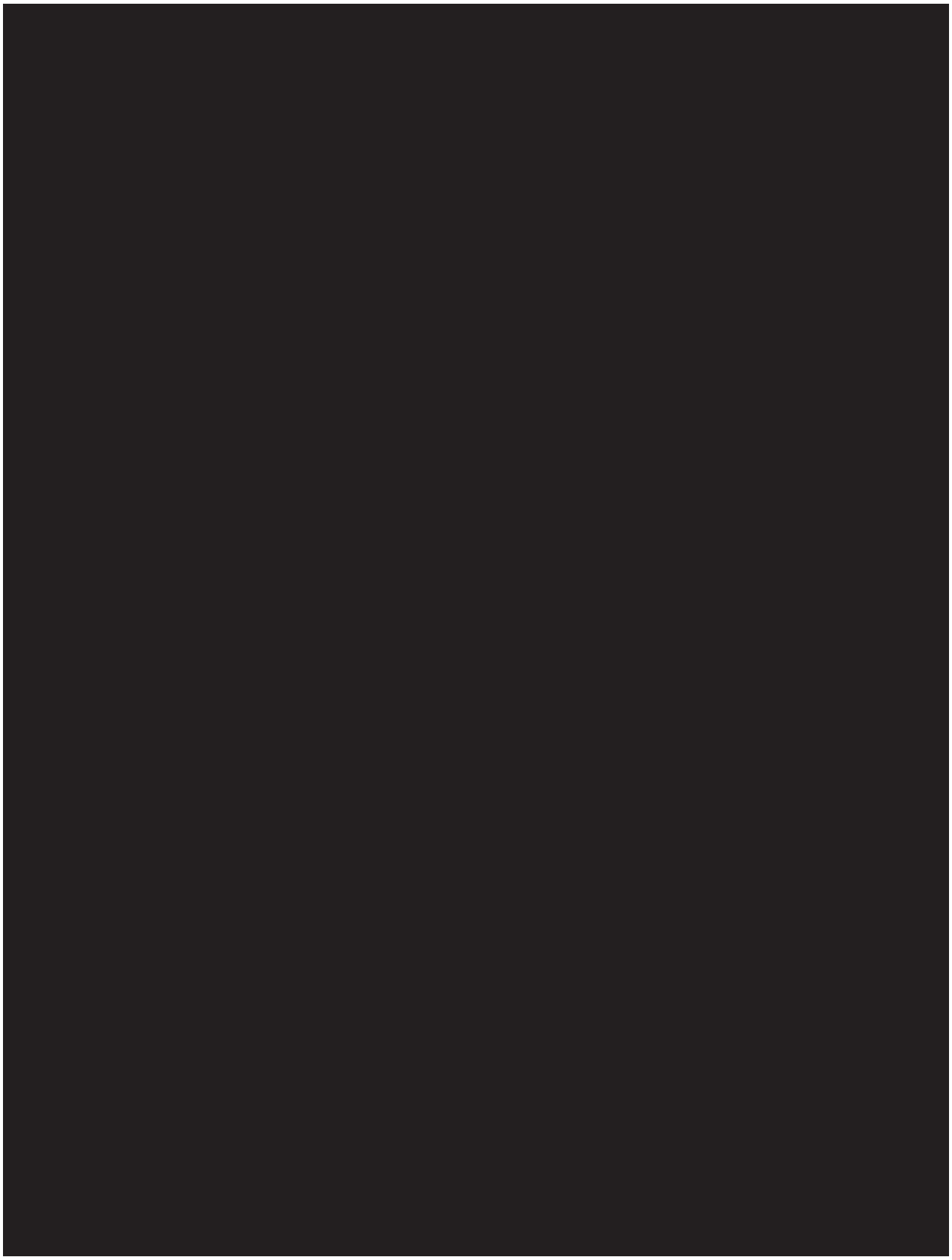
The NRI will be applied to the analyses of binary secondary efficacy endpoints for subjects who discontinue early, start a protocol prohibited medication/therapy that could improve psoriasis, or who have otherwise missing endpoint data prior to the specified timepoint.

For continuous secondary efficacy endpoints, a modified baseline observation carried forward (mBOCF) will be used for missing data. The baseline observation will be carried forward for subjects who discontinue study treatment due to:

- Lack of efficacy
- AEs

and for subjects who start a protocol prohibited medication/therapy that could improve psoriasis prior to the endpoint. The last valid observation will be carried forward for all other subjects with missing data.

At Week 24, subjects originally randomized to apremilast 30 mg BID who do not achieve PASI 50 response will be switched in a blinded manner to BMS-986165 6 mg QD. These subjects will be considered nonresponders to apremilast for the timepoints after the switch for the binary endpoints for the Week 52 comparisons. The mBOCF described above will be used for the continuous endpoints. Subjects will be analyzed according to their original randomized treatment group.



[redacted]

### 9.4.4 Time-to-Event Endpoints

The Kaplan-Meier product limit method will be used to estimate the distribution curve for time-to-loss (from Week 24) of PASI 75 response for the BMS-986165 treatment group.

## 9.5 Safety Analyses

Safety data will be analyzed for AEs, SAEs, laboratory analytes, vital signs, ECGs, and suicidality and depression. Safety will be summarized using the As-treated population. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

During the first 16 weeks of treatment, data will be presented for the following treatments:

- BMS-986165 6 mg QD
- Apremilast 30 mg BID
- Placebo

After Week 16, data will be presented for the following treatments:

- BMS-986165 6 mg QD
- Apremilast 30 mg BID
- Placebo to BMS-986165 6 mg QD (starting from Week 16 through Week 52)
- All BMS-986165 6 mg QD (all subjects exposed to BMS-986165 6 mg QD; includes subjects on placebo that switched to BMS-986165 6 mg QD)

### 9.5.1 Adverse Events

Treatment-emergent adverse events (TEAEs), SAEs and deaths, and AEs leading to study treatment discontinuation, AEs by maximum severity, and AEs by relationship will be summarized by the MedDRA system organ class and preferred term. All TEAEs, AEIs, as well as each AE

adjudicated category (ie, infections, cardiovascular, and SIB) will also be summarized by preferred term sorted by decreasing frequency.

### 9.5.2 Vital Signs and ECGs

Vital signs and ECGs will be summarized as raw, change from baseline, and change from maximum postbaseline value. Incidence of abnormal ECG findings will also be summarized.

### 9.5.3 Clinical Laboratory Tests

Laboratory analytes will be summarized as raw, change from baseline, and change from maximum postbaseline value. Incidence of abnormal, high, or low values will be summarized.

### 9.5.4 Suicidality and Depression Assessments

Suicidality and depression will be assessed using eC-SSRS and PHQ-8. Data will be summarized, as applicable.

## 9.6 Other Analyses

### 9.6.1 Demographics and Baseline Data

Demographics and baseline data will be summarized by treatment for each applicable analysis population. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

### 9.6.2 Prior and Concomitant Medications

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

### 9.6.3 Relevant Protocol Deviations

Relevant protocol deviations are deviations that can have an impact on the primary efficacy endpoints. The impact of relevant protocol deviations on the primary efficacy results will be assessed by excluding subjects from the FAS to define the PPS in supportive analyses of the primary efficacy endpoints. Relevant protocol deviations to be considered regarding exclusion of subjects from the FAS will include the following:

- Subject randomized but did not take any study treatment
- Subject failed to meet any study inclusion criteria but was randomized to receive study treatment
- Subject met a study exclusion criterion which may have an impact on the coprimary efficacy endpoints but was randomized to receive study treatment
- Subject noncompliant with study treatment within the first 16 weeks of treatment; defined as <80% compliant with study treatment
- Subject took prohibited concomitant medication prior to Week 16

- Subject received treatment different to intended treatment at any visit prior to Week 16

All subjects with relevant protocol deviations will be identified prior to database lock. Relevant protocol deviations will be summarized by treatment group and deviation category for the FAS population.

[redacted]

## 9.7 Interim Analyses

No interim analysis is currently planned.

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## 11 APPENDICES

## APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

| Term | Definition |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| AE | adverse event |
| AEI | adverse event of interest |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| [redacted] | [redacted] |
| Anti-HCV | hepatitis C virus antibody |
| [redacted] | [redacted] |
| AST | aspartate aminotransferase |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| BID | twice daily |
| BMS | Bristol-Myers Squibb |
| BSA | body surface area |
| BUN | blood urea nitrogen |
| Cavg, ss | average concentration at steady state |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| [redacted] | [redacted] |
| CMH | Cochran-Mantel-Haenszel |
| CK | creatine kinase |
| CT | computed tomography |
| [redacted] | [redacted] |
| CYP450 | cytochrome P450 |
| [redacted] | [redacted] |
| DILI | drug-induced liver injury |

| Term | Definition |
|---|---|
| DLQI | Dermatology Life Quality Index |
| DMC | Data Monitoring Committee |
| DNA | deoxyribonucleic acid |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eC-SSRS | electronic Columbia-Suicide Severity Rating Scale |
| eGFR | Estimated Glomerular Filtration Rate |
| [redacted] | [redacted] |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| GI | gastrointestinal |
| [redacted] | [redacted] |
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| hCG | human chorionic gonadotropin |
| Hct | hematocrit |
| HCV | hepatitis C virus |
| HDL | high density lipoprotein |
| Hgb | hemoglobin |
| HIV | human immunodeficiency virus |
| hs-CRP | high-sensitivity C-reactive protein |
| IB | Investigator Brochure |
| [redacted] | [redacted] |
| ICF | informed consent form |
| IEC | Independent Ethics Committee |
| IFN | interferon |

| Term | Definition |
|---|---|
| IFNγ | interferon gamma |
| Ig | immunoglobulin |
| IGRA | interferon gamma release assay |
| IL | interleukin |
| IM | intramuscular |
| IMP | investigational medicinal product |
| IP | investigational product |
| IRT | interactive response technology |
| ITT | intent-to-treat |
| IV | intravenous |
| JAK | Janus kinase |
| LDH | lactate dehydrogenase |
| LDL | low density lipoprotein |
| LOCF | last observation carried forward |
| LS | least-squares |
| LTBI | latent tuberculosis infection |
| MACE | Major Adverse Cardiovascular Events |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mBOCF | modified baseline observation carried forward |
| [redacted] | [redacted] |
| NRI | nonresponder imputation |
| PASE | psoriatic arthritis screening and evaluation |
| PASI | Psoriasis Area and Severity Index |
| PD | pharmacodynamics |
| PE | physical examination |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| PHQ-8 | Eight-Item Patient Health Questionnaire |
| PK | pharmacokinetics |
| [redacted] | [redacted] |

| Term | Definition |
|---|---|
| pp-PGA | palmoplantar Physician's Global Assessment |
| PPS | Per Protocol Set |
| PsA | psoriatic arthritis |
| PSSD | Psoriasis Symptoms and Signs Diary |
| [redacted] | [redacted] |
| QD | once daily |
| QOD | every other day |
| PGA-F | Physician Global Assessment- Fingernails |
| PUVA | Psoralens with ultraviolet A |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| [redacted] | [redacted] |
| SIB | Suicidal Ideation and Behavior |
| sPGA | static Physician Global Assessment |
| ss-PGA | scalp specific Physician's Global Assessment |
| STAT | signal transducer and activator of transcription |
| TB | tuberculosis |
| T4 | thyroxine |
| T3 | triiodothyronine |
| TEAE | treatment-emergent adverse event |
| [redacted] | [redacted] |
| TSH | thyroid-stimulating hormone |
| TNF | tumor necrosis factor |
| TYK2 | tyrosine kinase 2 |
| ULN | upper limit of normal |
| UVB | ultraviolet B |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| WOCBP | women of childbearing potential |

# APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

## Regulatory and Ethical Considerations

### Good Clinical Practice

This study will be conducted in accordance with:

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

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

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

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

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

### Institutional Review Board/Independent Ethics Committee

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

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

### Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

**Financial Disclosure**

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

**Informed Consent Process**

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

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

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

Investigators must:

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

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

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

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

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

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

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

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

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

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

**Source Documents**

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

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

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

**Study Treatment Records**

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

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

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

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

### Case Report Forms

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

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

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

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

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

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

**Monitoring**

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

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

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

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

**Records Retention**

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

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

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

**Return of Study Treatment**

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

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

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

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

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

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

**Clinical Study Report and Publications**

A Signatory Investigator must be selected to sign the CSR.

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

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

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

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

## Adverse Events

**Adverse Event Definition:**

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

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

**Events Meeting the AE Definition**

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

**Events NOT Meeting the AE Definition**

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

**DEFINITION OF SAE**

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

## Serious Adverse Events

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

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

## Evaluating AEs and SAEs

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

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

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

All SAEs must be followed to resolution or stabilization.

## Reporting of SAEs to Sponsor or Designee

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

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

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

**SAE Email Address:** [redacted]

**SAE Fax Number:**

**Americas:** [redacted]

**Europe/East Asia-Pacific:** [redacted]

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

**Americas:** [redacted]

**Europe/East Asia-Pacific:** [redacted]

# APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

## DEFINITIONS

### Woman of Childbearing Potential (WOCBP)

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

### Women in the following categories are not considered WOCBP

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

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

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

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

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

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

## CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILD BEARING POTENTIAL

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**<br>*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]<br>– oral<br>– intravaginal<br>– transdermal |
| • Progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |
| **Highly Effective Methods That Are User Independent** |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b]<br>• Intrauterine device (IUD)[c]<br>• Intrauterine hormone-releasing system (IUS)[c]<br>• Bilateral tubal occlusion |
| • Vasectomized partner<br>*A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* |

- Sexual abstinence

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

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

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

[c] Intrauterine 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)<br>• Withdrawal (coitus interruptus).<br>• Spermicide only<br>• Lactation amenorrhea method (LAM) |

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

Male subjects 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 subjects are required to use a condom for study duration and until the end of relevant systemic exposure defined as 3 days after the end of treatment in the male subject.
- 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 subject.
- Male subjects 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 for 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 8.2.6 and APPENDIX 3.

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

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

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

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

Physician's Static Global Assessment based upon above Total Average

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

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

# APPENDIX 6 PSORIASIS AREA AND SEVERITY INDEX (PASI)

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

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

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

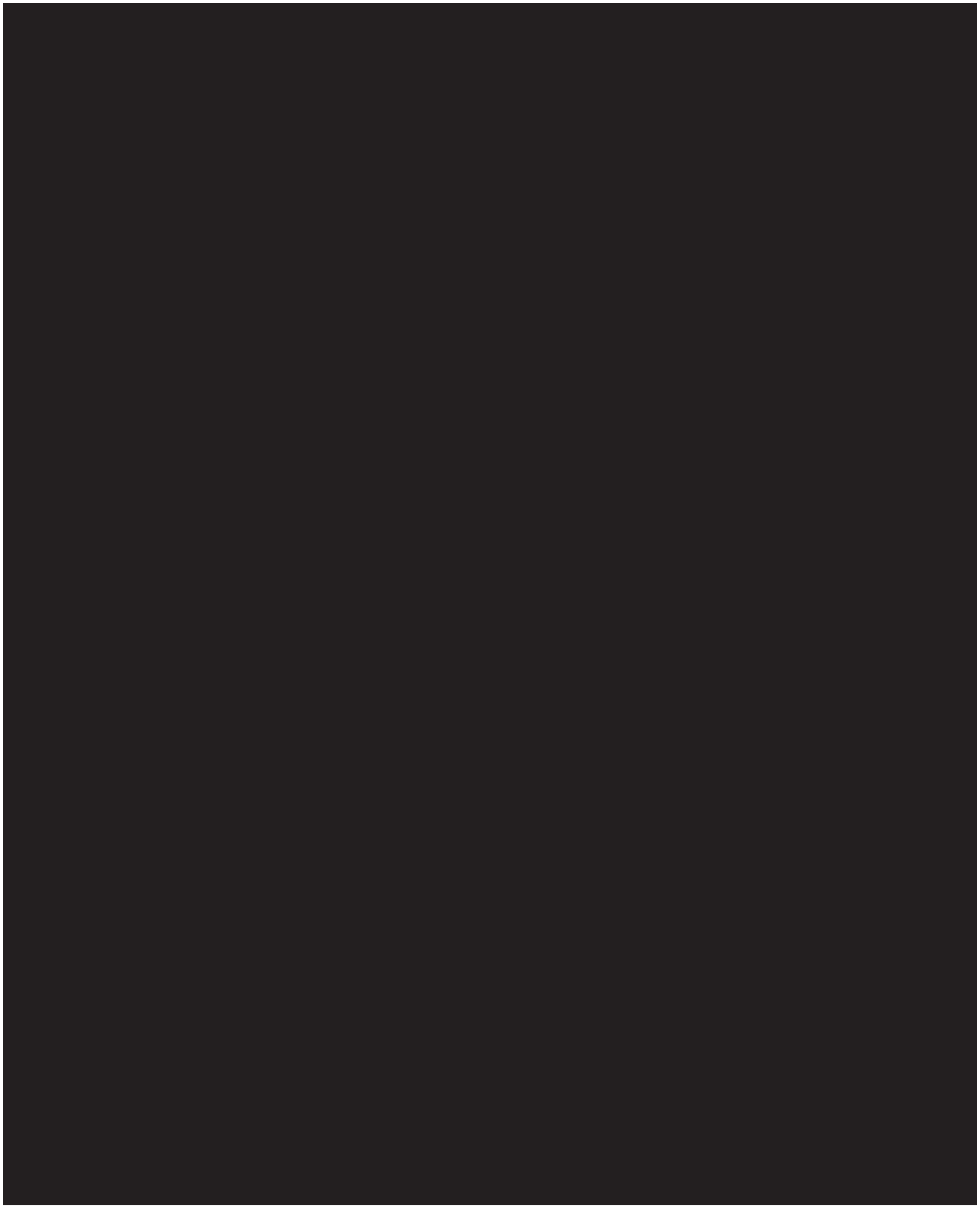
Please rate overall scalp psoriasis severity by selecting the overall score based on the following rating scale:

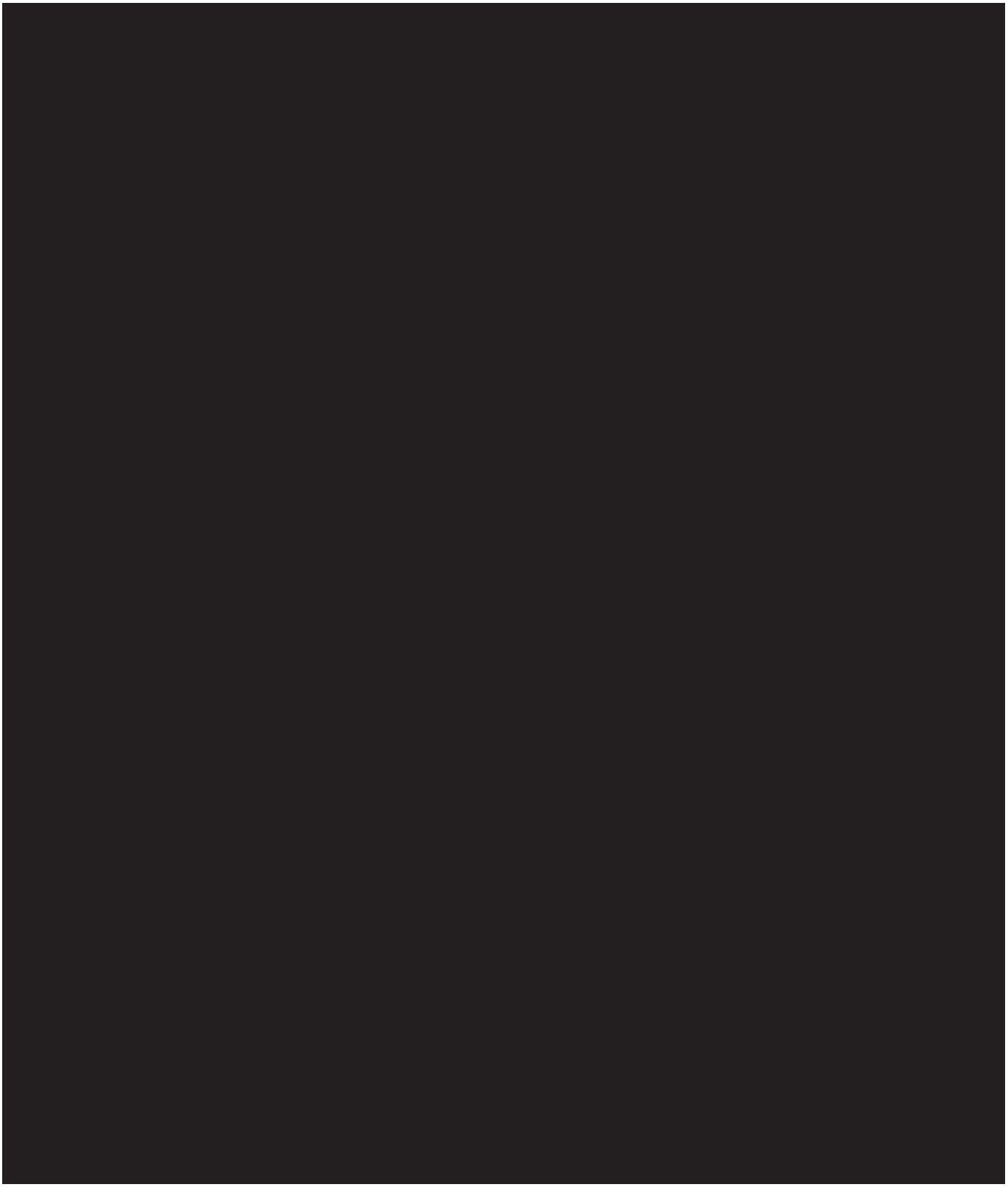
| Score | Category | Description |
|---|---|---|
| 0 | Absence of Disease | No evidence of redness, no evidence of thickness, and no evidence of scaliness on the scalp |
| 1 | Very Mild Disease | The overall clinical picture consists of flat lesions with barely perceptible erythema, with or without a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

# APPENDIX 9 PHYSICIAN'S GLOBAL ASSESSMENT-FINGERNAILS (PGA-F)

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

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

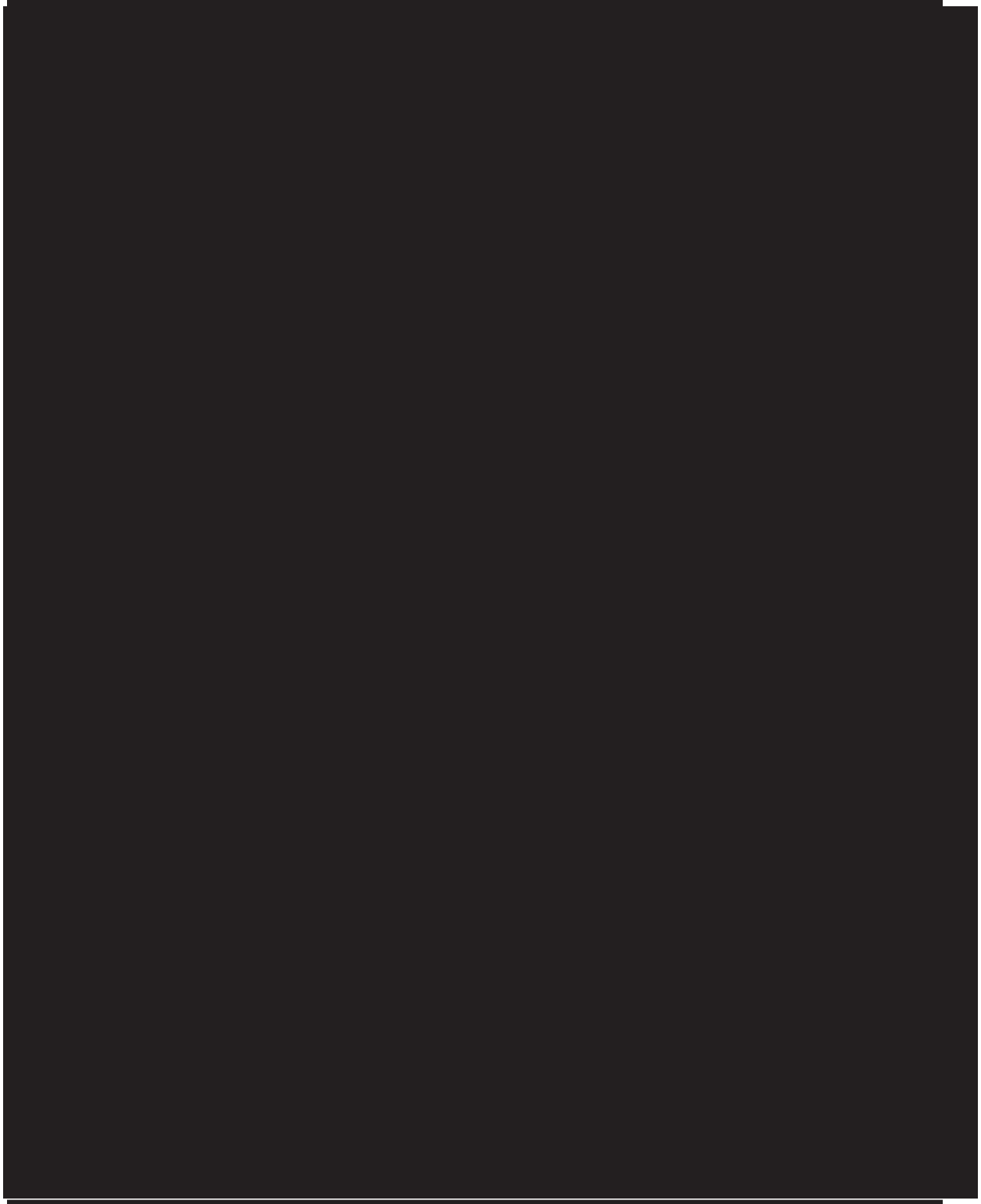




# APPENDIX 11 PALMOPLANTAR PSORIASIS PHYSICIAN'S GLOBAL ASSESSMENT (pp-PGA)

Palmoplantar (including finger and toe surfaces) psoriasis lesions are evaluated by the investigator based on overall severity, then scored on the following 5-point scale:

| Score | Category | Description |
|---|---|---|
| 0 | Clear | No signs of plaque psoriasis |
| 1 | Almost Clear | Just perceptible erythema and just perceptible scaling |
| 2 | Mild | Light pink erythema, with minimal scaling with or without pustules |
| 3 | Moderate | Dull red, clearly distinguishable erythema with diffuse scaling, some thickening of the skin, with or without fissures, with or without pustule formation |
| 4 | Severe | Deep, dark red erythema with obvious and diffuse scaling and thickening as well as numerous fissures with or without pustule formation |



# APPENDIX 13 PSORIASIS SYMPTOMS AND SIGNS DIARY (PSSD)

Please answer each question to the best of your ability. There are no right or wrong answers. Please pay close attention to the time period of interest. These questions ask you to think about the **past 24 hours**. **Please complete the diary at the same time every day.**

Individuals with psoriasis may experience a range of symptoms. Please indicate how severe each of the following skin symptoms was in the **past 24 hours**. Please select only one number for each item on the 0 to 10 scale (0=Absent and 10= Worst imaginable).

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Rate the severity of itch in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 2. Rate the severity of dryness in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 3. Rate the severity of cracking in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 4. Rate the severity of skin tightness in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 5. Rate the severity of scaling (build-up of skin) in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 6. Rate the severity of shedding or flaking in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 7. Rate the severity of redness in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 8. Rate the severity of bleeding in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 9. Rate the severity of burning in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 10. Rate the severity of stinging in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 11. Rate the severity of pain from your psoriasis lesions in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |

# APPENDIX 14 DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: Date: Score:

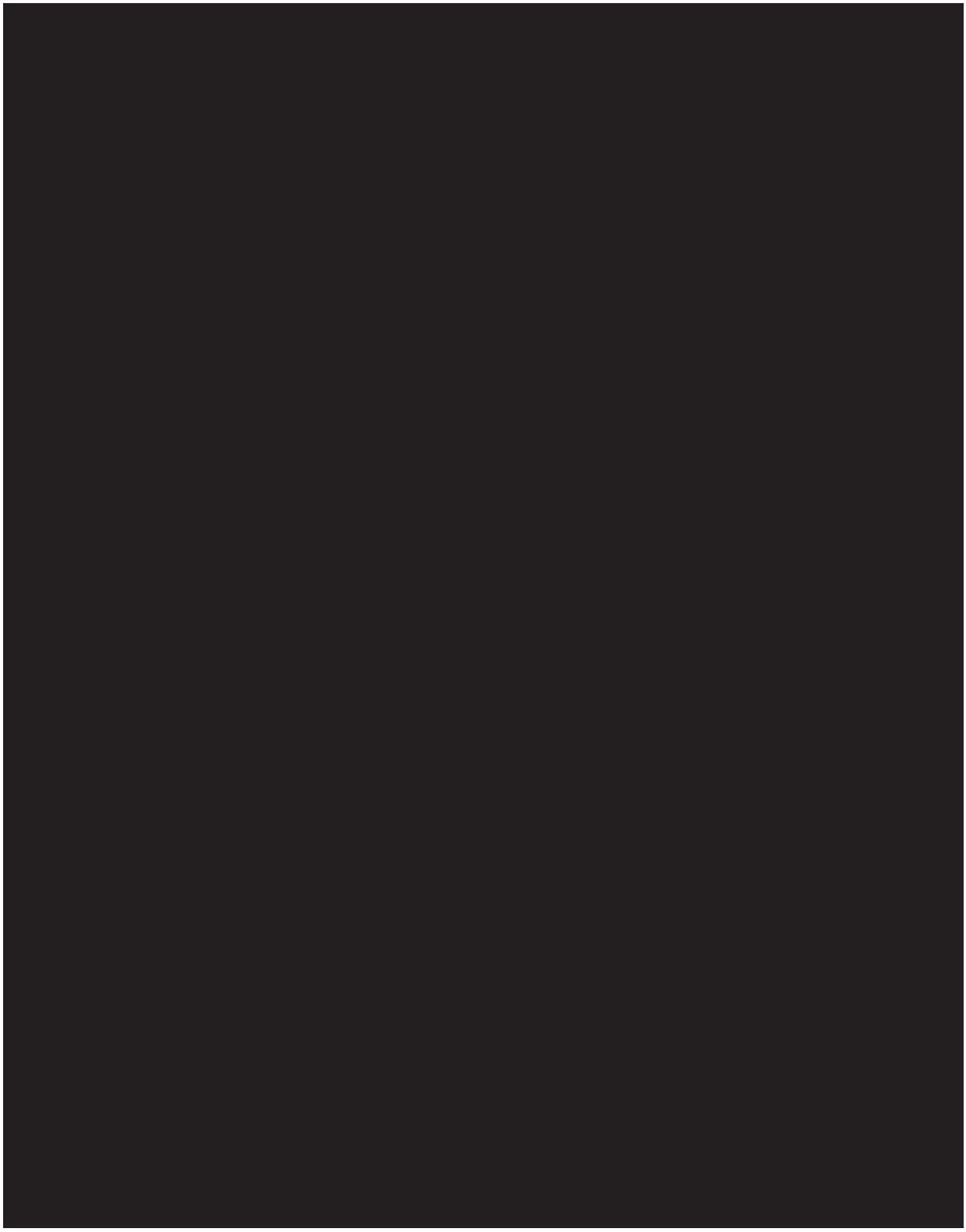
Name: Diagnosis:

Address:

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

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

**Please check you have answered EVERY question. Thank you**



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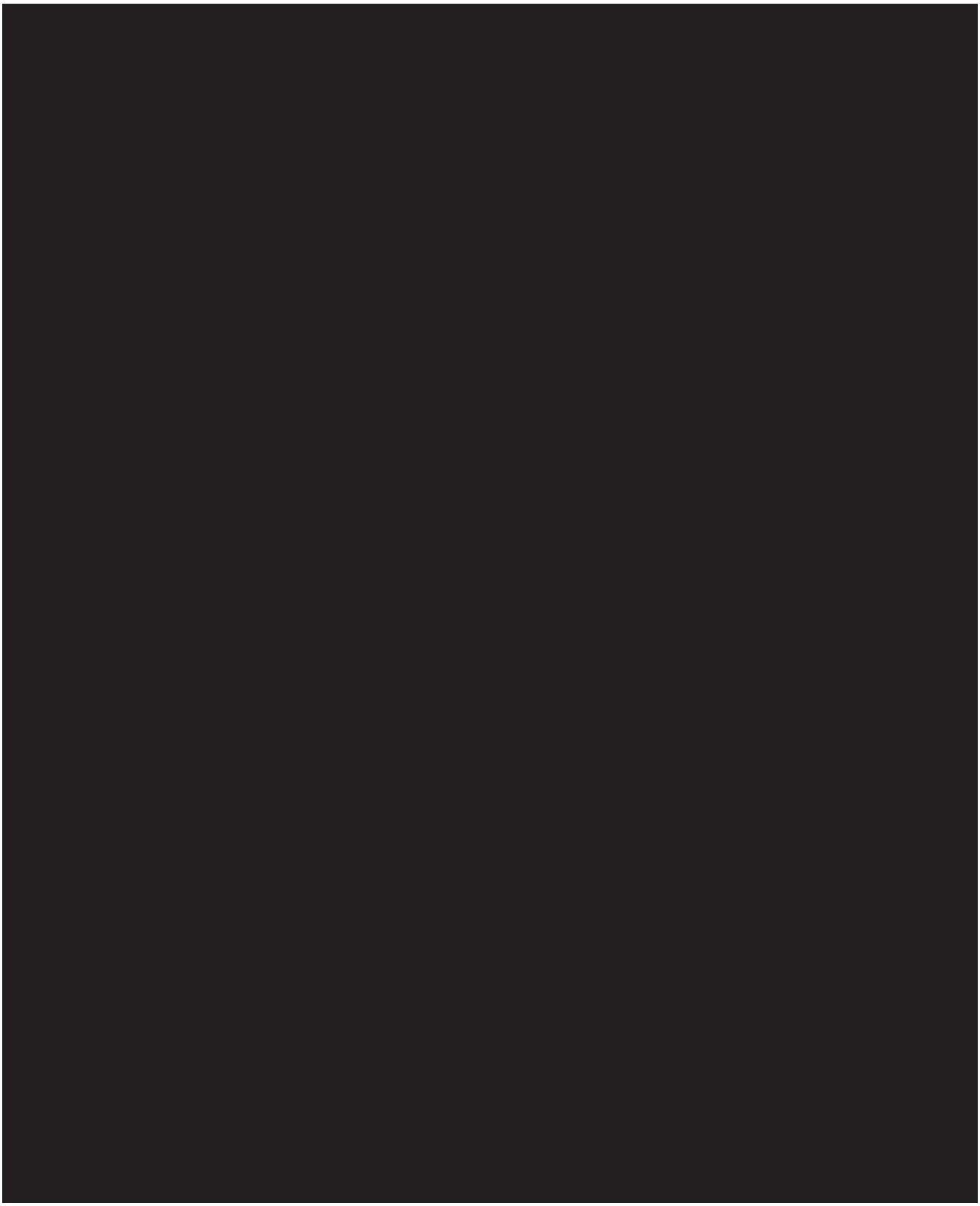

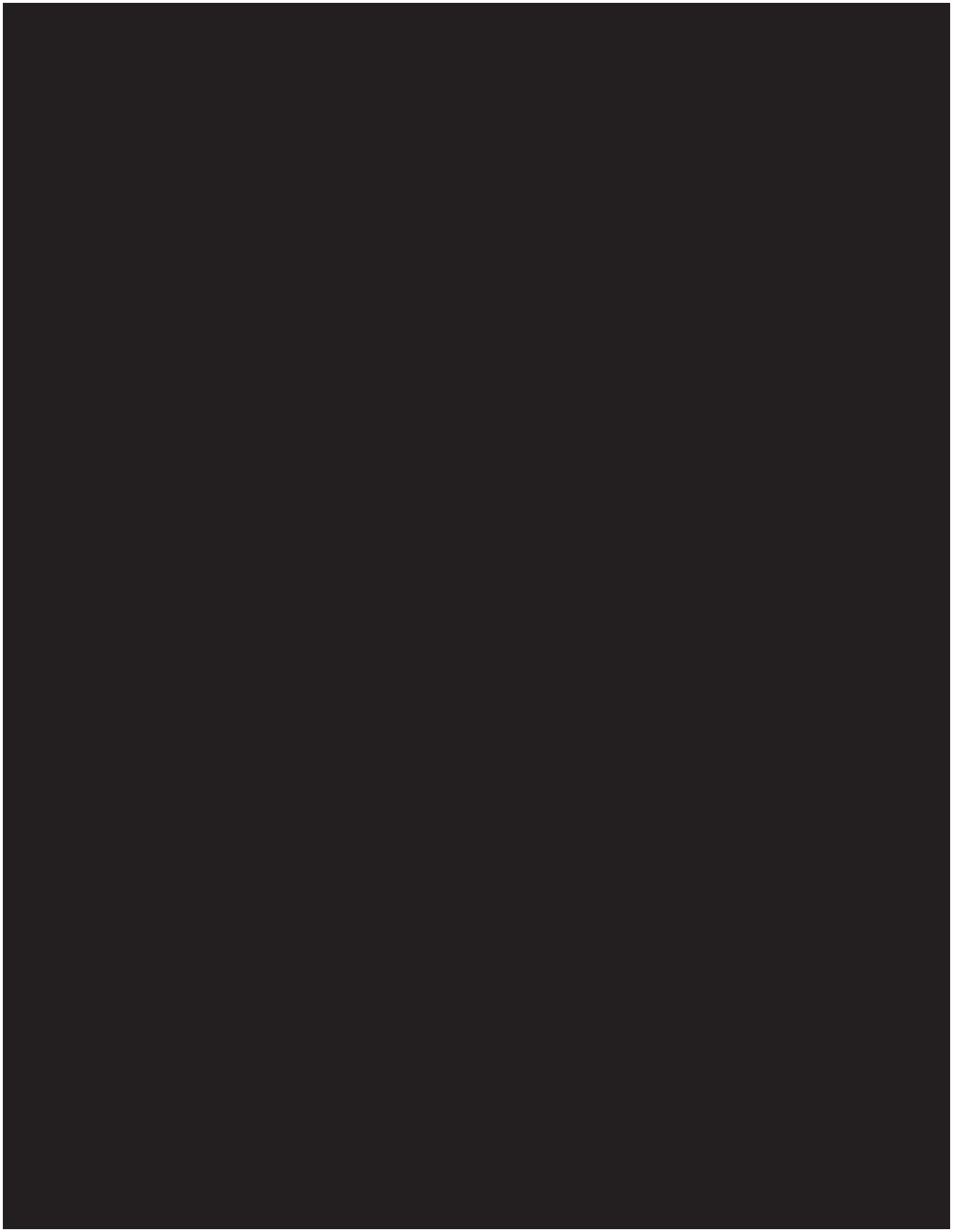

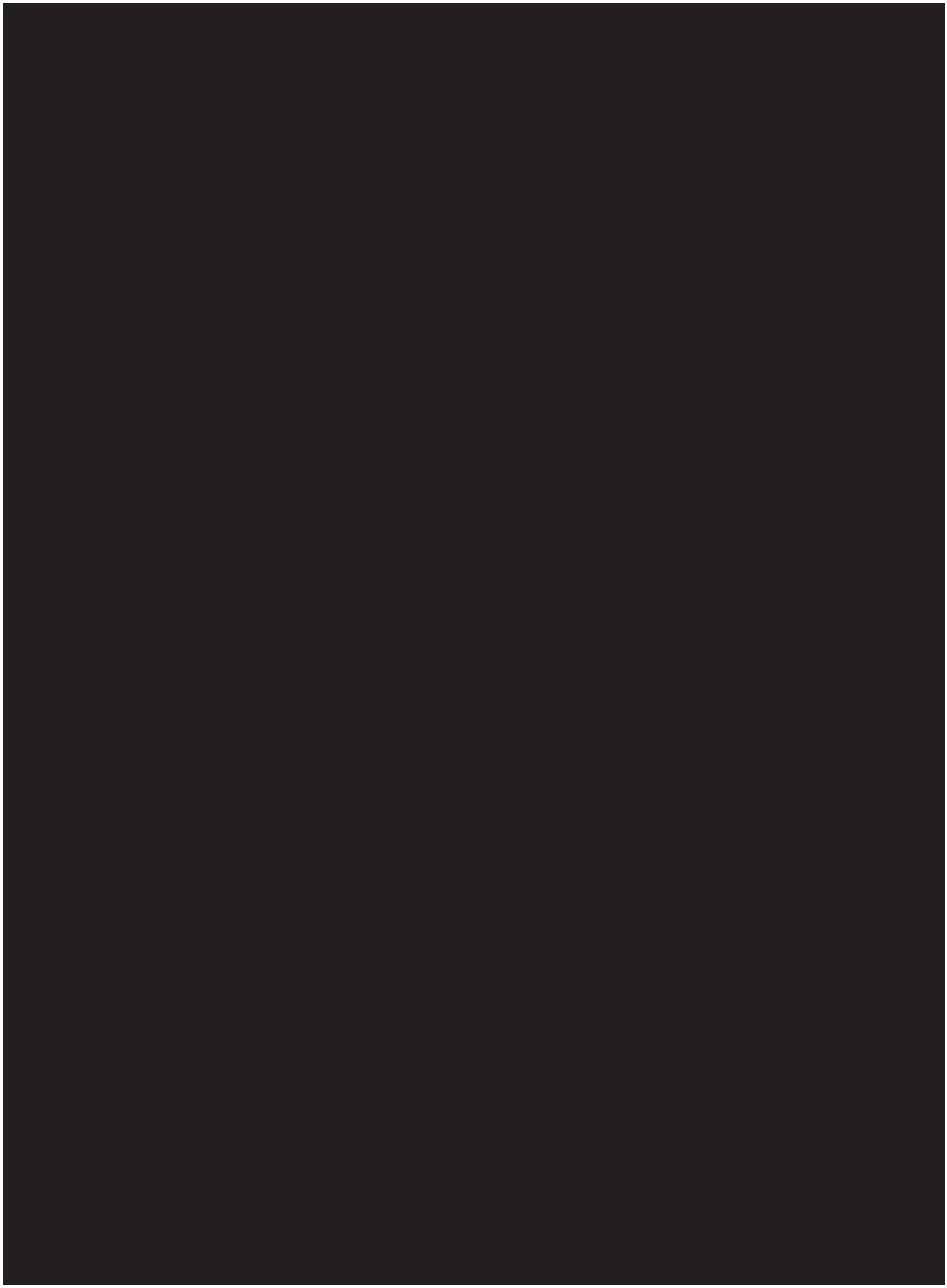

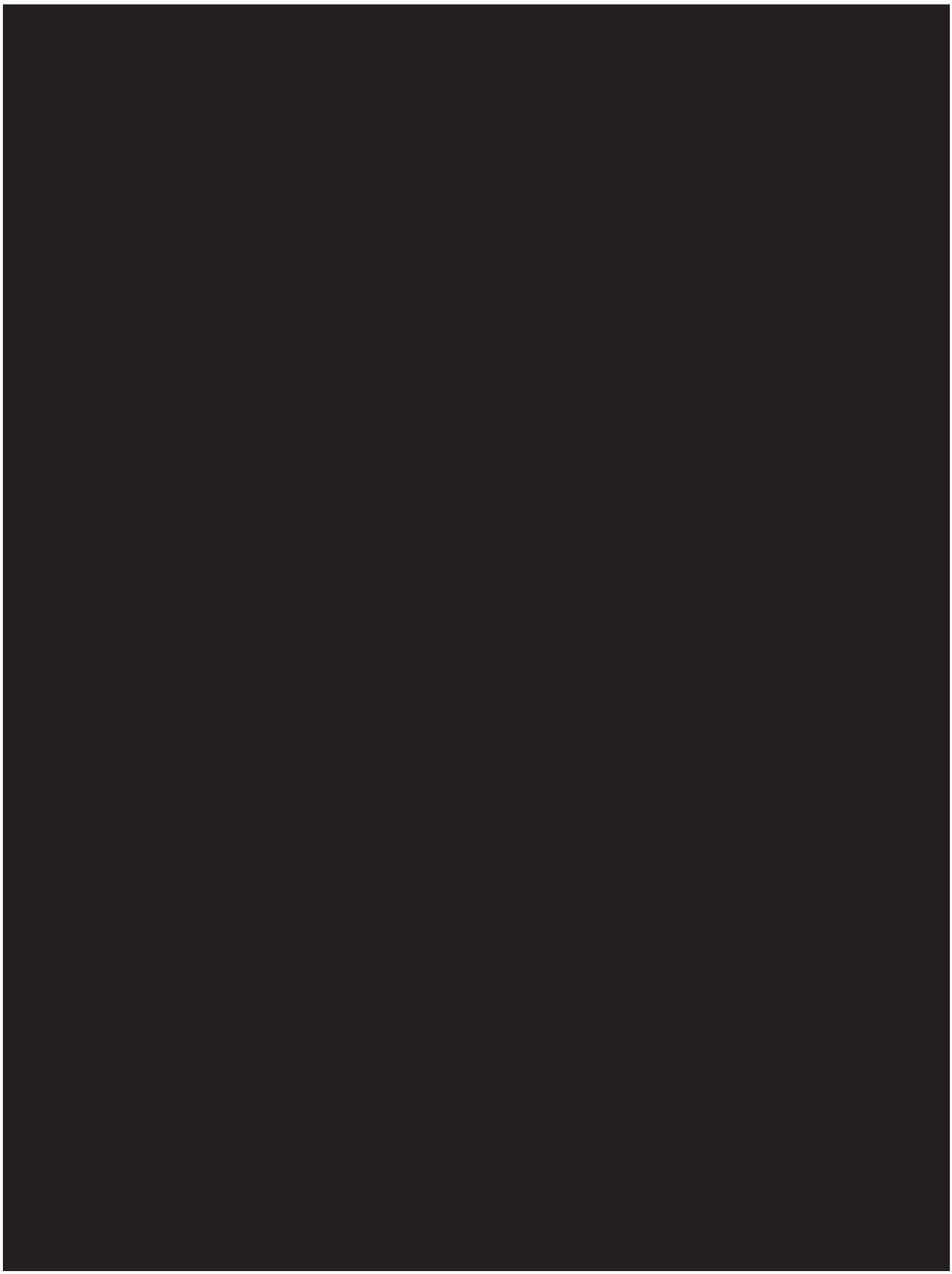

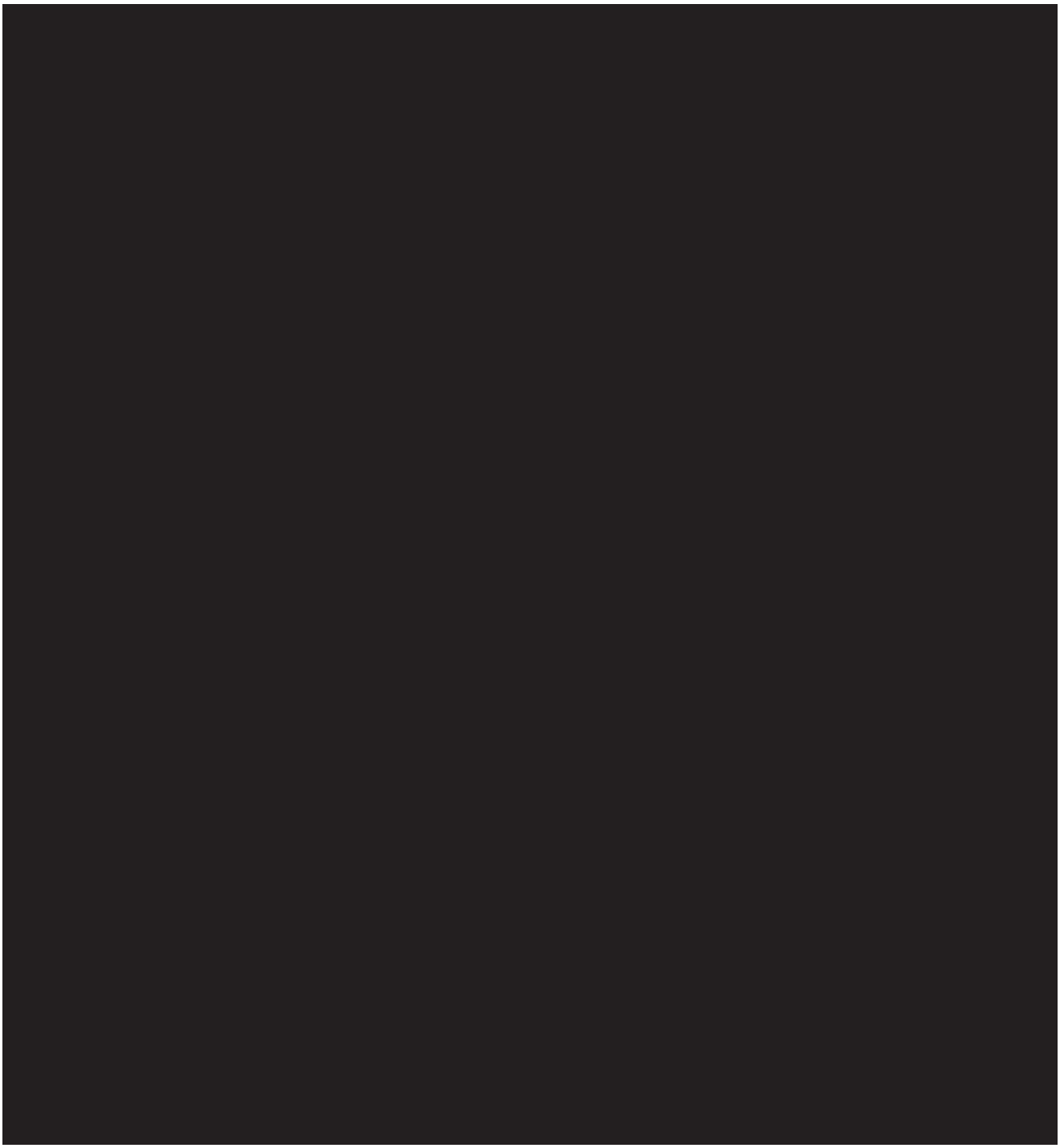

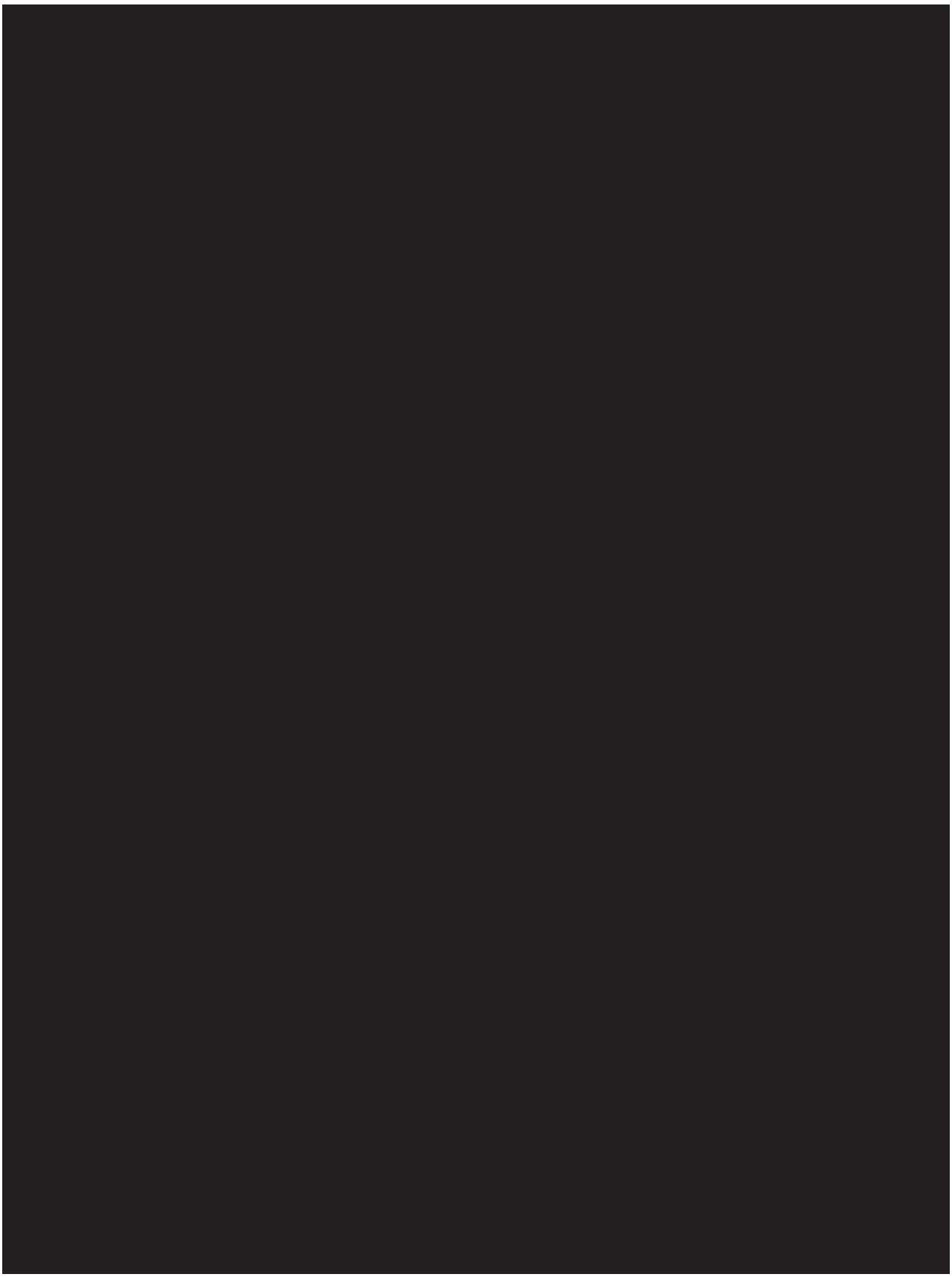

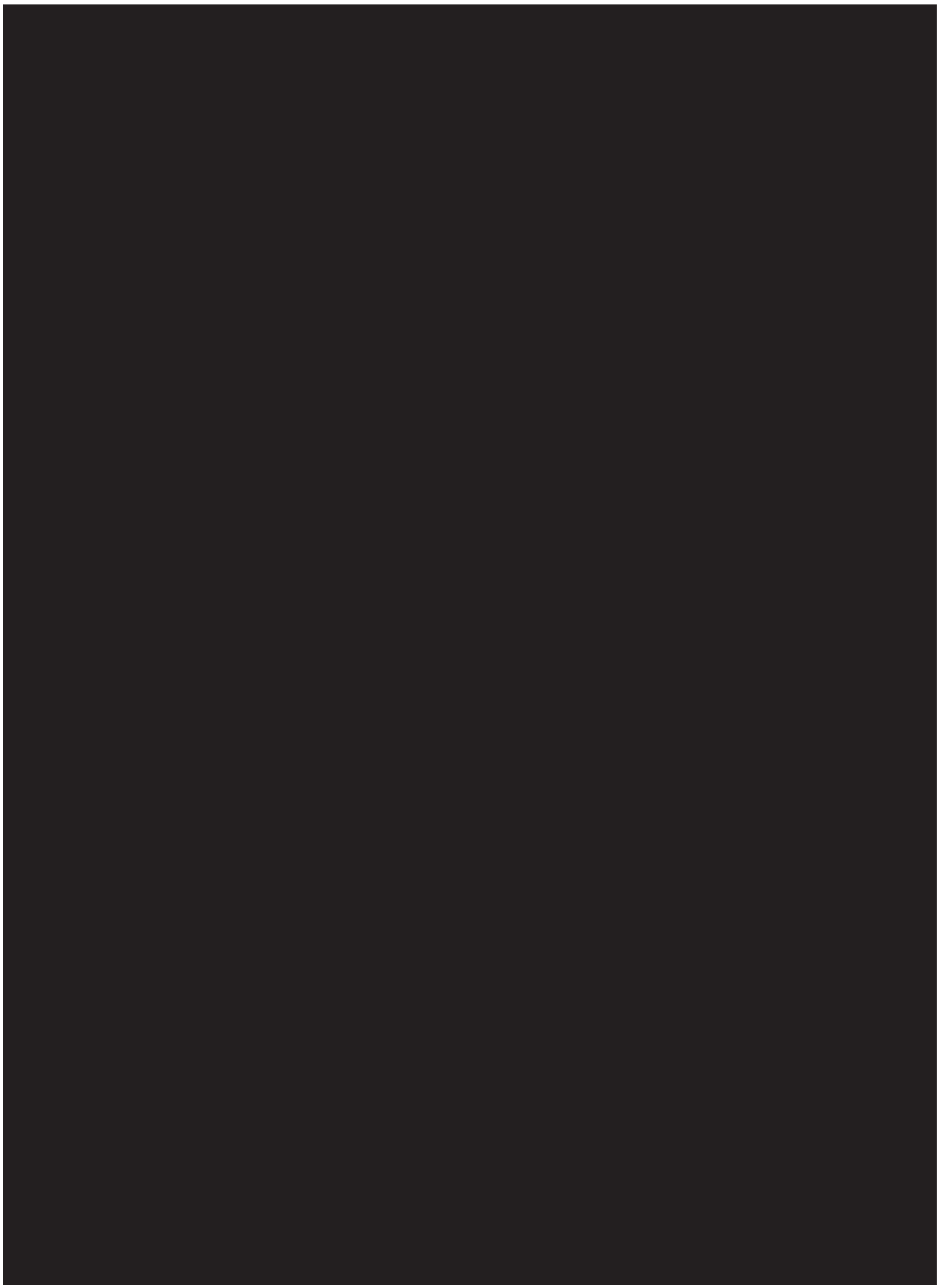

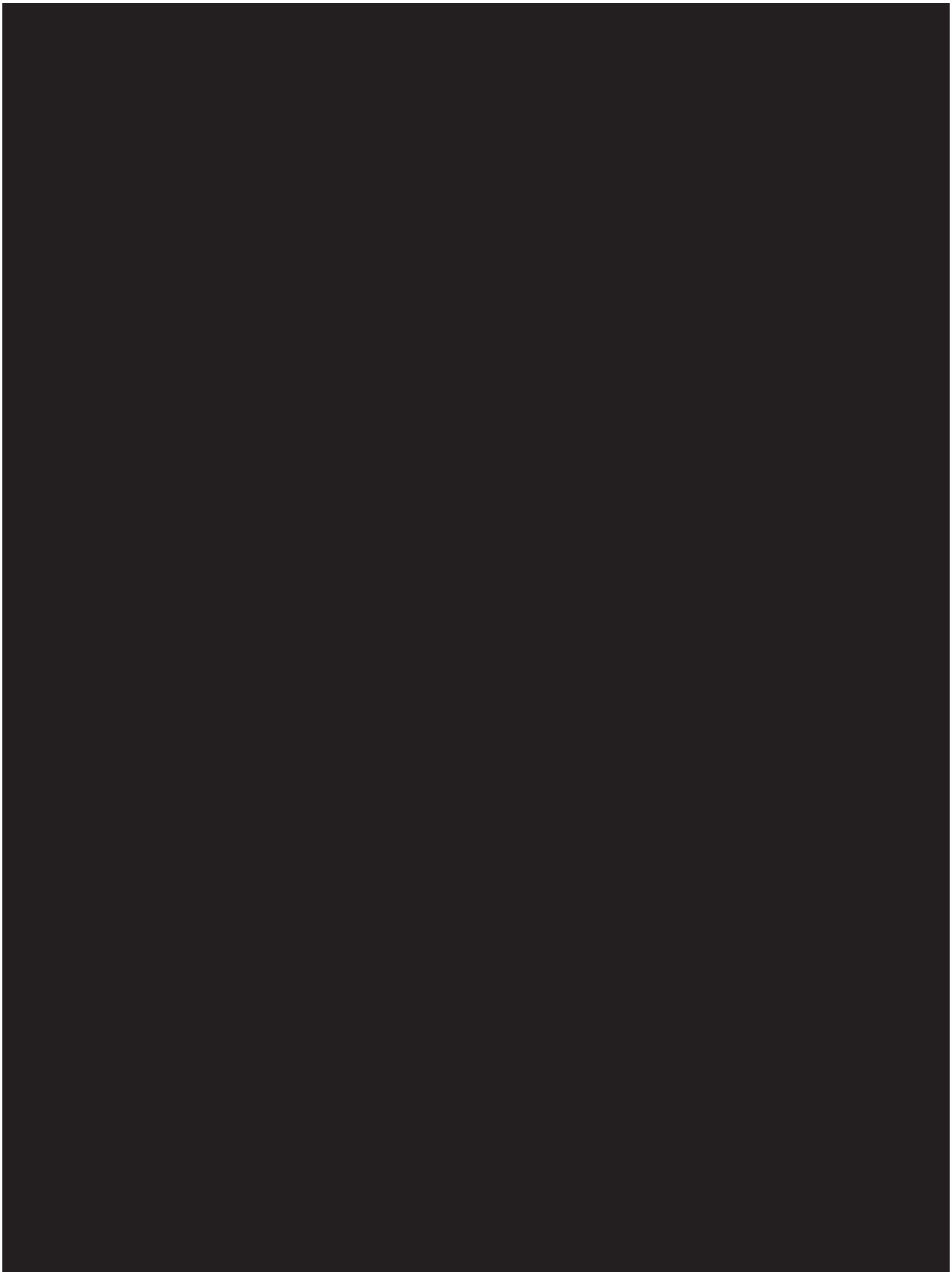

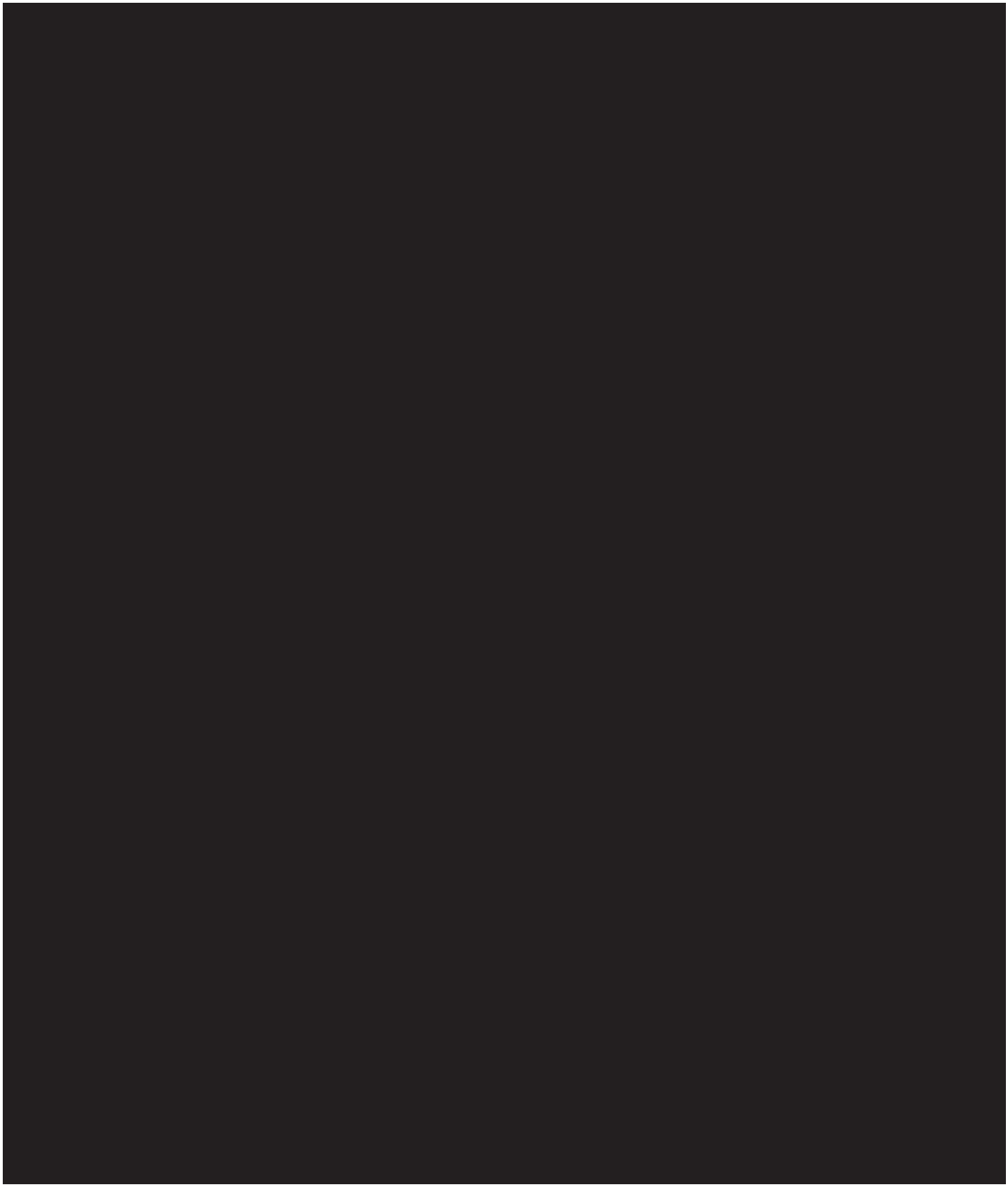

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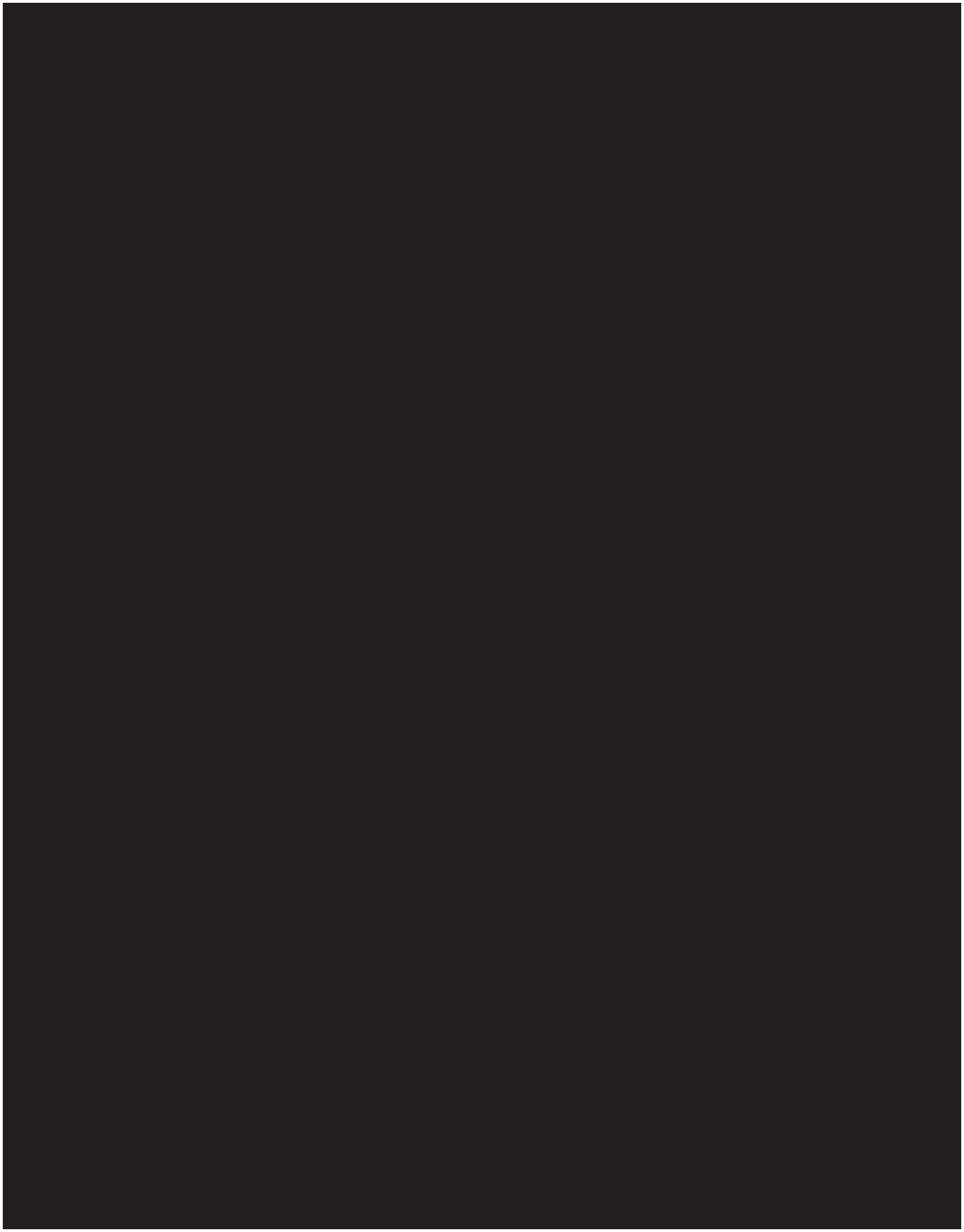

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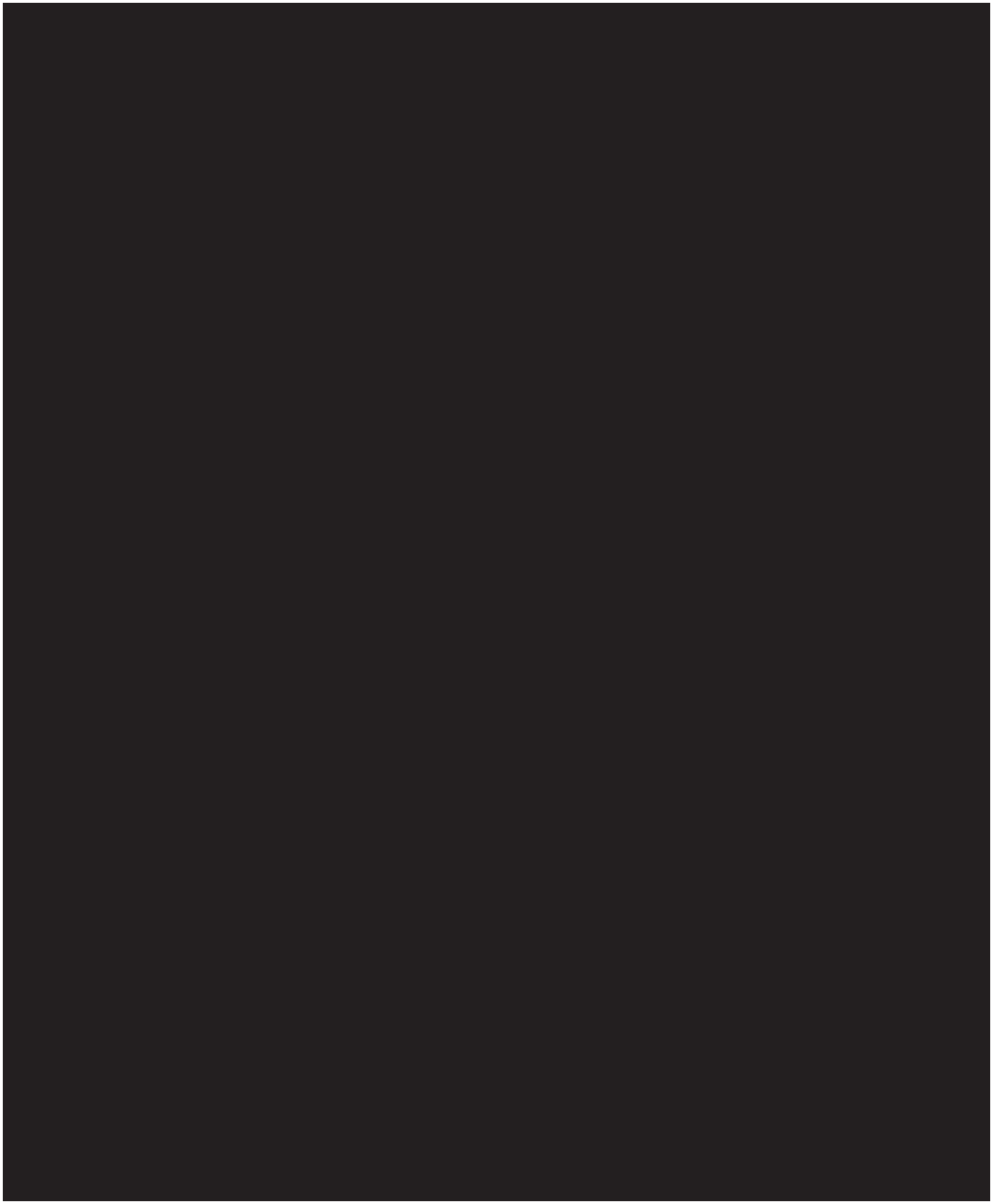


# APPENDIX 21 PSORIATIC ARTHRITIS SCREENING AND EVALUATION (PASE) QUESTIONNAIRE

## PSORIATIC ARTHRITIS SCREENING AND EVALUATION (PASE) QUESTIONNAIRE

Please circle or mark **ONLY ONE** of the five choices on the following 15 questions. The answers to these questions will help us better understand your symptoms. This should take about 5-6 minutes to complete. Thank you for your time.

| **Symptoms sub-scale** | **Strongly Disagree** | **Disagree** | **Neutral** | **Agree** | **Strongly Agree** |
|---|---|---|---|---|---|
| 1. I feel tired for most of the day | **1** | **2** | **3** | **4** | **5** |
| 2. My joints hurt | **1** | **2** | **3** | **4** | **5** |
| 3. My back hurts | **1** | **2** | **3** | **4** | **5** |
| 4. My joints become swollen | **1** | **2** | **3** | **4** | **5** |
| 5. My joints feel 'hot' | **1** | **2** | **3** | **4** | **5** |
| 6. Occasionally, an entire finger or toe becomes swollen, making it look like a 'sausage' | **1** | **2** | **3** | **4** | **5** |
| 7. I have noticed that the pain in my joints moves from one joint to another, eg my wrist will hurt for a few days then my knee will hurt and so on. | **1** | **2** | **3** | **4** | **5** |
| **SYMPTOM SCORE (Max 35)** | Add scores for questions 1-7 and write in box A | | | | A. |
| **Function sub-scale** | **Strongly Disagree** | **Disagree** | **Neutral** | **Agree** | **Strongly Agree** |
| 8. I feel that my joint problems have affected my ability to work | **1** | **2** | **3** | **4** | **5** |
| 9. My joint problems have affected my ability to care for myself, eg getting dressed or brushing my teeth | **1** | **2** | **3** | **4** | **5** |
| 10. I have had trouble wearing rings on my fingers or my watch | **1** | **2** | **3** | **4** | **5** |
| 11. I have had trouble getting into or out of a car | **1** | **2** | **3** | **4** | **5** |
| 12. I am unable to be as active as I used to be | **1** | **2** | **3** | **4** | **5** |
| 13. I feel stiff for more than 2 hours after waking up in the morning | **1** | **2** | **3** | **4** | **5** |
| 14. The morning is the worst time of day for me | **1** | **2** | **3** | **4** | **5** |
| 15. It takes me a few minutes to get moving to the best of my ability, any time of the day | **1** | **2** | **3** | **4** | **5** |
| **FUNCTION SCORE (Max 40)** | Add scores for questions 8-15 and write in box B | | | | B. |
| **TOTAL PASE SCORE (Max 75)** | Add scores in boxes A and B and write in box C | | | | C. |

## APPENDIX 22 EIGHT-ITEM PATIENT HEALTH QUESTIONNAIRE (PHQ-8)

The eight-item Patient Health Questionnaire depression scale is established as a valid self-administered diagnostic and severity measure for depressive disorders. It consists of 8 different questions, with an answer scale from 0-3. The overall score is determined by adding up each of the individual answers from each question.

Scoring interpretation is as follows: 0-4 no significant depressive symptoms, 5-9 mild depressive symptoms, 10-14 moderate depressive symptoms, 15-19 moderately severe depressive symptoms, and 20-24 severe depressive symptoms

**Over the last 2 weeks, how often have you been bothered by any of the following problems?**

| | Not at all | Several Days | More than half the days | Nearly every day |
|---|---|---|---|---|
| 1. Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| 2. Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| 3. Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| 4. Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| 5. Poor appetite or over eating | 0 | 1 | 2 | 3 |
| 6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down | 0 | 1 | 2 | 3 |
| 7. Trouble concentrating on things, such as reading the newspaper, or watching television | 0 | 1 | 2 | 3 |
| 8. Moving or speaking so slowly that other people could have noticed? Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |

Total Score:

# APPENDIX 23 SUICIDAL IDEATION AND BEHAVIOR CATEGORIES AND DEFINITIONS

## Suicidal Ideation

### Passive suicidal ideation: wish to be dead

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

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

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

### Active suicidal ideation: method, but no intent or plan

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

### Active suicidal ideation: method and intent, but no plan

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

### Active suicidal ideation: method, intent, and plan

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

## Suicidal Behavior

### Completed suicide

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

### Suicide attempt

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

**Interrupted suicide attempt**

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

**Aborted suicide attempt**

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

**Preparatory acts toward imminent suicidal behaviors**

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

**Self-Injurious Behavior Without Suicidal Intent**

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

# Statistical Analysis Plan

| | |
|---|---|
| **Sponsor:** | Bristol-Myers Squibb |
| **Protocol No:** | IM011046 |
| [redacted] | |
| **Version Date:** | 17-Dec-2019 |
| **Version No.:** | 6.0 |

| | |
|---|---|
| **Title:** | A Multi-Center, Randomized, Double-Blind, Placebo- and Active Comparator-controlled Phase 3 Study to Evaluate the Efficacy and Safety of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis |
| [redacted] | |
| **SAP No.** | 2.0 |





Approved v3.0 [redacted]

# Approvals

| [redacted] Author | |
|---|---|
| [redacted] Title: | [redacted] |
| Signature /Date: | |

| [redacted] Approvals | |
|---|---|
| [redacted] Title: | [redacted] |
| Signature /Date: | |

| BMS Approvals | |
|---|---|
| [redacted] | [redacted] |
| Signature /Date | |
| [redacted] | |
| Signature /Date: | |

# Table of Contents

# Abbreviations

| Glossary of Abbreviations: | |
|---|---|
| AE | Adverse event |
| AEI | Adverse event of interest |
| ANCOVA | Analysis of covariance |
| [redacted] | [redacted] |
| ATC | Anatomic Therapeutic Classification |
| BID | Twice daily |
| BSA | Body surface area |
| CI | Confidence interval |
| CK | Creatine kinase |
| CMH | Cochran-Mantel-Haenszel |
| CRF | Case Report Form |
| CSP | Clinical Safety Program |
| CSR | Clinical Study Report |
| CTCAE | Controlled Terminology Criteria for Adverse Events |
| DLQI | Dermatology Life Quality Index |
| DMC | Data Monitoring Committee |
| EAIR | Exposure-adjusted incidence rate |
| ECG | Electrocardiogram |
| eC-SSRS | Electronic Columbia-Suicide Severity Rating Scale |
| [redacted] | [redacted] |
| FAS | Full analysis set |
| [redacted] | [redacted] |
| IL | Interleukin |
| IRS | Independent Reporting Statistician |
| IRT | Interactive Response Technology |
| ITT | Intention-to-treat |
| LOCF | Last observation carried forward |
| LS | Least-squares |
| MAR | Missing at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mBOCF | Modified baseline observation carried forward |
| MI | Multiple imputation |

| Glossary of Abbreviations: | |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| NRI | Nonresponder imputation |
| PASE | Psoriatic arthritis screening and evaluation |
| PASI | Psoriasis Area and Severity Index |
| [redacted] | [redacted] |
| PDGD | Protocol deviation guidance document |
| PGA-F | Physician Global Assessment-Fingernails |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| PHQ-8 | Eight-Item Patient Health Questionnaire |
| [redacted] | [redacted] |
| PP | Per-protocol |
| [redacted] | [redacted] |
| pp-PGA | Palmoplantar Physician's Global Assessment |
| PPS | Per-protocol set |
| PSSD | Psoriasis Symptoms and Signs Diary |
| [redacted] | [redacted] |
| QD | Once daily |
| QoL | Quality of Life |
| QTcB | QT interval corrected using Bazett's formula |
| QTcF | QT interval corrected using Fridericia's formula |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| [redacted] | [redacted] |
| sPGA | static Physician Global Assessment |
| ss-PGA | Scalp specific Physician's Global Assessment |
| TEAE | Treatment-emergent adverse event |
| TFLs | Tables, figures, and listings |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

# 1.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under BMS Protocol IM011046.

The SAP outlines the following:

- Study design
- Study objectives
- Endpoints and assessments
- Analysis sets
- Statistical methodology
- Conventions and definitions

The SAP should be read in conjunction with the study protocol and case report form (CRF) according to the version on Page 1 of this document. Any further changes to the protocol or CRF may necessitate updates to the SAP. Changes following approval of the first version of the SAP will be tracked in the SAP Change Log and a final version of the updated SAP will be approved prior to final database lock.

# 2.0 Study Description

## 2.1 Study Design

This is a 52-week, multi-center, randomized, double-blind, double-dummy, placebo- and active comparator-controlled study to evaluate the safety and efficacy of BMS-986165 vs placebo and apremilast. A total of 600 qualified subjects with moderate-to-severe plaque psoriasis will be enrolled.

**Day 1 activities**
Following a screening period of up to 4 weeks, qualified subjects who have completed the screening procedures and have met the inclusion/exclusion criteria will be randomized in a blinded manner in a 2:1:1 ratio via interactive response technology (IRT) to one of the following 3 treatment groups:

- BMS-986165 6 mg once daily (QD)
- Placebo
- Apremilast as an active comparator that is marketed in various countries. It will be titrated to 30 mg twice daily (BID) as follows:
    - Day 1: 10 mg tablet in the morning
    - Day 2: 10 mg tablet in the morning and evening
    - Day 3: 10 mg tablet in the morning and 20 mg tablet in the evening
    - Day 4: 20 mg tablet in the morning and the evening
    - Day 5: 20 mg tablet in the morning and 30 mg tablet in the evening
    - Day 6 and thereafter: 30 mg tablet in the morning and the evening

Dummy tablets (placebo for the BMS-986165 6 mg tablet, placebo for apremilast 30 mg tablet BID, and placebo for apremilast 10 mg, 20 mg, 30 mg during titration) will be administered to the subjects to maintain blinding in a double-dummy fashion. Note that apremilast will not be used as a treatment arm in China due to lack of market approval of the agent in China.

**Week 16 activities**
The coprimary endpoints, static Physician Global Assessment (sPGA) 0/1 and Psoriasis Area and Severity Index (PASI) 75 will be assessed at Week 16. Subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD at Week 16. Subjects who are randomized to BMS-986165 6 mg QD or apremilast will continue on their assigned treatment regimen in a blinded manner.

**Week 24 activities**

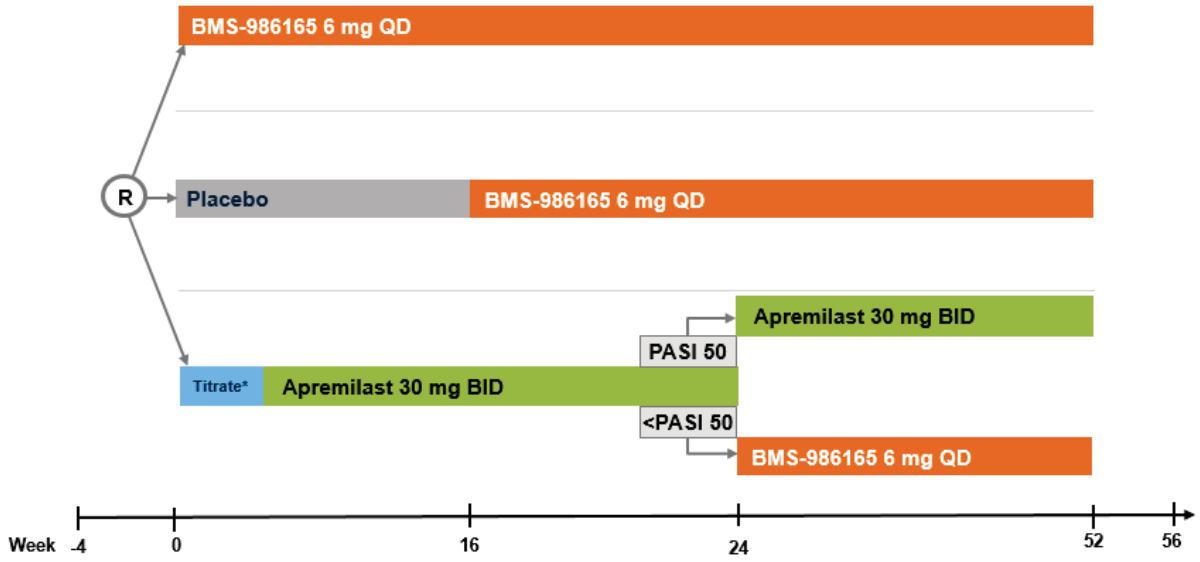
At Week 24, subjects originally randomized to apremilast who do not achieve PASI 50 response will be switched in a blinded manner to BMS-986165 6 mg QD. Subjects in the apremilast treatment arm who achieve PASI 50 response at Week 24 will continue to receive apremilast in a blinded manner through Week 52.

During the Week 24 assessment, a subject who has an sPGA ≥3 or ss-PGA≥3 may be treated with restricted topicals/shampoos as described in the protocol (Section 6.7.1). These treatments may only be initiated at Week 24, and not at subsequent time points. A subject who is provided these treatments at Week 24 may use them as needed per the investigator's judgement through Week 52.

**Study Design elements**

The duration of study participation is approximately 60 weeks and will be divided into the following periods: Screening (up to 4 weeks), Treatment (52 weeks), and Follow-up (4 weeks). A schedule of assessments can be found in the protocol. A study design schematic is provided in Figure 1.

Figure 1: Study Design Schematic




[redacted]

## 2.3 Treatment Assignment and Randomization

At Week 0 (Day 1), subjects who have met all criteria for enrollment will be centrally randomized by a computer-generated randomization schedule in a 2:1:1 ratio to the following treatments:

- BMS-986165 6 mg QD
- Placebo
- Apremilast 30 mg BID (titrated)

The randomization list was generated by the IRT vendor using a permuted block design within each stratum combination level. Randomization will be stratified by geographic region (U.S., Japan [body weight stratum will not be applied in Japan], China [body weight stratum will not be applied in China], Rest of World), previous biologic use (for psoriasis, psoriatic arthritis, or other inflammatory disease only; yes/no), and body weight (≥90 kg and <90 kg).

A treatment group will be assigned by IRT based on the above-described randomization schedule and each subject will be assigned a unique randomization number. In addition, a kit (container) number will be assigned to the subject by the IRT each time study treatment is dispensed. Dummy tablets (placebo to the BMS-986165 6 mg tablet and placebo to apremilast) will be administered to the subjects to maintain blinding. Apremilast will not be used as a treatment arm in China.

At Week 16, subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD.

At Week 24, subjects originally randomized to apremilast who do not achieve a PASI 50 response will be switched in a blinded manner to BMS-986165 6 mg QD. Subjects originally randomized to apremilast who achieve PASI 50 response at Week 24 will continue to receive apremilast in a blinded manner. The investigative site and other study personnel will not have knowledge of the PASI 50 score at this visit and will therefore remain blinded.

## 2.4 Unblinding Information

The Data Monitoring Committee (DMC) provides oversight of safety considerations throughout the study. A separate unblinded team, comprised of an unblinded Independent Reporting Statistician (IRS) and unblinded programmer(s), will produce output for the DMC using masked treatments. Treatment decodes may only be requested by the DMC Chair and will be provided by the IRS. Data summaries and listings will be transmitted via a secure portal by the IRS to only the DMC members. Additional details regarding the DMC process and unblinding are provided in the DMC charter.

[redacted]

## 2.5 Changes in Statistical Considerations from the Protocol

The following is a list of the important changes in the SAP from the Statistical Considerations section in the protocol:

- The hierarchical testing order for the key secondary endpoints has been updated and two separate hierarchies have been provided, one for US submission and one for ex-US submission (see Tables 1 and 2 in Sec. 6.1.3). The update to the hierarchies are due to emerging information from clinical trials conducted with other agents recently approved for the treatment of psoriasis. The hierarchies presented in this document supersede the one that is in the protocol.

- Key secondary endpoints were added for the comparison of BMS-986165 to apremilast for sPGA 0/1, PASI 75, and PASI 90 at Week 24.
- Imputation methods were updated to remove the prohibited medication/therapy criteria for binary and continuous endpoints.
- The Full Analysis Set was changed from “all subjects who were randomized to receive assigned study treatment” in the protocol to “all subjects who are randomized”.
- The list of relevant protocol deviations provided in the protocol was updated for determination of the Per Protocol population.
- Logistic regression analyses for binary endpoints were removed as these are similar to the CMH analyses.

# 3.0 **Objectives**

## 3.1 Primary Objective

- Assess whether BMS-986165 is superior to placebo at Week 16 in the treatment of subjects with moderate-to-severe plaque psoriasis

## 3.2 Secondary [redacted] Objectives

- Assess whether BMS-986165 is superior to apremilast at Week 16
- Assess whether BMS-986165 is superior to apremilast at Week 52
- Assess whether BMS-986165 is superior to placebo over the first 16 weeks of treatment
- Assess whether BMS-986165 is superior to apremilast over 52 weeks of treatment
- Assess whether BMS-986165 is superior to placebo in scalp psoriasis through Week 16 in those subjects who have baseline scalp severity Physician’s Global Assessment (ss-PGA) score ≥3
- [redacted]
- Assess whether BMS-986165 is superior to placebo in nail psoriasis through Week 16 in those subjects who have baseline Physician’s Global Assessment-Fingernail (PGA-F) psoriasis score ≥3
- [redacted]
- Assess whether BMS-986165 is superior to placebo in palmoplantar psoriasis through Week 16 in those subjects who have baseline palmoplantar Physician’s Global Assessment (pp-PGA) score ≥3
- Evaluate improvement in patient-reported outcomes for BMS-986165 compared with placebo through Week 16
- Evaluate improvement in patient-reported outcomes for BMS-986165 compared with apremilast through Week 52
- [redacted]

# 4.0 **Outcomes**

The description of assessments for efficacy and safety can be found in Section 8 of the protocol. The calculation of key measures are provided in Section 8.2 of the SAP.

## 4.1 Efficacy

### 4.1.1 Primary Endpoint(s)

The coprimary endpoints for BMS-986165 compared to placebo at Week 16 are defined as:

- sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least 2-point improvement from baseline.
- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score

### 4.1.2 Secondary Endpoint(s)

#### 4.1.2.1 Key Secondary Endpoints for Comparisons to Placebo

The key secondary efficacy endpoints for BMS-986165 compared to placebo at Week 16 are defined as:

- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in PASI score
- sPGA 0 response assessed as a proportion of subjects with an sPGA score of 0
- Scalp specific Physician's Global Assessment (ss-PGA) 0/1 assessed as a proportion of subjects with a ss-PGA score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA score ≥3
- PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥1
- PASI 100 response assessed as a proportion of subjects who achieve a 100% improvement from baseline in PASI score
- Physician Global Assessment-Fingernails (PGA-F) 0/1 assessed as a proportion of subjects with a PGA-F score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline PGA-F score ≥3
- DLQI 0/1 assessed as a proportion of subjects with a DLQI score of 0 or 1 among subjects with a baseline DLQI score ≥2 (Ex-US submission only)

#### 4.1.2.2 Key Secondary Endpoints for Comparisons to Apremilast

The key secondary endpoints for BMS-986165 compared to apremilast at Week 16 are defined as:

- sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least a 2-point improvement from baseline
- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score
- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score
- Change from baseline in PSSD symptom score
- ss-PGA 0/1 assessed as a proportion of subjects with a ss-PGA score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA score ≥3
- sPGA 0 response assessed as a proportion of subjects with an sPGA score of 0
- PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥1

The key secondary endpoints for BMS-986165 compared to apremilast at Week 24 are defined as:

- sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least a 2-point improvement from baseline at Week 24
- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score at Week 24
- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score at Week 24

The key secondary endpoints for BMS-986165 compared to apremilast through Week 52 are defined as:

- sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least a 2-point improvement from baseline at Week 52 and at Week 24
- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score at Week 52 and at Week 24
- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score at Week 52 and at Week 24

[redacted]

[redacted]

[redacted]

## 4.2 Safety

The safety outcomes include the following:

- Adverse events (AEs)
  - Treatment-emergent adverse events (TEAEs) – defined as:
    - AEs which occur after the first dose of study treatment through 30 days after the final dose of the study treatment or subject's participation in the study if the last scheduled visit occurs at a later time.
  - Treatment-emergent adverse events of interest (AEIs) for the following events:
    - Skin-related AEs
    - Infection AEs, including influenza
    - Creatine kinase (CK) elevation (evaluated as lab toxicity grade 2 or higher)
    - Malignancy
  - SAEs
  - Deaths
- Clinical laboratory parameters
  - Absolute and change from baseline values
  - Laboratory abnormalities (as determined by Controlled Terminology Criteria for Adverse Events [CTCAE v5.0] grading) presented as the worst postbaseline toxicity group
  - Shifts from baseline to maximum postbaseline value
  - Potential drug induced liver injury (DILI) is defined as a subject who meets the following criteria:
    - 1) ALT or AST elevation >3 times ULN

    AND

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

    AND

    - 3) No other immediately apparent possible causes of liver function test elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.
  - ALT or AST elevation >5 times ULN
- Vital signs
  - Absolute and change from baseline values
  - Marked abnormalities defined by the below categories:
    - Heart rate:
      - Value > 100 and change from baseline > 30
      - Value < 55 and change from baseline < -15
    - Systolic blood pressure:
      - Value > 140 and change from baseline > 20

        - Value < 90 and change from baseline < -20
    - Diastolic blood pressure:
        - Value > 90 and change from baseline > 10
        - Value < 55 and change from baseline < -10

- Electrocardiograms (ECGs)
    - Absolute and change from baseline values
    - Marked abnormalities defined by the below categories:
        - QT interval corrected using Fridericia's formula (QTcF):
            - 450 -< 480 msec
            - 480 -< 500 msec
            - ≥ 500 msec
            - 30 < change from baseline ≤ 60 msec
            - Change from baseline > 60 msec
            - Males: < 450 msec, ≥ 450 msec
            - Females: < 470 msec, ≥ 470 msec
        - PR interval ≥ 200 msec
        - QRS interval ≥ 200 msec

In cases where the QT interval is corrected using Bazett's (QTcB) formula is captured instead of QTcF, then QTcB will be converted to QTcF for analyses.

- Eight-Item Patient Health Questionnaire (PHQ-8) total score
    - Absolute and change from baseline values
    - Shifts from baseline scores
- Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)
    - Suicidal ideation and suicidal behavior responses by visit
    - Shifts from baseline to postbaseline value for suicidal ideation and suicidal behavior
    - Worst postbaseline value for suicidal ideation and behavior

[redacted]

[redacted]

# 5.0 Populations for Analyses

The following analysis sets will be used in the summary and analysis of study data:

- **Enrolled population**: All subjects who sign informed consent.
- **Full Analysis Set (FAS)**: All subjects who are randomized. Following the intent-to-treat (ITT) principle, subjects will be analyzed according to the treatment group assigned at randomization. The FAS will be the primary efficacy analysis population.
- **Per Protocol Set (PPS)**: A subset of the FAS who are compliant with study treatment and who do not have any relevant protocol deviations that may impact the coprimary efficacy endpoint assessments. The PPS will be analyzed according to the treatment assigned at randomization. The PPS will be a supportive efficacy analysis population and only the co-primary endpoints will be analyzed using this set.
- **As-treated population**: All randomized subjects who take at least one dose of study treatment. Subjects will be analyzed according to treatment received.

[redacted]

## 5.1 Relevant Protocol Deviations

Relevant protocol deviations are deviations that can have an impact on the primary efficacy endpoints. The impact of relevant protocol deviations on the primary efficacy results will be assessed by excluding subjects from the FAS to define the PPS in supportive analyses of the primary efficacy endpoints. Relevant protocol deviations to be considered regarding exclusion of subjects from the FAS will include the following:

- Randomized but did not take any study treatment
- No postbaseline PASI or sPGA
- Baseline BSA involvement < 10%
- Baseline PASI score < 12
- Baseline sPGA < 3
- Did not have non-plaque psoriasis at baseline
- Poor compliance to study medication within the first 16 weeks of treatment, <75% compliant with study treatment
- Failure to adhere to prohibited concomitant medication restrictions as described below:

  - Investigational drug or placebo taken outside of the study any time between Day 1 and the Week 16 assessment
  - Phototherapy within 4 weeks prior to the Week 16 assessment
  - Biologic medications (eg, adalimumab, etanercept, infliximab, ustekinumab) any time between Day 1 and the Week 16 assessment
  - Oral psoriasis medications any time between Day 1 and the Week 16 assessment
  - Oral corticosteroids (unless for the treatment of an adverse event) within 4 weeks prior to the Week 16 assessment
  - Topical medications/treatments that could affect psoriasis evaluations within 2 weeks prior to the Week 16 assessment
  - Medicated shampoos within 2 weeks prior to the Week 16 assessment
- Subject received treatment that was different than intended treatment at any visit prior to Week 16.

All subjects with relevant protocol deviations will be identified prior to database lock and unblinding of treatment assignment with the exception of subjects where actual treatment received is different than randomized treatment which will be determined after treatment unblinding. Relevant protocol deviations will be summarized by treatment group and deviation category for the FAS population.

# 6.0 Statistical Analyses

Descriptive summaries and analyses will be presented for data captured throughout the study using the following treatment groups.

During the first 16 weeks of treatment, summaries will be provided for the following treatment groups:

- BMS-986165 6 mg QD
- Apremilast
- Placebo

During the first 24 weeks of treatment, summaries will be provided for the following treatment groups:

- BMS-986165 6 mg QD (subjects continuously taking BMS-986165 6 mg QD)
- Apremilast

Summaries will be provided for subjects who have continuous treatment throughout the entire study with either BMS-986165 or apremilast using the following treatment groups:

- BMS-986165 6 mg QD
- Apremilast

Summaries of all subjects exposed to BMS-986165 6 mg QD will also be provided as applicable. Adverse events will be summarized using exposure-adjusted incidence rates (EAIR) for these summaries.

Please note that there will be no Chinese subjects in the apremilast group due to lack of market approval of the agent in China.

## 6.1 Efficacy Analyses

All efficacy analyses will be performed using the FAS, unless otherwise specified.

Tests of significance of BMS-986165 6 mg QD vs. placebo for the coprimary endpoints will be two-sided with a significance level of 0.05. Both coprimary endpoints need to demonstrate statistical significance to result in a successful study.

The key secondary endpoints will be tested with a two-sided significance level of 0.025 to compare BMS-986165 6mg QD vs. placebo and vs. apremilast. A hierarchical testing approach will be used for testing of

key secondary endpoints (see Section 6.1.3). Two-sided 95% confidence intervals (CIs) will be provided for all efficacy estimates. [redacted]

Coprimary and key secondary efficacy endpoints will be displayed graphically by treatment group and visit, as applicable. All efficacy endpoints will be summarized descriptively.

Due to small sample sizes in China and Japan and differences in stratification factors, analyses will be stratified by a combination of the stratification factors used in randomization. The stratified levels are provided below:

- US/PRIOR USE/< 90 KG
- US/PRIOR USE/>=90 KG
- US/NAÏVE/<90 KG
- US/NAÏVE/>=90 KG
- ROW/PRIOR USE/< 90 KG
- ROW/PRIOR USE/>=90 KG
- ROW/NAÏVE/<90 KG
- ROW/NAÏVE/>=90 KG
- JAPAN/PRIOR USE
- JAPAN/NAÏVE
- CHINA/PRIOR USE
- CHINA/NAÏVE

If there is not at least one subject per treatment group in each of the China and Japan strata, then these regions will be collapsed together to form the following stratified levels for analyses:

- US/PRIOR USE/< 90 KG
- US/PRIOR USE/>=90 KG
- US/NAÏVE/<90 KG
- US/NAÏVE/>=90 KG
- ROW/PRIOR USE/< 90 KG
- ROW/PRIOR USE/>=90 KG
- ROW/NAÏVE/<90 KG
- ROW/NAÏVE/>=90 KG
- ASIA/PRIOR USE
- ASIA/NAÏVE

## 6.1.1 Primary Endpoints

### 6.1.1.1 Primary Analysis

Analysis Model

A stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare the sPGA 0/1 response rates at Week 16 between BMS-986165 6 mg QD and placebo using the stratification factors from IRT specified in Section 6.1. The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the odds in the placebo group) and the corresponding 2-sided 95% CIs and p-values will be reported. Additionally, treatment differences in proportions and the 95% CI for the treatment difference will be provided. The common treatment difference in proportion with the confidence interval, common odds ratio with the confidence interval and p-value will be estimated by the Mantel-Haenszel method consistently.

A similar analysis will be performed to compare the PASI 75 response rates at Week 16 between BMS-986165 6mg QD and placebo.

Imputation Methodology

Non-responder imputation (NRI) will be used for coprimary efficacy endpoints for subjects who:

- Discontinue treatment or study prior to Week 16
- Have missing Week 16 endpoint data for any reason

NRI will be used as the primary method of imputation for the coprimary efficacy endpoints.

### 6.1.1.2 Sensitivity Analyses

As a method to assess the sensitivity of the primary imputation method for the coprimary endpoints, further imputation methods will be used to impute Week 16 data in subjects who:

- Discontinue treatment or study prior to Week 16
- Have missing Week 16 endpoint data for any reason

The coprimary endpoints will be analyzed using the primary analysis method for each sensitivity imputation method described below:

Last Observation Carried Forward (LOCF)

The last observed post-baseline value will be carried forward and used as the Week 16 value. Subjects without a post-baseline will be considered a nonresponder.

LOCF and NRI

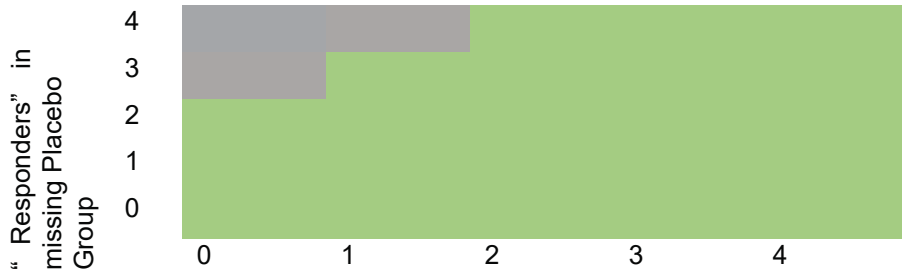
Subjects randomized to the placebo group will have the endpoint value imputed using LOCF (post-baseline). If a placebo subject does not have a post-baseline values, they will be considered a nonresponder. Subjects randomized to BMS-986165 6 mg QD will have their endpoint value imputed using the NRI methodology.

Tipping Point Analysis

Tipping point analysis will further be used to assess the robustness of the primary study results. Different number of events between treatment groups will be assessed until the study conclusion is changed. Each imputed value is initially imputed as a responder. The imputed values in the placebo group will remain as responders while the BMS-986165 imputed values are replaced as a nonresponders one at a time, therefore changing the number of events between groups. Once all imputed values in the BMS-986165 group have been replaced with nonresponders values, the data will reset to where the BMS-986165 group imputed values are all responders and one by one the imputed values in the placebo group are replaced with a nonresponder until all placebo are nonresponders and all BMS-986165 are responders. Furthermore, every pair of imputations between the placebo and BMS-986165 groups will be assessed similarly, creating a matrix of possible patterns.

At each iteration, the statistical analysis is assessed, and the direction of the analysis is recorded. A graph will be provided to identify at what point to which the difference in events cause a direction shift in study results. The tipping point analyses will be based on a two-sample chi-square test approach rather than a stratified CMH test approach for simplicity of the analysis.

Figure 1: Example of Tipping Point Analysis Direction Boundary



"Responders" in missing BMS-986165 Group

Figure 1 represents an example of the tipping-point analysis for all subjects with missing primary efficacy endpoint (responder/non-responder) in BMS-986165 group (N=5) and placebo group (n=5). Gray cells represent pairs where the statistical analysis resulted in non-significance. Green cells represent pairs where the statistical analysis resulted in significant difference between groups. The tipping-point boundary is where the green cells become gray.

Multiple Imputation

Multiple imputation (MI) will be used for sensitivity analyses for each of the coprimary efficacy endpoints, PASI 75 response at Week 16 and sPGA 0/1 response at Week 16. Multiple imputation of missing data for PASI 75 response and sPGA 0/1 response will be performed by fully conditional specification (FCS) using PROC MI in SAS with the FCS option. The FCS MI specifies the multivariate imputation model on a variable-by-variable basis by a set of conditional densities. For each missing value at Week *X*, the FCS MI will generate values from a conditional distribution for the missing data given the other data prior to Week *X*. The FCS MI model will include treatment group and stratification factors for randomization. A total of 1000 imputed (complete) datasets will be generated for the MI analysis. The same test procedure used for the main analysis (CMH test), will be used to analyze the responder endpoint from each imputed dataset. SAS PROC MIANALYZE will be used to pool the results from the CMH tests and generate an overall result by Rubin's rules (1987).

#### 6.1.1.3 Supportive Analyses

Per Protocol Population Analysis

The coprimary endpoints will be analyzed using the PPS using the primary analysis methodology and primary imputation method.

### 6.1.2 Key Secondary Endpoints

#### 6.1.2.1 Binary Endpoints

Analysis Model

CMH tests will be used to compare response rates between either BMS-986165 6mg QD and placebo or apremilast using the stratification factors from IRT specified in Section 6.1. The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the odds in the placebo or apremilast group) and the corresponding 2-sided 95% CIs and p-values will be reported. Additionally, treatment differences in proportions and the 95% CI for the treatment difference will be provided.

Imputation Methodology for Week 16 Endpoints

NRI will be used for key secondary efficacy endpoints for subjects who:

- Discontinue treatment or study prior to Week 16
- Have missing Week 16 endpoint data for any reason

Imputation Methodology for Week 24 Endpoints (for comparison of BMS-986165 6 mg QD to apremilast)

NRI will be used for key secondary efficacy endpoints for subjects who:

- Discontinue treatment or study prior to Week 24
- Have missing Week 24 endpoint data for any reason

Imputation Methodology for Week 52 Endpoints (for comparison of BMS-986165 6 mg QD to apremilast)

The key secondary endpoints included in this analysis are the following:

- sPGA 0/1 response with at least a 2-point improvement from baseline at Week 52 and at Week 24

- PASI 75 response at Week 52 and at Week 24
- PASI 90 response at Week 52 and at Week 24

Subjects must meet response criteria at both Weeks 24 and 52 in order to be considered a responder. Those who do not meet response criteria at both weeks will be considered a nonresponder. NRI will be used for the above key secondary endpoints for subjects who:

- Discontinue treatment or study prior to Week 52
- Have missing Week 52 or Week 24 endpoint data
- Switch from apremilast to BMS-986165 at Week 24 for Week 24 PASI 50 nonresponders

#### 6.1.2.2 Continuous Endpoints

Analysis Model

Analysis of covariance (ANCOVA) models will be used to compare the change between BMS-986165 6 mg QD and placebo or between BMS-986165 6 mg QD and apremilast at Week 16. Treatment group will be included in the model as well as the stratification factors from IRT specified in Section 6.1 and will be considered as fixed effects. The baseline value will be added into the model as a covariate. The adjusted least-squares (LS) means as well as the treatment differences based on LS means and the corresponding 2-sided 95% CIs will be provided for the difference between BMS-986165 6 mg QD and placebo or apremilast.

Imputation Methodology for Week 16 Endpoints

For continuous key secondary endpoints, a modified baseline observation carried forward (mBOCF) approach will be used for missing data. The baseline observation will be carried forward for subjects who discontinue study treatment prior to Week 16 due to:

- Lack of efficacy
- AEs

Subjects who discontinue study treatment prior to Week 16 for other reasons or who have a missing Week 16 value will have the last valid observation carried forward (including the baseline value as applicable).

Subjects with a missing baseline value will be excluded from the analysis for the change from baseline endpoint.

[redacted]

[redacted]

[redacted]

### 6.1.4 Subgroup Analyses

Subgroup analyses will be performed on the coprimary endpoints using the FAS. The primary imputation method will be applied for these analyses. The CMH test using the stratification factors from IRT will be the analysis method used. The following subgroups will be considered:

- Geographic region (U.S., Japan, China, Rest of World)
- Country
- Sex (male, female)
- Age group (<65 y, ≥65 y)
- Body weight (<90 kg, ≥90 kg) – from case report form
- Race
- Prior biologic use for psoriasis, psoriatic arthritis and other inflammatory diseases only (yes, no) – from case report form
- Prior systemic treatment use (yes/no)
- Prior phototherapy use (yes/no)
- sPGA (3, 4)
- PASI score (≤20, >20)
- BSA involvement (10-20, >20)
- Duration of disease (< 10 y, ≥ 10 y)
- Age at disease onset (<18, 18-39, ≥40)

[redacted]

[redacted]

[redacted]

## 6.2 Safety

Summaries of safety data will be presented by period and treatment group, as applicable, for the As-treated population.

### 6.2.1 Adverse Events

Adverse events will be presented for the number and percentage of subjects and the number of events. Treatment-emergent will be provided in listings. Summary tables will be reported in decreasing frequency based on the BMS-986165 column. Counting for frequency analysis will be by subject and not by AEs, and subjects are only counted once for recurring AEs within each system organ class (SOC) or preferred term (PT); however, the number of total AEs per subject, including multiple occurrences of individual AEs, will also be presented. For summaries of severity, AEs will be reported only at their maximum severity in each subject. Subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.

AE (including deaths) dates will be imputed according to algorithms detailed in Section 8.0. The imputed date of AE onset will be used to assess whether AEs should be considered as treatment-emergent and included in the safety summaries. The original, partial dates will be included in data listings. No imputation will be performed on missing AE seriousness, severity, or relationship; they will be reported as missing.

AEs will be included in a period if the start date of the AE is after the first dispensation date within a period.

An overall summary for the following categories will be presented:

- Deaths
- SAEs
- Related SAEs

- AEs
- Related AEs
- Discontinued treatment due to AEs

The following summaries will also be provided for the following:

- TEAEs by SOC and PT
- Treatment-related TEAEs by SOC and PT
- TEAEs by PT reported in ≥ 5% of subjects
- TEAEs by PT reported in ≥ 1% of subjects
- Treatment-related TEAEs by PT reported in ≥ 5% of subjects
- TEAEs categorized by severity by SOC and PT
- Exposure-adjusted incidence rate (EAIR) for TEAEs by SOC and PT – EAIR is defined in Section 8.1 of the SAP

#### 6.2.1.1 Adverse Events of Interest (AEI) and Other Important AEs

Summaries for treatment-emergent AEIs events will be provided by PT for each AEI category:

- Skin-related events
- Infection events
- Malignancy events

Creatine kinase (CK) elevation for CK elevation > 2.5 upper limit of normal will be summarized as CTCAE grade 2 or higher in the clinical laboratory summaries.

Additional information collected for some events as part of the clinical safety program and adjudicated events will also be summarized.

#### 6.2.1.2 Serious Adverse Events

Summaries for treatment-emergent SAEs will be provided for the following:

- Treatment-emergent SAEs by SOC and PT

#### 6.2.1.3 Adverse Events Leading to Discontinuation of Study Treatment or Study Treatment Interruption

Summaries for TEAEs leading to discontinuation of study treatment will be provided for the following:

- TEAEs by SOC and PT

Summaries for TEAEs leading to study treatment interruption will be provided for the following:

- TEAEs by SOC and PT

### 6.2.2 Deaths

All adverse events with an outcome of death will be listed.

### 6.2.3 Clinical Laboratory Data

Laboratory parameters will be summarized using the International System (SI) of Units and US conventional units. Data will be summarized by time point, as applicable. The following summaries will be provided for each parameter:

- Absolute and change from baseline values for continuous parameters

- Number and percentage of subjects for the following:
    - Maximum postbaseline CTCAE grade for each applicable laboratory parameter through Week 16
    - Shifts from baseline based on maximum postbaseline CTCAE grade through Week 16
- Drug-induced Liver Injury (DILI) and Hy's Law summaries

### 6.2.4 Vital Signs and Physical Findings

Vital signs, including weight, will be summarized by time point, as applicable. The following summaries will be provided for each parameter:

- Absolute and change from baseline values
- Number and percentage of subjects for the following:
    - Marked abnormality for each abnormality category as defined in Section 4.2

### 6.2.5 ECGs

ECG parameters will be summarized by time point, as applicable. The following summaries will be provided for each parameter:

- Absolute and change from baseline values
- Number and percentage of subjects for the following:
    - Marked abnormality for each abnormality category as defined in Section 4.2

### 6.2.6 Other Safety Data

#### 6.2.6.1 PHQ-8

PHQ-8 total score will be summarized by time point, as applicable. The following summaries will be provided:

- Absolute and change from baseline values
- Number and percentage of subjects:
    - Shifts from none, mild, moderate, moderately severe and severe scores at baseline and at each time point

#### 6.2.6.2 eC-SSRS

Suicidal ideation and behavior individual item responses will be summarized by time point, as applicable. The following summaries will be provided:

- Number and percentage of subjects with positive responses on suicidal ideation and/or suicidal behavior questions for each question and overall all questions within suicidal ideation and suicidal behavior
- Shifts from baseline based on maximum postbaseline response through Week 16
- Worst postbaseline value for suicidal ideation and behavior through Week 16

## 6.3 General Methodology

The following standards/ methods will be used:

- Statistical package(s) planned to be used
    - All analyses will use SAS version 9.4 or higher.
- Standard summary statistics for continuous and categorical variables:

- Unless otherwise noted, categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. The median, minimum and maximum values will be displayed to the same level of precision as the raw data, the mean to a further decimal place and the SD to two additional decimal places.
- Variables will be summarized by period, treatment group, and time point, as applicable.

### 6.3.1 Subject Populations and Disposition

The number of subjects enrolled/screened and the number and percentage of subjects randomized, treated, and in each analysis population will be presented. The number and percentage of subjects randomized in each region, country, and site will be presented.

Additionally, the following summaries will be provided for the FAS by treatment group and overall:

- Number and percentage of subjects who completed 16 weeks of treatment
- Number and percentage of subjects who discontinued treatment prior to Week 16 and reason for treatment discontinuation
- Number and percentage of subject who completed 24 weeks of treatment, who discontinued treatment prior to Week 24 and post Week 16, and those who discontinued at any time prior to week 24 and reason for treatment discontinuation. Denominator will be the number of subjects in the FAS.
- Number and percentages of subjects who completed 52 weeks of treatment, who discontinued treatment prior to Week 52 and post Week 24, and who discontinued treatment at any time and reason for treatment discontinuation. Denominator will be the number of subjects in the FAS.

### 6.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group for the FAS. Demographic characteristics include the following:

- Sex
- Race
- Ethnicity
- Age (in years, at time of signing informed consent) and age category (<65 vs ≥65)
- Weight (in kg, at baseline) and weight category (≥90 kg, <90 kg)
- Body mass index (BMI in kg/$m^2$, at baseline)
- Geographic region (U.S., Japan, China, Rest of World)
- Prior biologic use for psoriasis, psoriatic arthritis and other inflammatory diseases only (yes, no)
- Reason for discontinuation of prior biologic use
- Prior systemic treatment use (yes/no)
- Prior phototherapy use (yes/no)
- Stratification factors obtained from IRT: geographic region by prior biologic use and by body weight
- Stratification factors obtained from database: geographic region by prior biologic use and by body weight
- sPGA (3, 4)
- PASI score (≤20, >20)
- BSA involvement (10-20, >20)
- Duration of disease (< 10 y, ≥ 10 y)
- Age at disease onset (<18, 18-39, ≥40)

Additional demographics or baseline data may be added to summary tables.

General medical history and medical history related to psoriasis will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). General medical history data will be summarized for each SOC and PT by treatment group and overall for the FAS. Separate tables will be provided for psoriasis medical history.

### 6.3.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded according to World Health Organization-Drug Dictionary WHO-DD (version at the time of DBL) and will be summarized by Anatomic Therapeutic Classification (ATC) and preferred term (PT) by treatment group for the As-treated population. The number and percentage of subjects using at least one medication and each medication will be displayed by treatment group. Subjects taking more than one medication within the same ATC or PT will be counted once.

Summaries will be provided for prior medications and medications that started prior to first treatment and were ongoing after first treatment start date as well concomitant medications.

Medication dates will be imputed according to algorithms detailed in Section 8.0. The imputed dates will be used to assess whether medications should be included in the summaries as prior or concomitant, however the original, partial dates will be included in data listings.

#### 6.3.3.1 Psoriasis, Psoriatic Arthritis and Other Inflammatory Disease Related Systemic Medications

Prior medications and medications that started prior to first treatment and were ongoing after first treatment start date for systemic biologic and non-biologic medications will be summarized as described above for the number and percentage of subjects using each reported medication.

#### 6.3.3.2 Concomitant High Potency Corticosteroid Use

The number and percentage of subjects using at least one high potency topical corticosteroid at Week 24 will be summarized by treatment group. Additionally, corticosteroids will be summarized by ATC and PT.

### 6.3.4 Exposure

#### 6.3.4.1 Duration of Treatment

**Duration by Group**

Overall duration of each treatment, in days, will be calculated for each subject in each treatment group. Subjects are dispensed study treatment at each visit, starting with Day 1 (Week 0) and at each subsequent visit. The date of first dose of study treatment is the Week 0 [redacted] dosing date and is recorded on the eCRF. If this date is missing, then the earliest drug dispensation date will be used. The last dose date is recorded on the end of treatment page in the eCRF. If this date is missing, then the latest date from the [redacted] page or drug accountability return date will be used.

Duration of treatment will be summarized descriptively by randomized treatment group.

**BMS-986165:**

Subjects randomized to BMS-986165 will have their duration of treatment derived as:

- Date of last dose – date of first dose +1

**Placebo:**

For subjects randomized to placebo, duration is defined as:

- Placebo = Date of last dose of placebo – date of first dose +1
- BMS-986165 = Date of last dose of BMS-986165 – date of first dose of BMS-986165 +1

**Apremilast:**

For subjects randomized to apremilast, the Week 24 date will be used as the date of last dose of apremilast and the date of first dose of either apremilast or BMS-986165 for the subsequent period. Subjects who receive apremilast at Week 24 through to Week 52 will be counted as a sum of the first 24 weeks of treatment and the next treatment period.

- Apremilast (Wk 0 through Wk 24) = Week 24 date – date of first dose +1
- Apremilast (Wk 24 through Wk 52) = Date of last dose – Week 24 date
- Total Apremilast = Duration of apremilast Wk 0-24 + duration of apremilast Wk 24-52
- BMS-986165 = Date of last dose of BMS-986165 – Week 24 date

Total apremilast duration of treatment will be displayed as well as BMS-986165 treatment duration. If subject discontinues their study treatment during the initial 24 weeks of apremilast treatment, the date of last dose will be used as the duration of apremilast.

**Duration by Period**

Overall duration (in days) of each treatment received within each study period will be calculated. Duration within each period is defined for each treatment group as:

$$Last\ dose\ date\ in\ period\ - first\ dose\ date\ in\ period + 1$$

### 6.3.4.2 Summary of Dosing

The number of doses taken for each subject for each period will be determined using the eCRF drug accountability data and is defined as:

$$Doses\ Taken: (number\ of\ tablets\ dispensed - number\ of\ tablets\ returned)$$

The number of doses taken will be summarized descriptively by treatment group within each period and overall.

### 6.3.4.3 Compliance

Treatment compliance will be determined from data captured on the Drug Accountability eCRF.

$$Number\ of\ expected\ doses: (date\ of\ next\ visit - date\ of\ current\ visit)x3$$

Treatment compliance will be derived for each period. Compliance is defined as:

$$\left(\frac{Number\ of\ doses\ taken}{Number\ of\ expected\ doses}\right)x100$$

Period compliance will be calculated by summing over all visits within the period using descriptive statistics by treatment group. The number and percentage of subjects with <75%, 75% to 100%, and >100% compliance will be provided by treatment group for each period. If a subject does not return the container, then this dispensation event will be excluded in the calculation for the total number of doses taken, total number of expected doses, and total compliance.

[redacted]

[redacted]

## 6.6 Statistical Impacts Due to COVID-19

### 6.6.1 Impact on Efficacy Endpoints

There are no COVID-19-related impacts to the Week 16 and Week 24 endpoints as all subjects remaining in the trial completed these visits prior to COVID-19 restrictions. Key secondary efficacy endpoints involving later visits may be impacted by COVID-19 in the form of missing data and/or a treatment assignment defaulting to BMS-986165. If a subject has missing data or is switched to BMS-986165 from a different treatment due to COVID-19 during the Week 24 through Week 52 period, the subject will be excluded from the analysis.

Key secondary efficacy endpoints that may be impacted include the following:

- sPGA 0/1 response at Week 52 and at Week 24
- PASI 75 response at Week 52 and at Week 24
- PASI 90 response at Week 52 and at Week 24

A sensitivity analysis will also be performed for the above endpoints using the last observed value. The data handling rules to be used are as follows for subjects with missing data or for those subjects who switch to BMS-986165 from a different treatment due to COVID-19:

- If the subject is missing the Week 52 response value (ie, sPGA 0/1, PASI 75, PASI 90), then the last observed response value during the Week 24 through Week 52 period will be carried forward to the Week 52 value
- If the subject is switched to BMS-986165 from a different treatment due to COVID-19, then the last observed response value prior to the switch will be carried forward to the Week 52 value

Censoring rules will be applied to the time to first loss endpoints evaluated for the maintenance of efficacy of BMS-986165 through Week 52 in subjects who were originally randomized to BMS-986165 and impacted by COVID-19-related issues post Week 24:

- Subject has missing visits (ie, efficacy assessments not performed) after Week 24 and assuming loss of response was not observed prior to missing visits:

- If the subject returns at a later visit and is found to have had a loss of response, midpoint imputation will be used to determine time to first loss (ie, midpoint of the censoring interval).
- If the subject returns at a later visit and has not had a loss of response, then the subject will continue to be evaluated for time to first loss.
- If the subject is discontinued from the study treatment, then the subject will be censored at the time of study treatment discontinuation.

Time to first loss endpoints include:

- Time to first loss of PASI 75 among subjects that are PASI 75 responders at Week 24
- Time to first loss of sPGA 0/1 among subjects that are sPGA 0/1 responders at Week 24 where loss of sPGA 0/1 is defined as an sPGA score ≥ 2 (sPGA scores are rounded to the nearest whole number)

### 6.6.2 Impact on Safety Endpoints

No modifications will be made for the analysis of safety data due to COVID-19-related issues. There will not be any additional safety data handling considerations for missing data or treatment interruptions due to COVID-19.

# 7.0 Sequence of Planned Analyses

## 7.1 Interim Analyses

No interim analysis is planned for this study.

## 7.2 Final Analyses and Reporting

All final, planned analyses identified in this statistical analysis plan will be performed only after the last subject has completed the study and the database has been locked. The randomization codes for all subjects will not be unblinded until after the database has been locked.

Analyses of the palmoplantar pp-PGA 0/1 endpoint are provided for descriptive purposes within the individual CSR due to small sample sizes. A pooled analysis of data from IM011046 and IM011047 will be conducted for the submission.

# 8.0 Conventions

## 8.1 General Definitions

The following data definitions and handling conventions will be used for general analysis:

| Term | Definition |
|---|---|
| Study Day | Study day is calculated as:<br>assessment date – date of first dose + 1 |
| Baseline | Unless otherwise stated, Baseline is defined as the measurement at the randomization visit (Week 0). If the measurement at the randomization visit is missing, then a prior measurement during the screening period may be used as baseline. Baseline assessments must be performed per protocol and standard of care assessments may not be used for baseline.<br>Baseline for each PSSD question will be calculated as the average value over the 7 days prior to the randomization visit. In the event of missing values in the 7 days prior to the randomization visit, daily |

| | |
|---|---|
| | scores from at least 4 days out of the 7 days can be used to calculate the average score. If > 3 daily scores in the last 7 days are missing for a particular question, then the baseline value for that question will be missing. If any questions are missing baseline after using the described rule, then the baseline value for the subscore using that question and the baseline value for the total score will be missing. |
| Change from Baseline | Change from baseline is defined as (value at post-baseline visit – value at baseline). |
| Change in the maximum post-baseline value or change in the worst post-baseline value | Change from baseline in the maximum post-baseline value is defined as highest observed value or grade post-baseline. The change is calculated using this value as the post-baseline value.<br><br>Change from baseline in the worst post-baseline value is defined as worst observed value post-baseline. The change is calculated using this value as the post-baseline value. |
| Concomitant and Prior Medication | Prior medications are defined as medications with a stop date prior to the first dose of study treatment. Concomitant medications are defined as any medications ongoing at the start of study treatment or with a start date on or after the first dose date. |
| End of Study (EOS) Date | The EOS date is the date recorded on the eCRF that a randomized subject either discontinued or completed the study. If the subject is lost to follow-up, the EOS date will be the date of the last visit assessment obtained. |
| Exposure-adjusted incidence rate (EAIR) | EAIR = 100* 365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment that a subject is exposed. Where total exposure time for each AE within a treatment is calculated as follows:<br><br>• If a subject has at least 1 event while on a particular treatment, then the exposure time for that subject and AE on that treatment is:<br>o First AE onset date – treatment start date (of that particular treatment) +1<br>• If a subject does not have an event, exposure time for that AE is:<br>o Treatment stop date (of that particular treatment) – Treatment start date (of that particular treatment) + 1 + 30 days (if subject discontinued or subject completed Period 3 and is not rolling into IM011075 study)<br>o Treatment stop date (of that particular treatment) – Treatment start date (of that particular treatment) + 1 (if subject completed Period 3 and is rolling into IM011075 study)<br>• Total exposure time = sum of exposure time for each AE within a treatment |
| First Dose Date – Study | The date a subject received their first dose on Day 1 as recorded in the eCRF Week 0 [redacted] dosing date or the earliest drug dispensation date. |

| | |
|---|---|
| Last Dose Date – Study | The date of last recorded dose on the eCRF for a randomized subject. |
| First Dose Date – Period | The date a subject received their first dose as recorded in the eCRF Week 0 [redacted] dosing date or the earliest drug dispensation date for Treatment Period 1 and the earliest drug dispensation date for Treatment Periods 2 and 3. |
| Last Dose Date – Period | The date of the last visit in the periods – 1. If a subject prematurely discontinues study treatment within a period, the date of last recorded dose on the eCRF will be used as the last dose date for the period. |
| Percent Change from Baseline | Percent change from baseline is defined as ([value at post-baseline visit – value at baseline]/value at baseline) x 100.<br>If the baseline value is 0 and the post-baseline value is also 0, then the percent change from baseline is set to 0.<br>If the baseline value is 0 and the post-baseline is >0, then the percent change from baseline value will be missing. |

## 8.2 Calculation of Key Measures

The following efficacy assessments will be used to assess subjects' disease activity and severity during the study. Outcomes are reported via an eCOA tool at various times throughout the study as described in the protocol Schedule of Activities. At study visits, assessments by the investigator or subjects and results/responses will be reported directly into the eCOA tool at the time of the visit. The tool will open assessments in a sequential manner, meaning that the full assessment is to be completed prior to moving forward to the next assessment. This limits the possibility of partially missing data. Also, as investigators/subjects are prompted to enter data for each assessment for the visit, the possibility of a full assessment being missing is also negated.

Scoring of assessments where validated algorithms are not required will be derived in SAS datasets.

Scoring of assessments where validated scoring tools are required, licenses for these tools will be purchased and used for scoring prior to incorporating into the SAS datasets.

### 8.2.1 Investigator-Administered Assessments

Assessments will be performed by a qualified physician or dermatologist or trained designee who is experienced in the assessment of psoriasis patients. To limit variability, every effort will be made so that the same individual conducts the assessment at all subsequent visits.

#### 8.2.1.1 static Physician's Global assessment (sPGA)

The sPGA is a 5-point scale of an average assessment of all psoriatic lesions based on erythema, scale, and induration. The sPGA measure determines psoriasis severity at a single point in time (without taking into account the baseline disease condition) as clear (0), almost clear (1), mild (2), moderate (3), or severe (4). A higher score equates to higher severity of disease.

The individual scores at each visit for erythema (E), induration (I) and scaling (S) will be captured via the eCOA system. Scores will range from 0 to 4. A total score will also be computed based on the average of the 3 characteristic scores.

$$Total\ average\ score = \frac{E + I + S}{3}$$

The total average score will be calculated in the eCOA system. The average score will be rounded to the nearest whole number. For example, if the total average score is ≤1.49 the score will be rounded to 1. If

the score is ≥1.5 the score will be rounded to 2. The primary endpoint is derived from the total average score.

sPGA 0 is derived as the binary indicator for sPGA from the calculation above equal to 0 or not;

sPGA 0/1 is derived as the binary indicator for sPGA from the calculation above equal is less than 2 or not;

[redacted]

All individual scores and total average score assessed at each week throughout the study will be transferred to PRA for analysis. The endpoint derivations will be performed in the analysis datasets.

#### 8.2.1.2 Psoriasis Area and Severity Index (PASI)

The PASI is a measure of the average redness, thickness, and scaliness of psoriatic skin lesions (each graded on a 0–4 scale; 0 = none to 4 = very severe), weighted by the area of involvement (head, arms, trunk to groin, and legs to top of buttocks). The PASI produces a numeric score that can range from 0 to 72, with higher PASI scores denoting more severe disease activity. The PASI includes multiple subscores and a final total score that will be provided by the eCOA system. Individual plaque characteristic rating scores are provided for each body region as well as the weighted score. Additionally, the degree of involvement of each body region is assessed and that score is multiplied by the weighted plaque characteristic score for a final score for each body region. The total PASI score is a sum of the 4 body regions: Head, Upper Extremities, Trunk and Lower Extremities.

The PASI Total score will be used to assess response to treatment. The percent change from baseline will be calculated at each visit. The PASI 75 endpoint is the proportion of subjects who experience at least a 75% improvement in PASI score as compared with the baseline value.

1 = $If\ \left(\frac{Baseline\ PASI - Visit\ PASI}{Baseline\ PASI}\right) x100 \geq 75\ then\ subject\ is\ a\ PASI\ 75\ responder$

0 = otherwise

The PASI 50, PASI 90, and PASI 100 are defined similarly. The endpoint derivations will be performed in the analysis datasets.

#### 8.2.1.3 Body Surface Area (BSA)

Measurement of psoriasis BSA involvement is estimated using the handprint method with the size of a subject's handprint (including fingers and thumb) representing 1% of BSA involved. 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).

The Total BSA is the sum of each body region and is assessed at each visit and recorded in the eCOA system.

The product of BSA and sPGA will be calculated. At baseline, baseline BSA will be multiplied by baseline sPGA score. The derivation will be performed at each subsequent visit.

#### 8.2.1.4 scalp specific Physician's Global Assessment (ss-PGA)

The scalp specific assessment will only be performed in subjects with scalp involvement. If there is evidence of scalp involvement, scalp lesions are evaluated in terms of clinical signs of redness, thickness, and scaliness and scored on the following 5-point ss-PGA scale:

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

The ss-PGA is assessed at each visit throughout the study in subjects that have evidence of scalp psoriasis at baseline. The score will be collected in the eCOA system.

[redacted]

#### 8.2.1.6 Physician's Global Assessment-Fingernails (PGA-F)

In this assessment, fingernail psoriasis is evaluated. The PGA-F will be performed at baseline. If a subject shows evidence of psoriatic fingernail involvement, the assessment will be performed at each subsequent visit to assess severity and improvement over time. Only subjects with PGA-F at baseline will be assessed throughout the study. The overall condition of the fingernails is rated on a 5-point scale:

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

The rating score will be collected in the eCOA system.

[redacted]

#### 8.2.1.8 Palmoplantar PGA (pp-PGA)

This measure will be used for subjects with palmoplantar (finger and toe surfaces) involvement at baseline. Only subjects with baseline palmoplantar involvement will continue to have these assessments at each subsequent visit throughout the study. The pp-PGA uses a 5-point (0-4) overall severity scale:

0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe.

Scores are collected at each visit and entered in the eCOA system.

[redacted]

### 8.2.2 Subject-Reported Assessments

#### 8.2.2.1 Psoriasis Symptoms and Signs Diary (PSSD)

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

The following questions in the instrument are included in the symptom score: Q1, Q4, Q9, Q10, Q11

The following questions in the instrument are included in the sign score: Q2, Q3, Q5, Q6, Q7, Q8

Two versions of the PSSD were developed, one with a 24-hour recall period (PSSD-24h) and one with a 7-day recall period. The PSSD-24h will be administered daily in this trial to avoid recall bias with a longer recall period. Individual scores to each question are collected daily in the PSSD. For visit PSSD scoring, the daily scores (with 24-h recall periods) over the prior 7 day will be used and the average score to each of the 11 questions will be used as the score at that visit. In case missing data arise during the 7 days prior to the visit, daily scores of at least 4 days out of the 7 can be used. If >3 scores are missing, the average score will be missing. Baseline PSSD score is calculated based on the daily diary collected data during the screening period. Baseline for each PSSD question will be calculated as the average value over the 7 days

prior to the randomization visit. In the event of missing values in the 7 days prior to the randomization visit, daily scores from at least 4 days out of the 7 days can be used to calculate the average score. If > 3 daily scores in the last 7 days are missing for a particular question, then the baseline value for that question will be missing. If any questions are missing baseline after using the described rule, then the baseline value for the subscore using that question and the baseline value for the total score will be missing.

A symptom score will be derived by averaging the 5 questions included in the symptom score and multiplying by 10. To obtain a symptom score on a given day, responses to at least 2 of the 5 questions must be available. If 3 or more questions are missing, the symptom score is considered missing.

A sign score will be derived by averaging the 6 questions included in the sign score and multiplying by 10. Responses to at least 3 of the 6 questions must be available in order to obtain a sign score for a given day. If more than 3 questions are missing, the sign score is considered missing.

Both scores range from 0-100, where 0 representing the least severe symptom/sign and 100 the most severe. A total PSSD score with range 0-100 will be derived from taking the average of the symptom and sign scores.

[redacted]

### 8.2.2.4 Dermatology Life Quality Index (DLQI)

The DLQI 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 where 0="not at all", 1="a little", 2="a lot", or 3="very much". The scores are summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment). Question 7 includes 2 questions, if the subject answers ‘Yes’ to Q7, the score given is a 3. If the subject answers ‘No’ to Q7, they are asked the second question where a score of 0=’not at all’, 1=’a little’, or 2=’a lot’ is given. Certain questions include an option for not relevant. When scoring, any questions deemed ‘not relevant’ will take on a value of 0.

. Interpretation of DLQI scores is as follows:

- 0-1 = no effect at all on patient’s life
- 2-5 = small effect on patient’s life
- 6-10 = moderate effect on patient’s life
- 11-20 = very large effect on patient’s life
- 21-30 = extremely large effect on patient’s life

Individual scores for each question will be provided by the eCOA system. The DLQI score will be derived in the analysis datasets.

[redacted]

[redacted]

### 8.2.2.11 Psoriatic Arthritis Screening and Evaluation (PASE) Questionnaire

The PASE questionnaire will be administered at Screening in subjects with peripheral joint complaints. The PASE questionnaire is a self-administered tool that is used to screen for psoriatic arthritis among subjects who have psoriasis. The PASE questionnaire consists of 15 questions subdivided into 7 questions focusing on symptoms of psoriatic arthritis, and 8 questions focusing on the impact of psoriatic arthritis on function. Each question is scored on a 1 to 5 scale, with a maximum symptom sub-scale score of 35, a maximum function sub-scale score of 40 giving a total maximum score of 75. A score of 47 or above has been shown to distinguish between psoriatic arthritis and non-psoriatic arthritis. This questionnaire is only intended to be a screening tool for psoriatic arthritis and does not replace a comprehensive musculoskeletal exam performed by a rheumatologist. This information will not be summarized.

Individual score to each of the 15 questions will be collected in the eCOA system. The sub-scale scores and total score will be derived in the analysis datasets.

#### 8.2.2.12 Eight-Item Patient Health Questionnaire (PHQ-8)

The PHQ-8 is established as a valid diagnostic and severity measure for depressive disorders in large clinical studies. Each of the 8 questions is based on a 2-week recall and scored on a scale of 0 to 3 by a tick box as: 0=Not at All, 1=Several Days, 2=More than Half the Days, and 3=Nearly Every Day. A PHQ-8 score is derived by summing the scores for the 8 questions. The total PHQ-8 score ranges from 0-24. Scoring interpretation is as follows:

- 0-4 = no significant depressive symptoms
- 5-9 = mild depressive symptoms
- 10-14 = moderate depressive symptoms
- 15-19 = moderately severe depressive symptoms
- 20-24 = severe depressive symptoms

Response to each individual question is collected in the eCOA system. The total score will be derived in the analysis datasets.

#### 8.2.2.13 electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) is a computer-automated, patient-reported version of the C-SSRS instrument that defines 11 categories of suicidal ideation and behavior (SIB) events. Categories and definitions are provided in Appendix 23 of the protocol. The categories are as follows:

- Suicidal ideation
  1. Wish to be dead
  2. Non-specific active suicidal thoughts
  3. Active suicidal ideation with any methods without intent to act
  4. Active suicidal ideation with some intent to act, without specific plan
  5. Active suicidal ideation with specific plan and intent
- Suicidal behavior
  1. Preparatory acts or behavior
  2. Aborted attempt
  3. Interrupted attempt
  4. Actual attempt (Non-fatal)
  5. Completed suicide
- Self-injurious behavior, no suicidal intent

## 8.3 Missing, Unknown, or Partial Dates

| Start Date | | Stop Date | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Complete: *yyyymmdd* | | Partial: *yyyymm* | | Partial: *yyyy* | | Missing/ Ongoing |
| | | <1st dose | ≥1st dose | <1st dose *yyyymm* | ≥1st dose *yyyymm* | <1st dose *yyyy* | ≥1st dose *yyyy* | |
| Partial: *yyyymm* | = 1st dose *yyyymm* | 2 | 1 | n/a | 1 | n/a | 1 | 1 |
| | ≠ 1st dose *yyyymm* | | 2 | 2 | 2 | 2 | 2 | 2 |
| Partial: *yyyy* | = 1st dose *yyyy* | 3 | 1 | 3 | 1 | n/a | 1 | 1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ≠ 1st dose *yyyy* | | 3 | | 3 | 3 | 3 | 3 |
| Missing | | 4 | 1 | 4 | 1 | 4 | 1 | 1 |

**1** = Impute as the date of first dose
**2** = Impute as the first of the month
**3** = Impute as January 1 of the year
**4** = Impute as January 1 of the stop year
Note: If the start date imputation leads to a start date that is after the stop date, then there is a data error and the start date is not imputed.

Imputation rules for partial or missing stop dates:

1. Initial imputation
    a. For partial stop date "mmyyyy", impute the last of the month.
    b. For partial stop date "yyyy", impute December 31 of the year.
    c. For completely missing stop date, do not impute.
2. If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
3. If the stop date imputation leads to a stop date that is before the start date, then there is a data error and the stop date is not imputed.

Imputation rules for partial or missing death dates:

1. If death year and month are available but day is missing:
    a. If "mmyyyy" for last contact date = "mmyyyy" for death date, set death date to the day after the last contact date.
    b. If "mmyyyy" for last contact date < "mmyyyy" for death date, set death date to the first day of the death month.
    c. If "mmyyyy" for last contact date > "mmyyyy" for death date, data error and do not impute.

If both month and day are missing for death date or a death date is totally missing, set death date to the day after the last contact date.

## 8.4 Study Periods

Period 1 = Week 0 to Week 16 visit date

Period 2 = Week 16 visit date +1 to Week 24 visit date

Period 3 = Week 24 visit date +1 to Week 52 visit date

Follow-up = 4 week follow-up period

## 8.5 Day Ranges for Analysis Visits

Below are the day ranges for the analysis visit definitions. If more than one visit occurs within an analysis visit, then the visit that is closest to the target date should be used for analysis.

| **Period**<br>**Week** | **Target Day** | **Day Range** |
|---|---|---|
| **Baseline** | | Screening, 1 |
| **Period 1** | | |
| Week 1 | 8 | 2, 11 |
| Week 2 | 15 | 12, 18 |
| Week 4 | 29 | 19, 43 |
| Week 8 | 57 | 44, 71 |
| Week 12 | 85 | 72, 99 |
| Week 16 | 113 | 100, 127 (or Week 16 drug dispense date) |
| **Period 2** | | |
| Week 20 | 141 | 1st day after Week 16 drug dispense date, 155 |

| Period<br>Week | Target Day | Day Range |
|---|---|---|
| Week 24 | 169 | 156, 183 (or Week 24 drug dispense date) |
| **Period 3** | | |
| Week 28 | 197 | 1st day after Week 24 drug dispense date, 211 |
| Week 32 | 225 | 212, 239 |
| Week 36 | 253 | 240, 267 |
| Week 40 | 281 | 268, 295 |
| Week 44 | 309 | 296, 323 |
| Week 48 | 337 | 324, 351 |
| Week 52 | 365 | 352, last visit date prior to Safety Follow-up |
| Safety Follow-up | 393 | Safety Follow-up visit |

# 9.0 References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# 10.0 Document History

| Version Number | Version Date | Summary of Changes |
|---|---|---|
| 1.0 - Original Document | 09-Jun-2019 | Not applicable |
| 2.0 – Amendment 01 | 30-Sep-2020 | Revisions provided below. |

**Revisions for Amendment 01:** In addition to the revisions specified below, there were some minor typographical and formatting changes made. Additions are noted by bold text. Removals are noted by strikethrough.

| SAP Section | Revised Text | Rationale for Change |
|---|---|---|
| 2.1 Study Design | **Week 16 activities**<br>The coprimary endpoints, static Physician Global Assessment (sPGA) 0/1 and Psoriasis Area and Severity Index (PASI) 75 will be assessed at Week 16. Subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD at Week 16. Subjects who are randomized to BMS-986165 6 mg QD or apremilast will continue on their assigned treatment regimen **in a blinded manner**. | Minor edit to clarify subjects continue on assigned treatment in a blinded fashion. |
| 2.4 Unblinding Information | ~~No other unblinding prior to study completion and database lock is planned~~.<br>**Additionally, bioanalytical scientists involved in the processing of bioanalytical samples will be unblinded to randomized treatment assignments to minimize unnecessary sample bioanalysis of subjects who are on placebo.** | Added clarification that bioanalytical staff will be unblinded to facilitate bioanalytical sample processing. |
| 2.5 Changes in Statistical Considerations from the Protocol | ~~There are no changes in statistical considerations from the protocol at this time.~~ The following is a list of the important changes in the SAP from the Statistical Considerations section in the protocol:<br>• **The hierarchical testing order for the key secondary endpoints has been updated and two separate hierarchies have been provided, one for US submission and one for ex-US submission (see Tables 1 and 2 in Sec. 6.1.3). The hierarchies presented here supersede the one that is in the protocol.**<br>• **Key secondary endpoints were added for the comparison of BMS-986165 to apremilast for sPGA 0/1, PASI 75, and PASI 90 at Week 24.**<br>• **Imputation methods were updated to remove the prohibited medication/therapy criteria for binary and continuous endpoints.** | The definition for the Full Analysis Set was modified to include all randomized subjects as this is more representative of the ITT population.<br>Noted that the relevant deviation list was updated from the list in the protocol. |

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|---|---|---|
| | • **The Full Analysis Set was changed from "all subjects who were randomized to receive assigned study treatment" in the protocol to "all subjects who are randomized".**<br>• **The list of relevant protocol deviations provided in the protocol was updated for determination of the Per Protocol population.**<br>• **Logistic regression analyses for binary endpoints were removed as these are similar to the CMH analyses.** | Additional Week 24 endpoints were added.<br>Imputation methods were updated to remove prohibited medication/ therapy criteria.<br>Hierarchical testing order of key secondary endpoints were updated and accounting of regional regulatory needs.<br>Removed logistic regression analyses. |
| 4.1.2 Secondary Endpoints<br>4.1.2.1 Key Secondary Endpoints for Comparisons to Placebo | The key secondary efficacy endpoints for BMS-986165 compared to placebo at Week 16 are defined as:<br>• PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in PASI score<br>• sPGA 0 response assessed as a proportion of subjects with an sPGA score of 0<br>• Scalp specific Physician's Global Assessment (ss-PGA) 0/1 assessed as a proportion of subjects with a ss-PGA score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA score ≥3<br>• PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥1<br>• PASI 100 response assessed as a proportion of subjects who achieve a 100% improvement from baseline in PASI score<br>• Physician Global Assessment-Fingernails (PGA-F) 0/1 assessed as a proportion of subjects with a PGA-F score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline PGA-F score ≥3<br>• ~~Change from baseline in Psoriasis Symptoms and Signs Diary (PSSD) symptom score~~ | Updated key secondary endpoints compared to placebo and re-ordered. |

| | | |
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| | • DLQI 0/1 assessed as a proportion of subjects with a DLQI score of 0 or 1 among subjects with a baseline DLQI score ≥2 (Ex-US submission only)<br>• ~~Palmoplantar Physician's Global Assessment (pp-PGA) 0/1 assessed as a proportion of subjects with a pp-PGA score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline pp-PGA score ≥3~~ | |
| 4.1.2.2 Key Secondary Endpoints for Comparisons to Apremilast | The key secondary endpoints for BMS-986165 compared to apremilast at Week 16 are defined as:<br>• sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least a 2-point improvement from baseline<br>• PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score<br>• PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score<br>• Change from baseline in PSSD symptom score<br>• ss-PGA 0/1 assessed as a proportion of subjects with a ss-PGA score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA score ≥3<br>• ~~PASI 100 response assessed as a proportion of subjects who achieve a 100% improvement from baseline in the PASI score~~<br>• sPGA 0 response assessed as a proportion of subjects with an sPGA score of 0<br>• PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥1<br>**The key secondary endpoints for BMS-986165 compared to apremilast at Week 24 are defined as:**<br>• **sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least a 2-point improvement from baseline at Week 24**<br>• **PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score at Week 24**<br>• **PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score at Week 24**<br>The key secondary endpoints for BMS-986165 compared to apremilast through Week 52 are defined as:<br>• sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least a 2-point improvement from baseline at Week 52 and **at** Week 24 | Updated key secondary endpoints compared to apremilast and re-ordered.<br>Added some clarifying language. |

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| | • PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score at Week 52 and **at** Week 24<br>• PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score at Week 52 and **at** Week 24 | |
| [redacted] | | |
| 4.2 Safety | • Treatment-emergent adverse events (TEAEs) – defined as:<br>o ~~New nonserious~~ AEs which ~~first~~ occur after the first dose of study treatment through **30 days** ~~4 weeks~~ after the final dose of the study treatment or subject's participation in the study if the last scheduled visit occurs at a later time.~~; New serious adverse events (SAEs) which first occur after the first dose of study treatment through 4 weeks after the final dose of the study treatment or subject's participation in the study if the last scheduled visit occurs at a later time;~~<br>o ~~SAEs reported prior to first dose of study treatment that increase in severity or frequency after first dose of study treatment through 4 weeks after the final dose of the study treatment or subject's participation~~ | Removed redundant language for treatment-emergent adverse events.<br>Clarified final list for adverse events of interest.<br>Specified that deaths would be evaluated. |

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| | ~~in the study if the last scheduled visit occurs at a later time.~~<br><br>o Treatment-emergent adverse events of interest (AEIs) ~~as determined through the Clinical Safety Program (CSP)~~ for the following events:<br>▪ Skin-related AEs<br>▪ Infection AEs**, including influenza**<br>▪ Creatine kinase (CK) elevation **(evaluated as lab toxicity grade 2 or higher)**<br>▪ Malignancy<br><br>▪ **Deaths**<br><br>o Laboratory abnormalities (as determined by Common Terminology Criteria for Adverse Events [CTCAE **v5.0**] grading) **presented as the worst postbaseline toxicity group**<br>o Shifts from baseline **to maximum postbaseline value**<br><br>o **ALT or AST elevation >5 times ULN**<br><br>≥ 500 **msec**<br><br>**Males: < 450 msec, ≥ 450 msec**<br><br>**Females: < 470 msec, ≥ 470 msec**<br><br>**In cases where the QT interval is corrected using Bazett's (QTcB) formula is captured instead of QTcF, then QTcB will be converted to QTcF for analyses.**<br><br>• Eight-Item Patient Health Questionnaire (PHQ-8) total score<br>o Absolute and change from baseline values<br>o Shifts from baseline scores<br>o ~~PHQ-8 total scores ≥ 15~~<br><br>o Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)<br>o ~~eC-SSRS items~~**Suicidal ideation and suicidal behavior responses by visit**<br>o **Shifts from baseline to postbaseline value for suicidal ideation and suicidal behavior**<br>o **Worst postbaseline value for suicidal ideation and behavior through Week 16** | Version number added for CTCAE.<br><br>Provided additional clarifications for lab summaries.<br><br>Added missing msec for ECG category, new categories for ECG by males and females, and clarification that QTcB will be converted to QTcF for analysis.<br><br>Removed PHQ-8 total scores >=15 as this is provided in the shift table.<br><br>Clarified the variables for eC-SSRS to be summarized. |
| 5.0 Populations for Analysis | Full Analysis Set (FAS): All **subjects who are** randomized ~~subjects who are assigned study treatment~~. | The definition for the Full Analysis Set |

| | | |
|---|---|---|
| | Per Protocol Set (PPS): A subset of the FAS who are compliant with study treatment and who do not have any ~~statistically~~ relevant protocol deviations that may impact the coprimary efficacy endpoint assessments. | was modified to clarify that the population includes all randomized subjects.Removed "statistically" from relevant deviations in the PPS description to align with standard naming. |
| 5.1 Relevant Protocol Deviations | Relevant protocol deviations are deviations that can have an impact on the primary efficacy endpoints. The impact of relevant protocol deviations on the primary efficacy results will be assessed by excluding subjects from the FAS to define the PPS in supportive analyses of the primary efficacy endpoints. Relevant protocol deviations to be considered regarding exclusion of subjects from the FAS will include the following:<br>• Randomized but did not take any study treatment<br>• **No postbaseline PASI or sPGA**<br>• **Baseline BSA involvement < 10%**<br>• **Baseline PASI score < 12**<br>• **Baseline sPGA < 3**<br>• **Did not have non-plaque psoriasis at baseline**<br>• ~~Failed to meet study inclusion criteria but were entered into the study:~~<br>• ~~Met study exclusion criteria but were entered into the study: (only exclusion criteria expected to have an impact on the primary efficacy endpoints will be considered relevant)~~<br>• Poor compliance to study medication within the first 16 weeks of treatment defined as <~~80~~**75**% compliant with study<br>• Failure to adhere to prohibited concomitant medication restrictions **as described below**:<br>o **Investigational drug or placebo taken outside of the study any time between Day 1 and the Week 16 assessment**<br>o **Phototherapy within 4 weeks prior to the Week 16 assessment**<br>o **Biologic medications (eg, adalimumab, etanercept, infliximab, ustekinumab) any time between Day 1 and the Week 16 assessment**<br>o **Oral psoriasis medications any time between Day 1 and the Week 16 assessment**<br>o **Oral corticosteroids (unless for the treatment of an adverse event) within 4 weeks prior to the Week 16 assessment** | Deviations were updated with final categories. |

| | | |
|---|---|---|
| | ○ **Topical medications/treatments that could affect psoriasis evaluations within 2 weeks prior to the Week 16 assessment**<br>○ **Medicated shampoos within 2 weeks prior to the Week 16 assessment**<br>• ~~Subject overdosed, misused or abused study treatment prior to Week 16~~<br>• ~~Actual treatment received is different than randomized treatment~~**Subject received treatment that was different than intended treatment at any visit prior to Week 16.**<br><br>All subjects with relevant protocol deviations will be identified prior to database lock and unblinding of treatment assignment **with the exception of subjects where actual treatment received is different than randomized treatment which will be determined after treatment unblinding**. Relevant protocol deviations will be summarized by treatment group and deviation category for the FAS population.<br><br>~~Additionally, all important protocol deviations, which are deviations that may impact the efficacy and safety of subjects, will be identified prior to database lock and unblinding of treatment assignment. Important protocol deviations will be summarized by treatment group and deviation category for the FAS population.~~ | |
| 6.1 Efficacy Analyses | Coprimary and key secondary efficacy endpoints will be displayed graphically by treatment group and visit, as applicable. ~~Binary endpoints will be displayed using bar charts and continuous endpoints will be displayed using line plots.~~ All efficacy endpoints will be summarized descriptively.<br><br>The key secondary endpoints will be **tested with a** two-sided ~~with a~~ significance level of 0.025 to compare BMS-986165 6mg QD vs. placebo and vs. apremilast ~~(equivalent to 0.05 level of significance)~~. A hierarchical **testing** approach will be used ~~in~~ **for** testing of key secondary endpoints **(see Section 6.1.3)**~~within each comparison branch~~. Two-sided 95% confidence intervals (CIs) will be provided for all efficacy estimates. [redacted]<br><br>~~The analyses of the primary and secondary endpoints of all subjects including those from Japan and China will include baseline body weight as a factor in the model. Therefore, although the subjects coming from Japan and China may not be balanced by the body weight groups (<90 kg or ≥90 kg), analyses of the endpoints will be adjusted for any effect of the baseline body weight on efficacy.~~**Due to small sample sizes in China and Japan and differences in stratification factors, analyses will be stratified by a combination of the stratification factors used in randomization. The stratified levels are provided below:**<br><br>▪ **US/PRIOR USE/< 90 KG**<br>▪ **US/PRIOR USE/>=90 KG**<br>▪ **US/NAÏVE/<90 KG**<br>▪ **US/NAÏVE/>=90 KG** | Removed plot description to allow flexibility in data presentation plan.<br><br>Clarified the language for testing of secondary endpoints.<br><br>Updated the stratification levels to a combination stratification factor due to small sample sizes in China and Japan. |

| | | |
|---|---|---|
| | ▪ **ROW/PRIOR USE/< 90 KG**<br>▪ **ROW/PRIOR USE/>=90 KG**<br>▪ **ROW/NAÏVE/<90 KG**<br>▪ **ROW/NAÏVE/>=90 KG**<br>▪ **JAPAN/PRIOR USE**<br>▪ **JAPAN/NAÏVE**<br>▪ **CHINA/PRIOR USE**<br>▪ **CHINA/NAÏVE**<br>**If there is not at least one subject per treatment group in each of the China and Japan strata, then these regions will be collapsed together to form the following stratified levels for analyses:**<br>▪ **US/PRIOR USE/< 90 KG**<br>▪ **US/PRIOR USE/>=90 KG**<br>▪ **US/NAÏVE/<90 KG**<br>▪ **US/NAÏVE/>=90 KG**<br>▪ **ROW/PRIOR USE/< 90 KG**<br>▪ **ROW/PRIOR USE/>=90 KG**<br>▪ **ROW/NAÏVE/<90 KG**<br>▪ **ROW/NAÏVE/>=90 KG**<br>▪ **ASIA/PRIOR USE**<br>▪ **ASIA/NAÏVE** | |
| 6.1.1 Primary Endpoints<br>6.1.1.1 Primary Analysis | Analysis Model<br>A stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare the sPGA 0/1 response rates at Week 16 between BMS-986165 6 mg QD and placebo **using the stratification factors from IRT specified in Section 6.1**. ~~The following prognostic factors are included in the model: geographic region (U.S., Japan, China, Rest of World), body weight (<90 kg, ≥90 kg) and prior biologic use (yes/no).~~ The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the odds in the placebo group) and the corresponding 2-sided 95% CIs and p-values will be reported. Additionally, treatment differences in proportions and the 95% CI for the treatment difference will be provided. The common treatment difference in proportion with the confidence interval, common odds ratio with the confidence interval and p-value will be estimated by the Mantel-Haenszel method consistently.<br>A similar analysis will be performed to compare the PASI 75 response rates at Week 16 between BMS-986165 6mg QD and placebo.<br>Imputation Methodology<br>Non-responder imputation (NRI) will be used for coprimary efficacy endpoints for subjects who:<br>• Discontinue treatment or study prior to Week 16 | Clarified stratification to be used and removed prohibited medication criteria. |

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| | ~~• Start a protocol prohibited medication/therapy that could improve psoriasis during the first 16 weeks of treatment, or~~<br>• Have missing Week 16 endpoint data for any reason<br>~~Subjects taking protocol prohibited medications during the first 16 weeks of treatment will be identified prior to database lock and treatment unblinding.~~ NRI will be used as the primary method of imputation for the coprimary efficacy endpoints. | |
| 6.1.1.2 Sensitivity Analyses | As a method to assess the sensitivity of the primary imputation method for the coprimary endpoints, further imputation methods will be used to impute Week 16 data in subjects who:<br>• Discontinue treatment or study prior to Week 16<br>~~• Start a protocol prohibited medication/therapy that could improve psoriasis during the first 16 weeks of treatment, or~~<br>• Have missing Week 16 endpoint data for any reason<br><u>Tipping Point Analysis</u><br>Tipping point analysis will further be used to assess the robustness of the primary study results. Different number of events between treatment groups will be assessed until the study conclusion is changed. Each imputed value is initially imputed as a responder. The imputed values in the placebo group will remain as responders while the BMS-986165 imputed values are replaced as a nonresponders one at a time, therefore changing the number of events between groups. Once all imputed values in the BMS-986165 group have been replaced with nonresponders values, the data will reset to where the BMS-986165 group imputed values are all responders and one by one the imputed values in the placebo group are replaced with a nonresponder until all placebo are nonresponders and all BMS-986165 are responders. Furthermore, every pair of imputations between the placebo and BMS-986165 groups will be assessed similarly, creating a matrix of possible patterns.<br>At each iteration, the statistical analysis is assessed, and the direction of the analysis is recorded. A graph will be provided to identify at what point to which the difference in events cause a direction shift in study results. **The tipping point analyses will be based on a two-sample chi-square test approach rather than a stratified CMH test approach for simplicity of the analysis.**<br><br>**<u>Multiple Imputation</u>**<br>**Multiple imputation (MI) will be used for sensitivity analyses for each of the coprimary efficacy endpoints, PASI 75 response at Week 16 and sPGA 0/1 response at Week 16. Multiple imputation of missing data for PASI 75 response and sPGA 0/1 response will be performed by fully conditional specification (FCS) using PROC MI in SAS with the FCS option. The FCS MI specifies the multivariate imputation model on a variable-by-variable basis by a set of conditional densities. For each missing value at Week *X*, the FCS MI will generate values from a conditional distribution for the missing data given the other data prior to** | Removed prohibited medication criteria.<br>Provided some clarification for the tipping point analysis.<br>Added a sensitivity analysis for multiple imputation. |

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| | **Week *X*. The FCS MI model will include treatment group and stratification factors for randomization. A total of 1000 imputed (complete) datasets will be generated for the MI analysis. The same test procedure used for the main analysis (CMH test), will be used to analyze the responder endpoint from each imputed dataset. SAS PROC MIANALYZE will be used to pool the results from the CMH tests and generate an overall result by Rubin's rules (1987).** | |
| 6.1.1.3 Supportive Analyses | ~~Additional Analysis~~<br><br>~~Additionally, a logistic regression model will be used to compare the sPGA 0/1 response rates at Week 16 between BMS-986165 6mg QD and placebo. The prognostic factors will be included in the model as covariates. The estimated odds of response with corresponding 2-sided 95% CIs and p-values will be reported. A similar analysis will be performed on the PASI 75 response rates at Week 16. These analyses will be performed on the FAS.~~ | Removed this analysis since it similar to CMH analysis. |
| 6.1.2 Key Secondary Endpoints<br><br>6.1.2.1 Binary Endpoints | Analysis Model<br><br>CMH tests will be used to compare response rates between either BMS-986165 6mg QD and placebo or apremilast **using the stratification factors from IRT specified in Section 6.1**. ~~The following prognostic factors are included in the model: geographic region (U.S., Japan, China, Rest of World), body weight (<90 kg, ≥90 kg) and prior biologic use (yes/no).~~ The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the odds in the placebo **or apremilast** group) and the corresponding 2-sided 95% CIs and p-values will be reported. Additionally, treatment differences in proportions and the 95% CI for the treatment difference will be provided ~~from Chi-square tests~~.<br><br>Imputation Methodology for Week 16 Endpoints<br><br>NRI will be used for ~~coprimary~~**key secondary** efficacy endpoints for subjects who:<br><br>• Discontinue treatment or study prior to Week 16<br>• ~~Start a protocol prohibited medication/therapy that could improve psoriasis during the first 16 weeks of treatment, or~~<br>• Have missing Week 16 endpoint data for any reason<br><br>~~Subjects taking protocol prohibited medications during the first 16 weeks of treatment will be identified prior to database lock and treatment unblinding. NRI will be used as the primary method of imputation for the coprimaryefficacy endpoints.~~<br><br>**Imputation Methodology for Week 24 Endpoints (for comparison of BMS-986165 6 mg QD to apremilast)**<br><br>**NRI will be used for key secondary efficacy endpoints for subjects who:**<br><br>• **Discontinue treatment or study prior to Week 24**<br>• **Have missing Week 24 endpoint data for any reason** | Clarified stratification to be used and removed prohibited medication criteria.<br><br>Corrected coprimary to key secondary.<br><br>Added imputation for Week 24 endpoints.<br><br>Add clarifications for imputations of Week 52 endpoints and definition for meeting response criteria. |

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| | Imputation Methodology for Week 52 Endpoints **(for comparison of BMS-986165 6 mg QD to apremilast)**<br><br>**The key secondary endpoints included in this analysis are the following:**<br><br>• **sPGA 0/1 response with at least a 2-point improvement from baseline at Week 52 and at Week 24**<br>• **PASI 75 response at Week 52 and at Week 24**<br>• **PASI 90 response at Week 52 and at Week 24**<br><br>**Subjects must meet response criteria at both Weeks 24 and 52 in order to be considered a responder. Those who do not meet response criteria at both weeks will be considered a nonresponder.** NRI will be used for **the above** key secondary endpoints for subjects who:<br><br>• Discontinue treatment or study prior to Week 52<br>• ~~Start a protocol prohibited medication/therapy that could improve psoriasis during the first 52 weeks of treatment, or~~<br>• Have missing Week 52 or Week 24 endpoint data<br>• **Switch from apremilast to BMS-986165 at Week 24 for Week 24 PASI 50 nonresponders**<br><br>~~Subjects taking protocol prohibited medications will be identified prior to database lock and treatment unblinding.~~ | |
| 6.1.2.2 Continuous Endpoints | Analysis Model<br><br>Analysis of covariance (ANCOVA) models will be used to compare the change between BMS-986165 6 mg QD and placebo or between BMS-986165 6 mg QD and apremilast **at Week 16**. Treatment group will be included in the model as well as the **stratification factors from IRT specified in Section 6.1**~~following baseline prognostic factors: geographic region (U.S., Japan, China, Rest of World), body weight (<90 kg, ≥90 kg) and prior biologic use (yes/no)~~ and will be considered as fixed effects. The baseline value will be added into the model as a covariate. The adjusted least-squares (LS) means as well as the treatment differences based on LS means and the corresponding 2-sided 95% CIs will be provided for the difference between BMS-986165 6 mg QD and placebo or apremilast.<br><br>Imputation Methodology **for Week 16 Endpoints**<br><br>For continuous **key** secondary endpoints, a modified baseline observation carried forward (mBOCF) approach will be used for missing data. The baseline observation will be carried forward for subjects who discontinue study treatment **prior to Week 16** due to:<br><br>• Lack of efficacy<br>• AEs<br><br>Subjects who discontinue study treatment **prior to Week 16** for other reasons **or who have a missing Week 16 value** will have the last valid observation carried forward (including the baseline value as applicable). | Clarified stratification to be used and removed prohibited medication criteria.<br><br>Added a clarification that subjects with missing baseline values will be excluded from the analysis for change from baseline endpoint. |

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| | ~~For subjects who start a protocol prohibited medication/therapy that could improve psoriasis prior to the endpoint will also have their endpoint value imputed as the baseline value. The last valid observation will be carried forward for all other subjects with missing data.~~ **Subjects with a missing baseline value will be excluded from the analysis for the change from baseline endpoint.** | |

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| 6.1.4 Subgroup Analyses | Subgroup analyses will be performed on the coprimary endpoints using the FAS. The primary imputation method will be applied for these analyses. The CMH test The CMH test **using the stratification factors from IRT** will be the analysis method used where the stratification factor is the specified subgroup.will be the analysis method used ~~where the stratification factor is the specified subgroup~~. The following subgroups will be considered:<br>• Geographic region (U.S., Japan, China, Rest of World)<br>• Country<br>• Sex (male, female)<br>• Age group (<65 y, ≥65 y)<br>• Body weight (<90 kg, ≥90 kg) **– from case report form**<br>• Race<br>• Prior biologic use for psoriasis, psoriatic arthritis and other inflammatory diseases only (yes, no) **– from case report form**<br>• **Prior systemic treatment use (yes/no)**<br>• **Prior phototherapy use (yes/no)**<br>• sPGA (3, 4)<br>• PASI score (≤20, >20)<br>• BSA involvement (10-20, >20) | Removed some subgroups that will not be analyzed.<br>Clarified weight and prior biologic use to be taken from CRF and stratification factors for the CMH statement will use IRT stratification factors. |

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| | ~~• DLQI (0-5, 6-10, 11-30)~~<br>• Duration of disease (< 10 y, ≥ 10 y)<br>• Age at disease onset (<18, 18-39, ≥40)<br>~~• Smoking status:~~<br>~~Currently non-smoker – never smoked or quit smoking ≥6 months from the 1st treatment~~<br>~~Currently non-daily smoker or light smoker - smoked on no more than 25 days in the previous 30 days to < 5 cigarettes per day~~<br>~~• Currently moderate to heavy smoker – ≥10 cigarettes per day~~ | |

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| 6.2.1 Adverse Events | Adverse events ~~(AE)~~ will be presented for the number and percentage of subjects and the number of events. ~~All adverse events (t~~**T**reatment-emergent ~~[TEAE] and non-treatment emergent)~~ will be provided in listings. Summary tables will be reported in decreasing frequency based on the ~~total~~ **BMS-986165** column. Counting for frequency analysis will be by subject and not by AEs, and subjects are only counted once for recurring AEs within each system organ class (SOC) or preferred term (PT); however, the number of total AEs per subject, including multiple occurrences of individual AEs, will also be presented. For summaries of severity, AEs will be reported only at their maximum severity in each subject. Subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.<br><br>An overall summary for the following categories will be presented:<br>~~• Subjects with at least one TEAE~~<br>~~• Subjects with at least one related TEAE~~<br>~~• Subjects with at least one treatment-emergent SAE~~<br>~~• Subjects with at least one related treatment-emergent SAE~~<br>~~• Subjects discontinuing study treatment due to a TEAE~~<br>~~• Subjects discontinuing from study due to a TEAE~~<br>~~• Subjects who died due to an AE~~<br>~~• Subjects who died due to a TEAE~~<br>• **Deaths**<br>• **SAEs**<br>• **Related SAEs**<br>• **AEs**<br>• **Related AEs**<br>• **Discontinued treatment due to AEs**<br><br>~~A summary of TEAEs leading to discontinuation of study treatment or study will be provided, grouped by SOC and PT for all TEAEs and treatment-related TEAEs.~~ | Modified text for overall summary to align with the data presentation plan.<br><br>TEAEs leading to discontinuation was removed from this section as this is described in a separate section. |
| 6.2.1.1 Adverse Events of Interest (AEI) **and Other Important AEs** | Summaries for treatment-emergent AEIs events will be provided **by PT** for each AEI category~~for the following~~:<br>~~• TEAEs by SOC and PT~~<br>~~Skin Events~~<br>~~The number and percentage of subjects reporting each type of skin event and the corresponding location will be summarized.~~<br>~~Infections~~ | Modified the text for the final list of adverse events of interest and the adjudicated cardiovascular events. |

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| | ~~The number and percentage of subjects reporting infections will be summarized.~~<br><br>~~Creatine kinase (CK) elevation~~<br><br>~~The number and percentage of subjects reporting CK elevations will be summarized.~~<br><br>~~Malignancies~~<br><br>~~The number and percentage of subjects reporting malignancies will be summarized.~~<br><br>~~Cardiovascular~~<br><br>~~The number and percentage of subjects reporting cardiovascular event will be summarized.~~<br><br>• **Skin-related events**<br>• **Infection events**<br>• **Malignancy events**<br><br>**Creatine kinase (CK) elevation for CK elevation >2.5 upper limit of normal will be summarized as CTCAE grade 2 or higher in the clinical laboratory summaries.**<br><br>**Additional information collected for some events as part of the clinical safety program and adjudicated events will also be summarized.** | |
| 6.2.1.2 Serious Adverse Events | Summaries for treatment-emergent SAEs will be provided for the following:<br><br>• Treatment-emergent SAEs by SOC and PT<br>• ~~Treatment-related treatment-emergent SAEs by SOC and PT~~ | Aligned with the Data Presentation Plan |
| 6.2.1.3 Adverse Events Leading to Discontinuation of Study Treatment **or Study Treatment Interruption** | Summaries for TEAEs leading to discontinuation of study treatment will be provided for the following:<br><br>• TEAEs by SOC and PT<br>• ~~Treatment-related TEAEs by SOC and PT~~<br><br>**Summaries for TEAEs leading to study treatment interruption will be provided for the following:**<br><br>• **TEAEs by SOC and PT** | Added summary for TEAEs leading to study treatment interruption and aligned with the Data Presentation Plan. |
| 6.2.3 Clinical Laboratory Data | Laboratory parameters will be summarized using the International System (SI) of Units~~, unless otherwise specified~~ **and US conventional units**. Data will be summarized by time point, as applicable. The following summaries will be provided for each parameter:<br><br>• Absolute and change from baseline values for continuous parameters<br>• Number and percentage of subjects for the following:<br>~~o Categorical urinalysis parameter results~~ | Added summaries for US conventional units.<br><br>Removed urinalysis categorical summaries to align with data |

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| | o Maximum postbaseline CTCAE grade for each applicable laboratory parameter **through Week 16**<br>o Shifts from baseline based on maximum postbaseline CTCAE grade **through Week 16**<br>• Drug-induced Liver Injury (DILI) and Hy's Law summaries<br>All laboratory data specified in the summary tables will be present in listings. | presentation plan.<br>Added additional clarifications to align with data presentation plan. |
| 6.2.4 Vital Signs and Physical Findings | Vital signs**, including weight,** will be summarized by time point, as applicable. The following summaries will be provided for each parameter: | Clarified that weight will be summarized. |
| 6.2.6 Other Safety Data<br>6.2.6.1 PHQ-8 | PHQ-8 total score will be summarized by time point, as applicable. The following summaries will be provided:<br>• Absolute and change from baseline values<br>• Number and percentage of subjects:<br>o Shifts from none, mild, moderate, moderately severe and severe scores at baseline and at each time point<br>~~o PHQ-8 total scores ≥ 15~~ | Removed PHQ-8 total score >=15 summaries as this is provided in the shift summary. |
| 6.2.6.2 eC-SSRS | Suicidal ideation and behavior individual item responses will be summarized by time point, as applicable. The following summaries will be provided:<br>• Number and percentage of subjects with positive responses on suicidal ideation and/or suicidal behavior **questions**~~responses~~ **for each question and overall all questions within suicidal ideation and suicidal behavior**<br>• **Shifts from baseline based on maximum postbaseline response through Week 16**<br>• **Worst postbaseline value for suicidal ideation and behavior through Week 16** | Additional analyses have been added for eC-SSRS. |
| 6.3.1 Subject Populations and Disposition | The number of subjects enrolled/screened and the number and percentage of subjects randomized, treated, and in each analysis population will be presented. The number and percentage of subjects randomized in each region, country, and site will be presented.<br>Additionally, the following summaries will be provided for the FAS by treatment group and overall:<br>~~• Number and percentage of subjects on treatment at each visit week~~ | Aligned this section with the summaries in the Data Presentation Plan |
| 6.3.2 Demographic and Baseline Characteristics | Demographic **and baseline** characteristics will be summarized by treatment group for **the FAS** ~~all of the analysis populations~~**.** Demographic and baseline characteristics include the following:<br>• **Prior systemic treatment use (yes/no)**<br>• **Prior phototherapy use (yes/no)** | Updated populations to be used for summaries and removed baseline |

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| | ~~• DLQI (0-5, 6-10, 11-30)~~<br>~~• Smoking status (Current daily smoker and whether heavy vs. light, Current occasional smoker, former smoker, never smoker, smoker current status unknown, unknown if ever smoked)~~<br><br>Additional demographics or baseline data may be added to summary tables.<br><br>General medical history and medical history related to PsA will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). General medical history data will be summarized for each SOC and PT by treatment group and overall for the FAS ~~and Safety Set populations~~. Separate tables will be provided for ~~general~~ **psoriasis** medical history. | characteristic that will not be summarized. |
| 6.3.3 Prior and Concomitant Medications | Prior and concomitant medications will be coded according to World Health Organization-Drug Dictionary WHO-DD (version at the time of DBL) and will be summarized by Anatomic Therapeutic Classification (ATC) and preferred term (PT) by treatment group for the **As-treated population**~~FAS~~. The number and percentage of subjects using at least one medication and each medication will be displayed by treatment group. Subjects taking more than one medication within the same ATC or PT will be counted once.**Summaries will be provided for prior medications and medications that started prior to first treatment and were ongoing after first treatment start date as well as concomitant medications.** | Clarified summaries to be provided and the population to be used for the summaries. |
| 6.3.3.1 Psoriasis, Psoriatic Arthritis and Other Inflammatory Disease Related Systemic Medications | Prior **medications and medications that started prior to first treatment and were ongoing after first treatment start date for** systemic biologic and non-biologic medications will be summarized as described above for the number and percentage of subjects using each reported medication. Concomitant use of DMARDs like methotrexate will be summarized. | Added clarification for prior and ongoing medications to be summarized. |
| 6.3.3.2 Concomitant Corticosteroid Use | Additionally, corticosteroids will be summarized by ATC and PT ~~for the FAS~~. | Removed reference to analysis population as this is redundant information with Section 6.3.3. |
| 6.3.4 Exposure<br><br>6.3.4.1 Duration of Treatment | Duration by GroupOverall duration of each treatment, in days, will be calculated for each subject in each treatment group. Subjects are dispensed study treatment at each visit, starting with Day 1 (Week 0) and at each subsequent visit~~. Subjects are also to record daily dosing in an eDiary.~~ The ~~Day 1 dispensed date will be considered as the~~ date of first dose of study treatment **is the Week 0 PK dosing date** and is recorded on the eCRF. **If this date is missing, then the** | Updates to duration of exposure formula's were made to align with the manner in |

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| | **earliest drug dispensation date will be used.** The last **dose** date ~~of dose~~ is ~~defined as the last day a subject received drug and is~~ recorded on the end of treatment page in the eCRF. **If this date is missing, then the latest date from the [redacted] page or drug accountability return date will be used.**<br><br>~~If the date of last dose of study treatment is missing, i.e.: subject lost to follow-up, the end of study date or last contact date (whichever comes first) will be used to calculate duration of treatment.~~ Duration of treatment will be summarized descriptively by **randomized** treatment group.<br><br>Placebo:For subjects randomized to placebo, ~~the Week 16 date will be used as the date of last dose of placebo. Formula for~~ duration is defined as:<br><br>• Placebo = **Date of last dose of placebo** ~~Week 16 date~~ – date of first dose +1<br><br>• BMS-986165 = Date of last dose of BMS-986165 – ~~Week 16 date~~**date of first dose of BMS-986165 +1**<br><br>~~If a placebo subject discontinues study treatment on or before the Week 16 visit, the date of last dose will be used to calculate the duration of placebo.~~<br><br>**Apremilast:**<br><br>For subjects randomized to apremilast, the Week 24 date will be used as the date of last dose of apremilast and the date of first dose of either apremilast or BMS-986165 for the subsequent period. Subjects who receive apremilast at Week 24 through to Week 52 will be counted as a sum of the first 24 weeks of treatment and the next treatment period.<br><br>• Apremilast (Wk 0 through Wk 24) = Week 24 date – date of first dose +1<br><br>• Apremilast (Wk 24 through Wk 52) = Date of last dose – Week 24 date<br><br>• Total Apremilast = **Duration of ~~A~~a**premilast Wk 0-24 + **duration of** apremilast Wk 24-52<br><br>BMS-986165 = Date of last dose of BMS-986165 – Week 24 date<br><br>Duration by Period<br><br>Overall duration (in days) of each treatment received within each study period will be calculated. Duration within each period is defined for each treatment group as:<br><br>$$Last\ dose\ date\ \boldsymbol{in\ period} - first\ dose\ date\ \boldsymbol{in\ period} + 1$$<br><br>~~Subjects are dispensed study treatment at each visit, starting with Day 1 (Week 0) and at each subsequent visit. Subjects are also to record daily dosing in an eDiary. The dispensed drug date of Day 1 of the study period will be considered as the date of first dose of study treatment for that period and is recorded on the eCRF. The last date of dose within the period will be considered as the day prior to the next period start date.~~ | which data will be summarized. |

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| | ~~If the date of last dose of study treatment is missing, i.e.: subject lost to follow-up, the end of study date or last contact date (whichever comes first) will be used to calculate duration of treatment.~~ | |
| 6.3.4.2 Summary of Dosing | The number of doses taken for each subject for each period will be determined using the eCRF drug accountability data and is defined as:<br>$Doses\ Taken = \frac{(number\ of\ tablets\ dispensed - number\ of\ tablets\ returned)}{~~3~~}$<br>The number of doses taken will be summarized descriptively by treatment group **within each study period and overall**. | Clarified how data will be summarized. |
| 6.3.4.3 Compliance | Treatment compliance will be determined from data captured on the Drug Accountability eCRF.<br>~~The number and percentage of subjects who have missed at least one dose will be provided.~~<br>~~Additionally, descriptive statistics for the number of missed doses within each treatment period and overall will be provided by treatment group. The number of missed doses for each subject will be calculated for each period.~~<br>$Number\ of\ expected\ doses: (date\ of\ next\ visit - date\ of\ current\ visit) x3$<br>~~$Number\ of\ missed\ doses: Number\ of\ expected\ doses - number\ of\ doses\ taken$~~<br>Treatment compliance will be derived for each period ~~and overall~~. Compliance is defined as:<br>$\left(\frac{Number\ of\ doses\ taken}{Number\ of\ expected\ doses}\right) x100$<br>Period compliance will be calculated by summing over all visits within the period ~~and overall compliance will be calculated by summing each visit in the study~~ and summarized using descriptive statistics by treatment group. The number and percentage of subjects with <~~80~~**75**%, ~~80~~**75**% to 1**20**0%, and >1**20**0% compliance will be provided by treatment group for each ~~visit,~~ period ~~and overall~~. **If a subject does not return the container, then this dispensation event will be excluded in the calculation for the total number of doses taken, total number of expected doses, and total compliance.** | Clarified how data will be summarized. |

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| 6.6 Statistical Impacts Due to COVID-19<br>6.61 Impact on Efficacy Endpoints<br>6.6.2 Impact on Safety Endpoints | **Statistical Impacts Due to COVID-19**<br>**Impact on Efficacy Endpoints**<br>**There are no COVID-19-related impacts to the Week 16 and Week 24 endpoints as all subjects remaining in the trial completed these visits prior to COVID-19 restrictions. Key secondary efficacy endpoints involving later visits may be impacted by COVID-19 in the form of missing data and/or a treatment assignment defaulting to BMS-986165. If a subject has missing data or is switched to BMS-986165 from a different treatment due to Covid-19 during the Week 24 through Week 52 period, the subject will be excluded from the analysis.**<br>**Key secondary efficacy endpoints that may be impacted include the following:**<br>• **sPGA 0/1 response at Week 52 and at Week 24**<br>• **PASI 75 response at Week 52 and at Week 24**<br>• **PASI 90 response at Week 52 and at Week 24**<br>**A sensitivity analysis will also be performed for the above endpoints using the last observed value. The data handling rules to be used are as follows for subjects with missing data or for those who switch to BMS-986165 from a different treatment due to COVID-19:**<br>• **If the subject is missing the Week 52 response value (ie, sPGA 0/1, PASI 75, PASI 90), then the last observed response value during the Week 24 through Week 52 period will be carried forward to the Week 52 value**<br>• **If the subject is switched to BMS-986165 from a different treatment due to COVID-19, then the last observed response value prior to the switch will be carried forward to the Week 52 value**<br>[redacted] | New section added to address COVID-19. |

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| | [redacted]<br><br>**Time to first loss endpoints include:**<br>• **Time to first loss of PASI 75 among subjects that are PASI 75 responders at Week 24**<br>• **Time to first loss of sPGA 0/1 among subjects that are sPGA 0/1 responders at Week 24 where loss of sPGA 0/1 is defined as an sPGA score ≥ 2 (sPGA scores are rounded to the nearest whole number)**<br>**Impact on Safety Endpoints**<br>**No modifications will be made for the analysis of safety data due to COVID-19-related issues. There will not be any additional safety data handling considerations for missing data or treatment interruptions due to COVID-19.** | |
| 7.2 Sequence of Planned Analyses | [redacted] | |
| 7.2.2 Final Analyses and Reporting | **Analyses of the palmoplantar pp-PGA 0/1 endpoint are provided for descriptive purposes within the individual CSR due to small sample sizes. A pooled analysis of data from IM011046 and IM011047 will be conducted for the submission.** | Added clarification for the analyses of palmoplantar (pp-PGA 0/1 endpoint). |
| 8.1 General Definitions | Study day is calculated as:<br>assessment date – date **of first dose** ~~the subject is randomized~~ + 1<br>Baseline - Unless otherwise stated, Baseline is defined as the ~~last~~ measurement ~~prior to dosing on Day 1~~ **at the randomization visit** (Week 0). If the measurement **at the randomization visit**~~on Day 1~~ is missing~~ or not available~~, then a prior measurement during the screening period may be used as baseline. Baseline assessments must be performed per protocol and standard of care assessments may not be used for baseline.<br>**Baseline for each PSSD question will be calculated as the average value over the 7 days prior to the randomization visit. In the event of missing values in the 7 days prior to the randomization visit, daily scores from at least 4 days out of the 7 days can be used to calculate the average score. If > 3 daily scores in the last 7 days are missing for a particular question, then the baseline value for that question will be missing. If any questions are missing baseline after using the described rule, then the baseline value for the subscore using that** | Updated first and last dose date definitions and other definitions.<br>Added an additional rule for percent change from baseline. |

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| | **question and the baseline value for the total score will be missing.**<br><br>First Dose Date – Study: The date a subject received their first dose on Day 1 as recorded in the eCRF ~~as date study treatment was dispensed~~**Week 0 [redacted] dosing date or the earliest drug dispensation date**.<br><br>First Dose Date – Period: The date a subject received their first dose ~~in the defined study period~~ as recorded in the eCRF ~~as date study treatment was dispensed~~**Week 0 [redacted] dosing date or the earliest drug dispensation date for Treatment Period 1 and earliest drug dispensation date for Treatment Periods 2 and 3**.<br><br>Change from baseline in the maximum post-baseline value is defined as highest observed value **or grade** post-baseline. The change is calculated using this value as the post-baseline value.<br><br>Change in the maximum post-baseline value **or change in the worst post-baseline value: Change from baseline in the worst post-baseline value is defined as worst observed value post-baseline. The change is calculated using this value as the post-baseline value.**<br><br>**If the baseline value is 0 and the post-baseline is >0, then the percent change from baseline value will be missing.**<br><br>EAIR:<br><br>EAIR = 100*~~The number of subjects with a specific event divided by the total exposure time (in years) among the subjects in the treatment group, where the total exposure time in years is calculated by dividing the sum of exposure time in days over all subjects included in the treatment group*~~365.25***(total number of subjects with the AE)/total exposure time for the selected AE under each treatment that a subject is exposed. Where total exposure time for each AE within a treatment is calculated as follows:**<br><br>• **If a subject has at least 1 event while on a particular treatment, then the exposure time for that subject and AE on that treatment is:**<br>  o **First AE onset date – treatment start date (of that particular treatment) +1**<br>• **If a subject does not have an event, exposure time for that AE is:**<br>  o **Treatment stop date (of that particular treatment) – Treatment start date (of that particular treatment) + 1 + 30 days (if subject discontinued or subject completed Period 3 and is not rolling into IM011075 study)**<br>  o **Treatment stop date (of that particular treatment) – Treatment start date (of that particular treatment) + 1 (if subject completed Period 3 and is rolling into IM011075 study)**<br>• **Total exposure time = sum of exposure time for each AE within a treatment** | |

| | | |
|---|---|---|
| 8.2.1.3 Body Surface Area (BSA) | The product of BSA and sPGA will be **calculated**~~derived as a potential proxy measure to PASI scores~~. | Updated the product score language. |
| 8.2.2.1 Psoriasis Symptoms and Signs Diary (PSSD) | **Baseline for each PSSD question will be calculated as the average value over the 7 days prior to the randomization visit. In the event of missing values in the 7 days prior to the randomization visit, daily scores from at least 4 days out of the 7 days can be used to calculate the average score. If > 3 daily scores in the last 7 days are missing for a particular question, then the baseline value for that question will be missing. If any questions are missing baseline after using the described rule, then the baseline value for the subscore using that question and the baseline value for the total score will be missing.** | Clarified baseline definition for PSSD. |

[redacted]

[redacted]

| | | |
|---|---|---|
| 8.2.2.11 Psoriatic Arthritis Screening and Evaluation (PASE) Questionnaire | The PASE questionnaire will be administered at Screening in subjects with peripheral joint complaints. The PASE questionnaire is a self-administered tool that is used to screen for psoriatic arthritis among subjects who have psoriasis. The PASE questionnaire consists of 15 questions subdivided into 7 questions focusing on symptoms of psoriatic arthritis, and 8 questions focusing on the impact of psoriatic arthritis on function. Each question is scored on a 1 to 5 scale, with a maximum symptom sub-scale score of 35, a maximum function sub-scale score of 40 giving a total maximum score of 75. A score of 47 or above has been shown to distinguish between psoriatic arthritis and non-psoriatic arthritis. This questionnaire is only intended to be a screening tool for psoriatic arthritis and does not replace a comprehensive musculoskeletal exam performed by a rheumatologist. **This information will not be summarized.**<br><br>~~Individual score to each of the 15 questions will be collected in the eCOA system. The sub-scale scores and total score will be derived in the analysis datasets.~~ | Clarified that PASE information will not be summarized. |
| 8.2.2.13 electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) | The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) is a computer-automated, patient-reported version of the C-SSRS instrument that defines 11 categories of suicidal ideation and behavior (SIB) events. Categories and definitions are provided in Appendix 23 of the protocol. The categories are as follows:<br>• Suicidal ideation<br>6. **Wish to be dead**~~Passive~~<br>7. **Non-specific active suicidal thoughts**~~Active: Nonspecific (no method, intent, or plan)~~<br>8. **Active suicidal ideation with any methods without intent to act**~~Active: Method, but no intent or plan~~ | Updated descriptions of categories to align with data presentation plan and put behavior categories in proper ascending order. |

| | | |
|---|---|---|
| | 9. **Active suicidal ideation with some intent to act, without specific plan**~~Active: Method and intent, but no plan~~<br>10. **Active suicidal ideation with specific plan and intent**~~Active: Method, intent, and plan~~<br>• Suicidal behavior<br>6. **Preparatory acts or behavior**~~Completed suicide~~<br>7. **Aborted attempt**~~Suicide attempt~~<br>8. Interrupted attempt<br>9. **Actual attempt (Non-fatal)**~~Aborted attempt~~<br>10. **Completed suicide**~~Preparatory actions toward imminent suicidal behaviors~~<br><br>Self-injurious behavior, no suicidal intent | |
| 8.4 Study Periods | Period 1 = ~~the first 16 weeks of treatment~~**Week 0 to Week 16 visit date**<br><br>Period 2 = **Week 16 visit date +1 to Week 24 visit date** ~~after Week 16 to Week 24~~<br><br>Period 3 = **Week 24 visit date +1 to Week 52 visit date**~~after Week 24~~<br><br>**Follow-up = 4 week follow-up period** | Clarified study periods. |
| 8.5 Day Ranges for Analysis Visits | Week 16 100, 127 (or Week 16 drug dispense date ~~if earlier~~)<br>Week 24 156, 183 (or Week 24 drug dispense date ~~if earlier~~) | Clarified Week 16 and Week 24 analysis range criteria |

## Appendix 1 Planned Analyses

| List of Planned Analyses: Comparisons of BMS-986165 6 mg QD vs. Placebo | | |
|---|---|---|
| **Measure of Interest** | **Population** | **Analysis at Week 16** |
| sPGA 0/1 – coprimary<br>PASI 75 - coprimary | FAS | NRI+CMH - primary |
| sPGA 0/1 – coprimary<br>PASI 75 – coprimary | FAS | LOCF+CMH – sensitivity<br>LOCF/NRI+CMH – sensitivity<br>Tipping Point+CMH – sensitivity<br>Multiple Imputation + CMH - sensitivity |
| sPGA 0/1 – coprimary<br>PASI 75 – coprimary | PPS | NRI+CMH - supportive |
| sPGA 0/1 – coprimary<br>PASI 75 - coprimary | FAS | NRI+CMH – subgroups |
| PASI 90 – key secondary | FAS | NRI+CMH |
| sPGA 0 – key secondary | FAS | NRI+CMH |
| ss-PGA 0/1 among subjects with a baseline ss-PGA ≥ 3 – key secondary | FAS | NRI+CMH |
| PSSD symptom score of 0 – key secondary | FAS | NRI+CMH |
| DLQI 0/1 – key secondary (EX-US submission only) | FAS | NRI+CMH |
| PGA-F 0/1 among subjects with a baseline PGA-F ≥ 3 | FAS | NRI+CMH |

| List of Planned Analyses: Comparisons of BMS-986165 6 mg QD vs. Apremilast | | |
|---|---|---|
| **Measure of Interest** | **Population** | **Primary Analysis at Week 16/24/52** |
| sPGA 0/1 at Week 16 – key secondary<br>PASI 75 at Week 16 – key secondary | FAS | NRI+CMH |
| PASI 90 at Week 16 – key secondary | FAS | NRI+CMH |
| Change from baseline in PSSD symptom score at Week 16 – key secondary | FAS | mBOCF+ANCOVA |
| ss-PGA 0/1 among subjects with a baseline ss-PGA ≥ 3 at Week 16 – key secondary | FAS | NRI+CMH |
| sPGA 0 at Week 16 – key secondary | FAS | NRI+CMH |
| PSSD symptom score of 0 at Week 16 – key secondary | FAS | NRI+CMH |
| sPGA 0/1 at Week 24 – key secondary<br>PASI 75 at Week 24 – key secondary | FAS | NRI+CMH |
| PASI 90 at Week 24 – key secondary | FAS | NRI+CMH |
| | | |
| sPGA 0/1 at Week 52 and Week 24 – key secondary | FAS | NRI+CMH |
| PASI 75 at Week 52 and Week 24 – key secondary | FAS | NRI+CMH |

| List of Planned Analyses: Comparisons of BMS-986165 6 mg QD vs. Apremilast | | | |
|---|---|---|---|
| **Measure of Interest** | **Population** | **Primary Analysis at Week 16/24/52** | [redacted] |
| PASI 90 at Week 52 and Week 24 – key secondary | FAS | NRI+CMH | |

## Appendix 2 Summary of Efficacy Assessments

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| sPGA (Sec 8.2.1.1) | sPGA 0/1 with at least 2 point improvement from baseline | W16 | BMS vs. PBO | CMH, sensitivity analyses including tipping point analysis, multiple imputation (Sec 6.1.1.1-3) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | W24/52 | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | [redacted] | | |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | Baseline->W52 over time | BMS vs. apremilast | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | sPGA 0 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | [redacted] | | |
| | [redacted] | | | |
| PASI (Sec 8.2.1.2) | PASI 75 | W16 | BMS vs. PBO | CMH, sensitivity analyses including tipping point analysis, multiple imputation (Sec 6.1.1.1-3) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | W24/52 | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | [redacted] | | |

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| | | [redacted] | | |
| | | Baseline->Week 16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | Baseline->Week 52 over time | BMS vs. apremilast | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | PASI 90 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | W52 | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | Baseline->W52 over time | BMS vs. apremilast | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | PASI 100 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | Baseline->W52 over time | BMS vs. apremilast | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | [redacted] | | | |
| [redacted] | | | | |

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| [redacted] | | | | |
| ss-PGA (Sec 8.2.1.4) | ss-PGA 0/1 among subjects with a baseline ss-PGA ≥3 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | [redacted] | | |
| [redacted] | | | | |
| PGA-F (Sec 8.2.1.6) | PGA-F 0/1 among subjects with a baseline PGA-F score ≥3 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | [redacted] | | |
| [redacted] | | | | |
| pp-PGA (Sec 8.2.1.8) | | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | CMH by Week (Sec 6.1.5.1) |

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| | pp-PGA 0/1 among subjects with a baseline pp-PGA ≥3 | [redacted] | | |
| [redacted] | | | | |
| PSSD / Symptom Score (Sec 8.2.2.1) | PSSD/Symptom 0 among subjects with baseline PSSD/symptom score ≥1 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | [redacted] | | |
| [redacted] | | | | |

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| [redacted] | | | | |
| DLQI (Sec 8.2.2.4) | DLQI 0/1 among subjects with a baseline DLQI score ≥2 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | [redacted] | | |

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| [redacted] | | | | |
| PASE (Sec 8.2.2.11) | PASE | Screening only | | No Analysis |

| | |
|---|---|
| Protocol Number: | IM011047 |
| IND Number: | 131,993 |
| EX-US | Non-IND |
| EUDRACT Number: | 2018-001925-24 |
| Date, Version: | 21 May 2020, Global Protocol v7.0, Revised Protocol 09 Final Approved |

# Clinical Protocol IM011047

A Multi-Center, Randomized, Double-Blind, Placebo- and Active Comparator-Controlled Phase 3 Study with Randomized Withdrawal and Retreatment to Evaluate the Efficacy and Safety of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis

**Short Title**: Efficacy, Safety, and Durability of Response of BMS-986165 versus Placebo and Active Comparator in Subjects with Psoriasis

| Clinical Trial Physician | Medical Monitor |
|---|---|
| [redacted] | |

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## DOCUMENT HISTORY

| Document | Date of Issue | Approver(s) | Summary of Change |
|---|---|---|---|
| Original Protocol | 11-May-2018 | [redacted] | Not applicable |
| Amendment 01 | 15-June-2018 | | Clarified that Psoriasis Symptoms and Signs Diary (PSSD) daily data collection will begin at the Screening Visit and, for randomized subjects, will continue daily through Week 52. |
| Amendment 02 | 20-Nov-2018 | | Updated the Sponsor's contact information, made typographic corrections to the protocol, clarified certain procedures, updated wording in Appendix 3 to be consistent across studies of BMS-986165, described treatment assignment details, and revised certain exclusion criteria to be consistent with certain elements of the Phase 2 study of BMS-986165 in psoriasis as well as other Phase 3 studies in psoriasis |
| Amendment 03 | 12-Dec-2018 | | German-Specific Amendment |

| | | | |
|---|---|---|---|
| | | [redacted] | |
| Amendment 04 | 13-Mar-2019 | [redacted] | Italy-Specific Amendment |
| Amendment 05 | 14-May-2019 | | As this is designed to be a global study across multiple countries, randomization in each country will be targeted to approximately 35% or less of the total sample size. This change is being implemented to achieve geographical representation across countries and to minimize the potential for any single country to have a disproportionate impact on the overall efficacy and/or safety profile.<br>Other changes include:<br>-Updated text in the definition of sPGA in Section 8.1.1.1 to be consistent with the description in Appendix 5.<br>-Updated the description for the following endpoints: 'Time to relapse until Week 52' and 'Time to rebound in subjects re-randomized to placebo' |

| | | | |
|---|---|---|---|
| | | | -Added the 'Time to relapse until Week 52' endpoint to Section 9.3.2.1 and to the Testing Order of Key Secondary Endpoints table in Section 9.4.3 in place of the 'Maintenance of PASI 75' endpoint.<br>[redacted]<br>-Section 9.4.4 was updated to define relapse during the Randomized Withdrawal and Maintenance Period. |
| Amendment 06 | 06-June-2019 | [redacted] | Revised the testing order (hierarchy) of key secondary endpoints [redacted] and revised the text in Sections 9.3.2.1 and 9.3.2.2 accordingly as follows:<br>• Removed endpoints containing 'PSSD sign score.' The reason for this change is that PSSD sign score is redundant with components assessed by PASI and sPGA which are already in the hierarchy.<br>• Removed 'change from baseline in DLQI score.' The reason for this change is that DLQI endpoint 'DLQI 0/1 among subjects with baseline DLQI score ≥2' is clinically meaningful and is already in the hierarchy. |
| Amendment 07 | 12-Jul-2019 | [redacted] | Germany-Specific Amendment – Included changes listed above for Global Amendment 02, 05 and 06. |

| | | | |
|---|---|---|---|
| Global Revised Protocol 08 | 17-Dec-2019 | [redacted] | Made the following updates:<br>• provided clarifications in the protocol to aid sites and subjects in the conduct of the study.<br>• added and updated relevant protocol deviation criteria for the Per Protocol Set<br>• corrected typographical errors<br>• added a new analysis for systemic treatment-naïve subjects to the set of subgroup analysis for the coprimary efficacy endpoints |
| Global Revised Protocol 09<br><br>(im011047-revprot07) | 21-May-2020 | [redacted] | This global protocol amendment outlines changes for subjects who are unable or unwilling to attend protocol-specified trial visits and procedures during the COVID-19 pandemic, including:<br>• method of study treatment assignment when COVID-19 related issues result in the Week 24 visit and/or subsequent visits being missed or conducted<br>• statistical impacts due to COVID-19 |

## SUMMARY OF CHANGES

**Rationale:**

The primary purpose of this global revised protocol is to outline changes resulting from visits being missed or conducted remotely due to the COVID-19 pandemic, including:

- method of study treatment assignment when COVID-19-related issues result in the Week 24 and/or subsequent visits being missed or conducted remotely
- statistical impacts due to COVID-19

Changes made to the previous version of the global protocol and the rationale for these changes are noted below in the summary of key changes table. All changes applied to the protocol body were applied to the synopsis, as necessary; synopsis changes are not included in the summary of key changes table. Only major additions and deletions are provided in this summary document; all minor grammatical, formatting, stylistic changes, or clarifications as well as organizational changes are not included.

| Protocol Section | Revised Protocol Text | Rationale for Change |
|---|---|---|
| 6.2.1 Method of Study Treatment Assignment at Week 24 and Subsequent Visits Impacted by COVID-19-related Issues | New Section Text:<br>**6.2.1 Method of Study Treatment Assignment at Week 24 and Subsequent Visits Impacted by COVID-19-related Issues**<br>At Week 24, when COVID-19-related issues result in the subject visit being missed or conducted remotely the study treatment assigned by the IRT system will not be determined by the PASI 75 response, because PASI assessments will not be done. The study treatment assigned by the IRT system will be defaulted to BMS-986165 6 mg QD for the duration of the study.<br>For all subsequent visits post Week 24, when COVID-19-related issues result in the subject visit being missed or conducted remotely, the study treatment assigned by the IRT system will not be determined by the PASI relapse response, because PASI assessments will not be done. Study treatment assignment will be done as per the following:<br>o <u>Missed visits:</u> the study treatment assigned by the IRT system will be the study treatment assigned at the previous visit<br>o <u>Visits conducted remotely:</u> the study treatment assigned by the IRT system will be defaulted to BMS-986165 6 mg QD for the duration of the study | To address study treatment assignment at Week 24 and post Week 24 for subjects who have visits missed or conducted remotely. |

| Protocol Section | Revised Protocol Text | Rationale for Change |
|---|---|---|
| 9.8 Statistical Impacts Due to COVID-19<br><br>9.8.1 Impact on Efficacy Endpoints<br><br>9.8.2 Impact on Safety Variables | New Section Text:<br>**9.8 Statistical Impacts Due to COVID-19**<br>**9.8.1 *Impact on Efficacy Endpoints***<br>There are no COVID-19-related impacts to the Week 16 efficacy endpoints as all subjects remaining in the trial completed the Week 16 visit prior to COVID-19 site restrictions. Efficacy endpoints involving Week 24 and later visits may be impacted by COVID-19 in the form of missing data and/or study treatment assignment defaulting to BMS-986165.<br>Censoring rules will be applied to the PASI 75 time-to-relapse endpoint for re-randomized subjects due to the following COVID-19-related issues post Week 24:<br>• Subject's study treatment assignment was defaulted to BMS-986165 because they had a remote safety monitoring visit due to COVID-19 and efficacy assessments were not performed. The subject will be censored at the time of the remote visit if relapse had not been observed already;<br>• Subject has missing visit(s) (ie, efficacy assessments not performed) after Week 24 and assuming relapse was not observed prior to missed visit(s):<br>o If the subject returns at a later visit and is found to have relapsed, midpoint imputation will be used to determine time-to-relapse (ie, midpoint of the censoring interval).<br>o If the subject returns at a later visit and has not relapsed, then the subject will continue to be evaluated for relapse.<br>o If the subject is discontinued from study treatment, then the subject will be censored at the time of study treatment discontinuation.<br>Sensitivity analyses for time-to-relapse may be performed with additional details provided in the statistical analysis plan prior to database lock.<br>Data handling due to COVID-19-related issues for other efficacy endpoints [redacted] will be described in the statistical analysis plan prior to database lock.<br>***9.8.2 Impact on Safety Variables***<br>No modifications are planned for the analysis of safety data due to COVID-19-related issues. There will not be any additional safety data handling considerations for missing data or treatment interruptions due to COVID-19. | To specify impact on efficacy endpoints and safety variables due to COVID-19. |

## TABLE OF CONTENTS

[redacted]

## LIST OF TABLES



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## LIST OF FIGURES

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:** A Multi-Center, Randomized, Double-Blind, Placebo- and Active Comparator-Controlled Phase 3 Study with Randomized Withdrawal and Retreatment to Evaluate the Efficacy and Safety of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis

**Short Title:** Efficacy, Safety, and Durability of Response of BMS-986165 versus Placebo and Active Comparator in Subjects with Psoriasis

**Study Phase:** 3

**Rationale:**

BMS-986165 could be a therapeutic option for the treatment of subjects with moderate-to-severe plaque psoriasis based on results of a recently completed 12-week randomized Phase 2, placebo-controlled, parallel-group study (Study IM011011) with 5 different BMS-986165 treatment arms: 3 mg every other day (QOD); 3 mg once daily (QD); 3 mg twice daily (BID); 6 mg BID and 12 mg QD. Overall, 267 subjects were randomized (44 to 45 subjects per treatment arm) in the Phase 2 study. All BMS-986165 treatment groups, except 3 mg QOD, achieved the primary endpoint of superiority compared with placebo in the proportion of subjects experiencing at least a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) after 12 weeks of treatment. Compared with the placebo treatment group (6.7%), 38.6% ($P = 0.0003$), 68.9% ($P < 0.0001$), 66.7% ($P < 0.0001$), and 75% ($P < 0.0001$) of the subjects treated with BMS-986165 at 3 mg QD, 3 mg BID, 6 mg BID, and 12 mg QD doses achieved a PASI 75 response, respectively. The PASI 75 responses plateaued at a dose of 3 mg BID. The current Phase 3 study is designed to confirm the efficacy and safety of BMS-986165 6 mg QD, which is expected to have equivalent efficacy as the 3 mg BID dose in Phase 2, in a larger global population of subjects with stable moderate-to-severe plaque psoriasis and will assess the durability of a PASI 75 response after treatment withdrawal.

**Study Population:**

Men and women ≥18 years of age diagnosed with stable (defined as no morphology changes or significant flares of disease activity in the opinion of the investigator) moderate-to-severe plaque psoriasis for ≥ 6 months and with ≥10% of body surface area (BSA) involvement, who have a static Physician's Global Assessment (sPGA) ≥3, a PASI score ≥12, and who are candidates for phototherapy or systemic therapy may be eligible to participate in the study.

**Objectives and Endpoints:**

| Objective | Endpoint |
|---|---|
| **Primary** | |
| • Assess whether BMS-986165 is superior to placebo at Week 16 in the treatment of subjects with moderate-to-severe plaque psoriasis | • sPGA 0/1<br>• PASI 75 |
| **Selected Secondary Endpoints** | |
| • Assess whether BMS-986165 is superior to apremilast at Week 16 | • sPGA 0/1<br>• PASI 75<br>• PASI 90<br>• sPGA 0<br>• PASI 100 |
| • Assess whether BMS-986165 is superior to apremilast at Week 24 | • sPGA 0/1<br>• PASI 75<br>• PASI 90<br>[redacted] |
| • Assess whether BMS-986165 is superior to placebo over the first 16 weeks of treatment | • sPGA 0/1<br>• PASI 75<br>• PASI 90<br>• sPGA 0<br>• PASI 100 |
| • Evaluate improvement in patient-reported outcomes for BMS-986165 compared with placebo through Week 16<br>• Evaluate improvement in patient-reported outcomes for BMS-986165 compared with apremilast through Week 24 | • Change from baseline in Psoriasis Symptoms and Signs Diary (PSSD) symptom score, sign score, and total score<br>• Change from baseline in Dermatology Life Quality Index (DLQI) score |
| • Evaluate maintenance and durability of efficacy of BMS-986165 during the randomized withdrawal period through Week 52 among Week 24 PASI 75 responders continuing on treatment compared with those re-randomized to placebo | [redacted] |

| Objective | Endpoint |
|---|---|
| | [redacted]<br>• Time to relapse until Week 52<br>[redacted] |

**Overall Design:**

This will be a 52-week, multi-center, randomized double-blind, double-dummy, placebo- and active comparator-controlled study in subjects with stable moderate-to-severe plaque psoriasis. Subjects will undergo screening evaluations within 28 days prior to administration of study medication to determine eligibility.

***Active Comparator-Controlled Period***

Following the screening process, qualified subjects will be randomized in a 2:1:1 ratio to one of the following 3 treatment groups:

- BMS-986165 6 mg QD
- Placebo
- Apremilast 30 mg BID (with initial titration per label)

Randomization should not occur until at least 8 days after the screening visit to allow collection of PSSD data during screening in order to calculate a baseline PSSD score. Randomization will be stratified by geographic region (US/rest of the world), previous biologic use for psoriasis, psoriatic arthritis or other inflammatory disease (yes/no), and body weight (≥90 kg and <90 kg). As this is designed to be a global study across multiple countries, randomization in each country will be targeted to approximately 35% or less of the total sample size. This change is being implemented

to achieve geographical representation across countries and to minimize the potential for any single country to have a disproportionate impact on the overall efficacy and/or safety profile.

- At Week 16, subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD.

Subjects in the other treatment groups will continue their current regimen through Week 24.

***Randomized Withdrawal and Maintenance Period***

At Week 24, subjects originally randomized to BMS-986165 6 mg QD who do not achieve PASI 75 response will continue to receive BMS-986165 6 mg QD in a blinded manner. Subjects who achieve PASI 75 response will enter the randomized withdrawal and maintenance period. These subjects will be re-randomized in a blinded manner to one of the following 2 treatment groups in a 1:1 ratio:

- BMS-986165 6 mg QD
- Placebo

If the subjects re-randomized to placebo experience a relapse as defined below at any visit during this period, they will be treated with BMS-986165 6 mg QD until the end of the maintenance period (Week 52).

At Week 24, subjects receiving apremilast who achieve PASI 75 response will be switched in a blinded manner to placebo. If a subject experiences a relapse at any visit during this period, the subject will be treated with BMS-986165 6 mg QD until the end of the maintenance period (Week 52). Subjects who do not achieve PASI 75 response at Week 24 will be switched to BMS-986165 6 mg QD.

During the randomized withdrawal period, relapse will be defined as at least a 50% loss of Week 24 PASI percent improvement from baseline.

Please refer to Section 6.2.1 for information regarding the method of study treatment assignment when COVID-19-related issues result in the at Week 24 and/or post Week 24 visits being missed or conducted remotely.

Any subject with sPGA ≥ 3 at Week 24 may be treated with restricted topical medications, such as topical high potency corticosteroids (WHO Classes I-V), only at this time point at the discretion of the investigator.

**Number of Subjects:**

Approximately 1000 qualified subjects will be randomized in a 2:1:1 ratio to BMS-986165 6 mg QD, apremilast 30 mg BID, and placebo, respectively. This sample size will provide adequate power (≥90%) to compare BMS-986165 6 mg QD with placebo for each of the coprimary efficacy endpoints (sPGA 0/1 and PASI 75 at Week 16) and BMS-986165 6 mg QD compared with apremilast for sPGA 0/1 and PASI 75 (Week 16).

**Treatment Arms and Duration:**

**Study treatment:** Subjects in all treatment groups will take oral doses of the investigational product (IP) for 52 weeks during treatment as follows: BMS-986165 6 mg QD, apremilast 30 mg BID (titrated as per label), or placebo QD.

| **Study Treatment for IM011047** | | |
|---|---|---|
| **Medication** | **Potency** | **IP/Non-IP** |
| BMS-986165 tablet | 6 mg | IP |
| apremilast tablet | 10 mg* | IP |
| apremilast tablet | 20 mg† | IP |
| apremilast tablet | 30 mg‡ | IP |
| placebo tablet | n/a | IP |

IP = investigational produce; n/a = non-applicable

*Used for titration Day 1 through Day 3 morning dose
†Used for titration Day 3 evening dose through Day 5 morning dose.
‡From Day 5 evening dose onwards

**Statistical Methods:**

General Methodology

The primary efficacy analysis population will be the Full Analysis Set (FAS). The FAS will include all randomized subjects who are dispensed study drug.

The analysis model for the coprimary efficacy endpoints and secondary binary endpoints will use stratified Cochran-Mantel-Haenszel (CMH) tests stratified by geographic region (US and rest of world), prior biologic treatment use for psoriasis, psoriatic arthritis or other inflammatory disease (yes/no), and body weight (≥90 kg and <90 kg) to compare the response rates of BMS-986165 6 mg QD to placebo. If expected cell counts are not sufficient for each strata level, then strata levels will be combined for the analysis. Non-responder imputation will be used for binary endpoints for subjects who discontinue study or treatment of study prior to Week 16, start a protocol prohibited medication/therapy that could improve psoriasis during the first 16 weeks of treatment, or who have otherwise missing endpoint data at the specified timepoint.

The analysis model for continuous secondary endpoints will use analysis of covariance (ANCOVA) with treatment, geographic region (US and rest of world), prior biologic treatment use for psoriasis, psoriatic arthritis or other inflammatory disease (yes/no), and body weight (≥90 kg and <90 kg) as fixed effects. The baseline value will be added into the model as a covariate. Treatment differences based on least-squares (LS) means and the corresponding 2-sided

95% confidence intervals will be provided for the difference between BMS-986165 6 mg QD and placebo or active comparator depending on the endpoint being assessed.

For continuous secondary efficacy endpoints, baseline observation carried forward (BOCF) will be used for subjects who discontinue study treatment due to:

- Lack of efficacy
- Adverse events

Additionally, BOCF will be used for subjects who start a protocol prohibited medication/therapy that could improve psoriasis. LOCF will be used for all other missing data.

The Kaplan-Meier product limit method will be used to estimate the distribution curves for time-to-relapse during the randomized withdrawal period. Treatment comparisons of subjects re-randomized during the Maintenance Period for BMS-986165 6 mg QD and placebo will be performed using the log-rank test stratified by geographic region (US and rest of world), prior biologic treatment use for psoriasis, psoriatic arthritis or other inflammatory disease, and body weight (≥90 kg and <90 kg).

Testing Strategy for Efficacy Endpoints

The primary family of coprimary endpoints will each be tested at a Type I error =0.05 first and, if significant for both endpoints, testing will proceed for the secondary family of key secondary endpoints [redacted]. The primary family of coprimary endpoints will be the serial gatekeeper for proceeding with testing of the secondary family of key secondary efficacy endpoints.

Primary Family – Coprimary endpoints compared with placebo; both must be significant at a Type I error=0.05 in order to proceed with the secondary family tests for the key secondary endpoints:

- Primary 1: Proportion of subjects who achieve sPGA 0/1 at Week 16
- Primary 2: Proportion of subjects who achieve PASI 75 at Week 16

In order to control for Type I error rate inflation within the secondary family of key secondary endpoints, separate testing branches with a 2-sided Type I error=0.025 will be used for comparisons of BMS-986165 6 mg QD compared to placebo and BMS-986165 6 mg QD compared to apremilast. A hierarchical testing method within each testing branch will be implemented for the key secondary endpoints. The hierarchical test may only proceed to the next key secondary endpoint within each testing branch if the null hypothesis is rejected at a Type I error=0.025. If an endpoint fails at any step, then all subsequent comparisons will be considered descriptive.

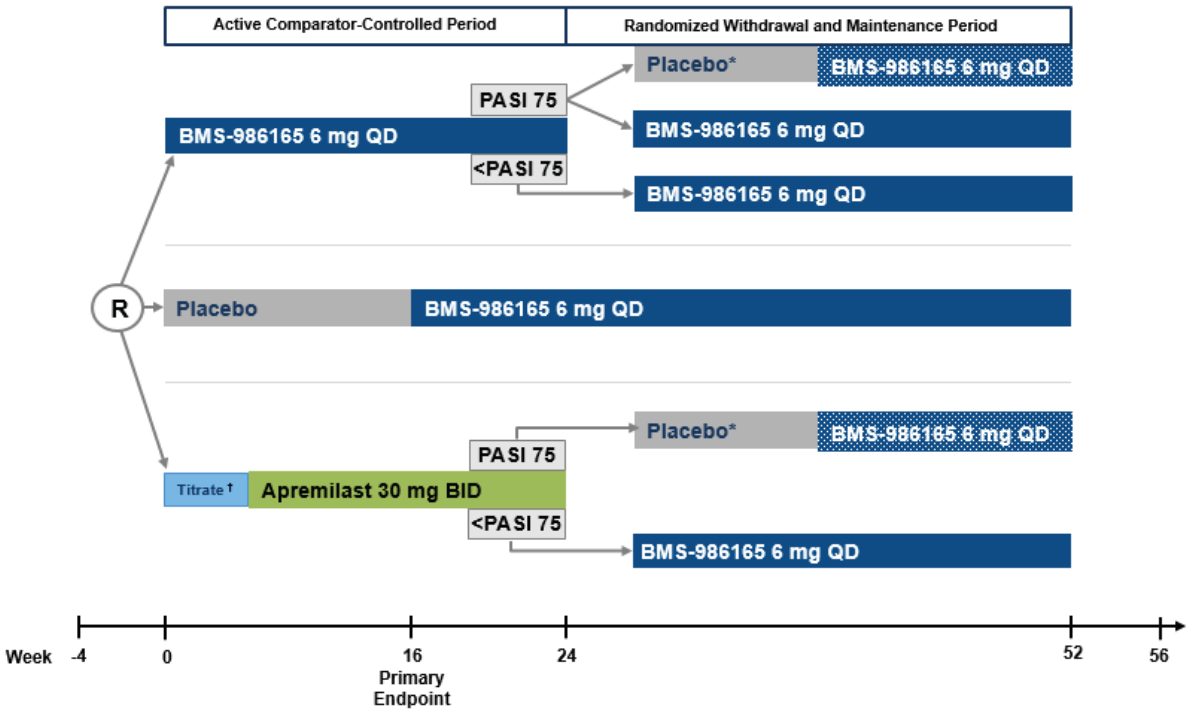
Please refer to Section 9.8.1 for the impact on efficacy endpoints due to COVID-19.

Safety Analysis

Safety data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency distributions (counts and percentages) for categorical variables.

Please refer to Section 9.8.2 for the impact on safety variables due to COVID-19.

## 1.2 Schema




*Upon relapse (at least a 50% loss of Week 24 PASI percent improvement from baseline), subjects will be switched to BMS-986165 6 mg QD.
†Apremilast is titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
Abbreviations: BID = twice daily; PASI = Psoriasis Area and Severity Index; QD = once daily; R = randomize

The coprimary endpoints will be evaluated at Week 16. The duration of the study for each subject will be up to 52 weeks on treatment, and 4 additional weeks for safety follow-up.

## 1.3 Schedule of Activities (SOA)

The schedules of assessments and procedures are documented in Table 1 for screening, Table 2 for the active comparator-controlled period (through Week 20), and Table 3 for the Randomized Withdrawal and Maintenance Period (Week 24 and after).

**Table 1: Screening Procedural Outline (IM011047)**

| Procedure | Screening V1 | Notes |
|---|---|---|
| **Eligibility Assessments** | | |
| Informed Consent | X | A subject is considered enrolled only when a protocol specific informed consent is signed |
| Enroll Subject | X | Obtain number from IRT |
| Inclusion/Exclusion Criteria | X | Includes duration of plaque psoriasis and documentation of presence of plaque psoriasis by the investigator |
| Medical History | X | See Section 5.2 for complete eligibility criteria associated with medical history. Of note, subjects need to be screened for any current uncontrolled neuropsychiatric illness or history of suicidality; any history of TB; any congenital or acquired immunodeficiency; any significant drug allergy such as anaphylaxis; any cancer currently or in the previous 5 years. Investigators are encouraged to check whether subjects have had preventive health measures such as cancer screening (e.g. Pap smear, colonoscopy, mammograms) that is up to date according to local guidelines. |
| History of Tobacco Use | X | Include description of current tobacco use. |
| Psoriasis-related History | X | Includes scalp symptoms, PsA/joint pain, nail involvement, palmoplantar involvement, genital involvement, history of other forms of psoriasis |
| Psoriasis-related Systemic Treatment | X | History of: conventional systemic (eg, methotrexate), biologic, and/or phototherapy. For each therapy, include length of time on treatment and reason(s) for discontinuation (eg, lack of efficacy, intolerance, side effects, loss of access to treatment) if applicable. |
| Other Prior and Concomitant Treatments | X | This includes topical treatments for psoriasis and all medications for other conditions such as cardiovascular and mood disorders. |
| **Safety Assessments** | | |
| Physical Examination | X | Complete PE |
| Physical Measurements | X | Includes height and weight |
| 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. |

**Table 1: Screening Procedural Outline (IM011047)**

| Procedure | Screening V1 | Notes |
|---|---|---|
| Electrocardiogram | X | ECGs should be recorded after the subject has been supine for at least 5 minutes |
| Chest Imaging (eg, Chest x-ray) | X | Chest imaging is required if not performed within 6 months of Screening Visit, copy of radiology report must be on file and reviewed by the investigator. Section 8.4.4 |
| Neuropsychiatric Illness Assessment | X | Based on subject/family response, medical history/medical records, investigator judgment |
| PHQ-8 | X | For establishing baseline depression severity. |
| Suicidal Ideation and Behavior Assessment | X | Based on subject/family response, medical history/medical records, investigator judgment |
| eC-SSRS | X | eC-SSRS Assessment: Response of "Actual Suicide Attempt-Lifetime" or suicidal ideation (Severity of 4 or 5) or suicidal behavior will be exclusionary. Rescreening will not be allowed. Section 8.4.7 |
| Monitor for Serious Adverse Events | X | All SAEs must be collected from the date of subject's written consent until 30 days post discontinuation of dosing or subject's participation in the study. |
| **Laboratory Tests** | | Section 8.4.5 |
| Hematology | X | Complete Blood Count (CBC) with differential |
| Chemistry Panel | X | |
| Lipid Panel | X | |
| Urinalysis | X | |
| Hemoglobin A1C | X | |
| TSH | X | If TSH above normal reference range, test free T4; if TSH below normal range, test free T4 & T3 |
| hs-CRP | X | |
| Serology | X | Includes HCV antibody, HBsAg, HBsAb, HBcAb, HBV DNA, and HIV antibodies. |
| Tuberculosis Test | X | In accordance with QuantiFERON-TB Gold; details are described in Section 5.2 Criterion 3)d. |

**Table 1: Screening Procedural Outline (IM011047)**

| Procedure | Screening V1 | Notes |
|---|---|---|
| Pregnancy Test (serum) | X | For WOCBP only |
| FSH | X | To confirm menopausal status (see APPENDIX 4) |
| **Clinical Efficacy/Health Outcomes** | | |
| sPGA | X | |
| PASI | X | |
| BSA | X | |
| PASE Questionnaire | X | For subjects with peripheral joint complaints to screen for presence of psoriatic arthritis |
| PSSD | X | All consented subjects will be given a diary device at the Screening Visit and will begin recording psoriasis signs and symptoms on a daily basis in the diary device. Subjects who are not randomized will stop recording and return their diary device to the site. Subjects who are randomized will continue recording their psoriasis signs and symptoms on a daily basis in the diary device through Week 52. |

BSA = body surface area; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = High-sensitivity C-reactive protein; IRT = Interactive Response Technology; PASE = psoriatic arthritis screening and evaluation; PASI = Psoriasis Area and Severity Index; PE = physical examination; PHQ-8 = Eight-item Patient Health Questionnaire; PsA = psoriatic arthritis; PSSD = Psoriasis Symptoms and Signs Diary; SAE = serious adverse event; sPGA = static Physician Global Assessment; T3 = triiodothyronine; T4 = thyroxine; TB = tuberculosis; TSH = thyroid-stimulating hormone; V = Visit; WOCBP = women of childbearing potential

**Table 2: On Treatment Procedural Outline (IM011047): Week 0 through Week 20**

| Procedure | Week 0 Baseline / D1 V2 | Week 1 D8 (±3 d) V3 | Week 2 D15 (±3 d) V4 | Week 4 D29 (±3 d) V5 | Week 8 D57 (±3 d) V6 | Week 12 D85 (±3 d) V7 | Week 16 D113 (±3 d) V8 | Week 20 D141 (±3 d) V9 | Notes |
|---|---|---|---|---|---|---|---|---|---|
| **Clinical Efficacy/Health Outcomes** | | | | | | | | | |
| DLQI | X | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | |
| sPGA | X | X | X | X | X | X | X | X | |
| PASI | X | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | |
| ss-PGA* | X | X | X | X | X | X | | | |
| [redacted] | | | | | | | | | |
| PGA-F† | X | | | X | X | X | | | |
| [redacted] | | | | | | | | | |


Approved v2.0 [redacted]

**Table 2: On Treatment Procedural Outline (IM011047): Week 0 through Week 20**

| Procedure | Week 0 Baseline / D1 V2 | Week 1 D8 (±3 d) V3 | Week 2 D15 (±3 d) V4 | Week 4 D29 (±3 d) V5 | Week 8 D57 (±3 d) V6 | Week 12 D85 (±3 d) V7 | Week 16 D113 (±3 d) V8 | Week 20 D141 (±3 d) V9 | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Palmoplantar PGA‡ | X | X | X | X | X | X | X | [redacted] | |
| [redacted] | | | | | | | | | |
| PSSD | → | → | → | → | → | → | → | [redacted] | |
| **Safety Assessments** | | | | | | | | | |
| Complete PE | X | | | | | | X | | |
| Targeted PE | | X | X | X | X | X | | X | See Section 8.4.1 |
| Body Weight | X | | | | X | | X | | |
| Vital Signs | X | X | X | X | X | X | X | X | |
| Electrocardiogram | X | | | | | | X | | |
| PHQ-8 | X | | | | X | | X | | See Section 8.4.6.1 |
| eC-SSRS Assessment | X | | | | X | | X | | Suicidal Ideation and Behavior since last visit |
| Adverse Event Assessment | X | X | X | X | X | X | X | X | |
| Concomitant Medication Use | X | X | X | X | X | X | X | X | |
| **Laboratory Tests** | | | | | | | | | |
| Hematology | X | X | X | X | X | X | X | X | |
| Lymphocyte Subsets (TBNK) | X | | | | X | | X | | |
| Chemistry Panel | X | X | X | X | X | X | X | X | If CK >2.5 × ULN, reflex testing is |

**Table 2: On Treatment Procedural Outline (IM011047): Week 0 through Week 20**

| Procedure | Week 0 Baseline / D1 V2 | Week 1 D8 (±3 d) V3 | Week 2 D15 (±3 d) V4 | Week 4 D29 (±3 d) V5 | Week 8 D57 (±3 d) V6 | Week 12 D85 (±3 d) V7 | Week 16 D113 (±3 d) V8 | Week 20 D141 (±3 d) V9 | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | required (see Section 8.4.5) |
| Hemoglobin A1C | X | | | | | | X | | |
| hs-CRP | X | X | X | X | X | | X | | |
| Fasting Lipid Panel | X | | | | X | | X | | |
| Fasting Plasma Glucose | X | | | | X | | X | | |
| Urinalysis | X | | | | | | X | | |
| Serum Immunoglobulin Levels (IgM, IgG, IgA, IgE) | X | | | | X | | X | | |
| Pregnancy Test (Urine) | X | | | X | X | X | X | X | WOCBP only |
| **Study Treatment** | | | | | | | | | |
| Randomize | X | | | | | | | | |
| Dispense Study Treatment | X | | X | X | X | X | X | X | |
| Study Treatment Compliance | | X | X | X | X | X | X | X | See Section 6.6 |
| [redacted] | | | | | | | | | |

**Table 2: On Treatment Procedural Outline (IM011047): Week 0 through Week 20**

| Procedure | Week 0 Baseline / D1 V2 | Week 1 D8 (±3 d) V3 | Week 2 D15 (±3 d) V4 | Week 4 D29 (±3 d) V5 | Week 8 D57 (±3 d) V6 | Week 12 D85 (±3 d) V7 | Week 16 D113 (±3 d) V8 | Week 20 D141 (±3 d) V9 | Notes |
|---|---|---|---|---|---|---|---|---|---|
| [redacted] | | | | | | | | | |

[redacted] eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; CK = creatine kinase; [redacted] D = Day; d = days; DLQI = Dermatology Life Quality Index; [redacted] ECG – electrocardiogram; [redacted] hs-CRP = High-sensitivity C-reactive protein; [redacted] PASI = Psoriasis Area and Severity Index; PE = physical examination; PGA-F = Physician Global Assessment-Fingernails; [redacted] PSSD = Psoriasis Symptoms and Signs Diary; [redacted] sPGA = static Physician Global Assessment; [redacted] TBNK = T cells, B cells, and natural killer cells; ULN = upper limit of normal; [redacted] V = Visit; Wk = Week; WOCBP = women of childbearing potential

*In subjects with scalp psoriasis at baseline; †In subjects with nail psoriasis at baseline; ‡In subjects with palmoplantar psoriasis at baseline; §If sample is missed, it may be taken at any visit once informed consent is obtained.

When multiple assessments are conducted at a single visit, the following is the recommended order in which they should be done:
1) Health outcomes assessments
2) Safety assessments (eg, vitals, AEs)
3) Clinical efficacy assessments
4) Laboratory tests (eg, safety laboratory tests, [redacted])

On fasting days, safety assessments can be done first followed by blood draws, and then health outcomes and finally efficacy assessments.
The dose of the drug on a visit day is to be taken after blood draws.

**Table 3: On Treatment Procedural Outline (IM011047): Week 24 Through Week 52**

| Procedure | Week 24 D169 (±3 d) V10 | Week 28 D197 (±3 d) V11 | Week 32 D225 (±3 d) V12 | Week 36 D253 (±3 d) V13 | Week 40 D281 (±3 d) V14 | Week 44 D309 (±3 d) V15 | Week 48 D337 (±3 d) V16 | Week 52# (or early DC) D365 (±3 d) V17 | Safety Follow-Up* (Week 56) D393 (±3 d) V18 | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| **Clinical Efficacy/Health Outcomes** | | | | | | | | | | |
| DLQI | | [redacted] | | | | | | | | |
| sPGA | | | | | | | | | | |
| PASI | X | X | X | X | X | X | X | X | | |
| [redacted] | | | | | | | | | | |

**Table 3: On Treatment Procedural Outline (IM011047): Week 24 Through Week 52**

| Procedure | Week 24 D169 (±3 d) V10 | Week 28 D197 (±3 d) V11 | Week 32 D225 (±3 d) V12 | Week 36 D253 (±3 d) V13 | Week 40 D281 (±3 d) V14 | Week 44 D309 (±3 d) V15 | Week 48 D337 (±3 d) V16 | Week 52# (or early DC) D365 (±3 d) V17 | Safety Follow-Up* (Week 56) D393 (±3 d) V18 | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| PSSD | | [redacted] | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | |
| Full Physical Examination | X | | | | | | | X | X | |
| Targeted Physical Examination | | X | X | X | X | X | X | | | |
| Body Weight | X | | | X | | | | X | X | |
| Vital Signs | X | X | X | X | X | X | X | X | X | |
| Electrocardiogram | X | | | | | | | X | | |
| PHQ-8 | | X | | | X | | | X | | See Section 8.4.6.1 |
| eC-SSRS | | X | | | X | | | X | | Suicidal Ideation and Behavior since last visit |
| Adverse Event Assessment | X | X | X | X | X | X | X | X | X | |
| Concomitant Medication Use | X | X | X | X | X | X | X | X | X | |
| **Laboratory Tests** | | | | | | | | | | |
| Hematology | X | X | X | X | X | X | X | X | X | |
| Lymphocyte Subsets (TBNK) | | | | X | | | | X | | |
| Chemistry Panel | X | X | X | X | X | X | X | X | X | If CK > 2.5 x ULN, reflex testing is required (see Section 8.4.5) |
| Fasting Lipid Panel | X | | | | | | | X | | |

**Table 3: On Treatment Procedural Outline (IM011047): Week 24 Through Week 52**

| Procedure | Week 24 D169 (±3 d) V10 | Week 28 D197 (±3 d) V11 | Week 32 D225 (±3 d) V12 | Week 36 D253 (±3 d) V13 | Week 40 D281 (±3 d) V14 | Week 44 D309 (±3 d) V15 | Week 48 D337 (±3 d) V16 | Week 52# (or early DC) D365 (±3 d) V17 | Safety Follow-Up* (Week 56) D393 (±3 d) V18 | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| Fasting Plasma Glucose | X | | | | | | | X | | |
| hs-CRP | X | | | X | | | | X | | |
| Hemoglobin A1C | | | | X | | | | X | | |
| Urinalysis | | | | X | | | | X | X | |
| Serum Immunoglobulin Levels (IgM, IgG, IgA, IgE) | | | | X | | | | X | | |
| Pregnancy Test (Urine) | X | X | X | X | X | X | X | X | X | WOCBP only |
| [redacted] | | | | | | | | | | |
| **Study Treatment** | | | | | | | | | | |
| Blinded PASI Response Transferred Electronically to IRT | X | X | X | X | X | X | X | X | | To determine PASI 75 response at Week 24 and to monitor for relapse and rebound afterwards |
| Dispense Study Treatment | X | X | X | X | X | X | X | | | |

**Table 3: On Treatment Procedural Outline (IM011047): Week 24 Through Week 52**

| Procedure | Week 24 D169 (±3 d) V10 | Week 28 D197 (±3 d) V11 | Week 32 D225 (±3 d) V12 | Week 36 D253 (±3 d) V13 | Week 40 D281 (±3 d) V14 | Week 44 D309 (±3 d) V15 | Week 48 D337 (±3 d) V16 | Week 52# (or early DC) D365 (±3 d) V17 | Safety Follow-Up* (Week 56) D393 (±3 d) V18 | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| Study Treatment Compliance | X | X | X | X | X | X | X | X | | |

[redacted] CK = creatine kinase; [redacted] D = Day; d = days; DC = discontinuation; [redacted] eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; [redacted] hs-CRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; IRT = interactive response technology; [redacted] PASI = Psoriasis Area and Severity Index; [redacted] PHQ-8 = Eight-item Patient Health Questionnaire; [redacted] sPGA = static Physician Global Assessment; [redacted] TBNK = T cells, B cells, and natural killer cells; ULN = upper limit of normal; V = Visit; [redacted] WOCBP = women of childbearing potential

*For subjects who do not continue in a long-term extension study: [redacted]

#For subjects who discontinue study treatment prior to Week 52, please refer to Section 7.1 for more details.

When multiple assessments are conducted at a single visit, the following is the recommended order in which they should be done:
1) Health outcomes assessments
2) Safety assessments (eg, vitals, AEs)
3) Clinical efficacy assessments
4) Laboratory tests (eg, safety laboratory tests, [redacted])

On fasting days, safety assessments can be done first followed by blood draws, and then health outcomes and finally efficacy assessments.
The dose of the drug on a visit day is to be taken after blood draws.

## STUDY ACKNOWLEDGMENT/DISCLOSURE

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

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

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

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

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

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

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

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

Original Protocol ☐ Revised Protocol ☒

Protocol Number: IM011047_____ Site Number: _____

Date of Protocol or Revised Protocol: 21 May 2020

IND Number: 131,993 EUDRACT Number: 2018-001925-24

Investigator _____ Date_____
(signature)

_____
(printed name*)

# 2 INTRODUCTION

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

Treatments include topical preparations, eg, corticosteroids, vitamin D analogues, calcineurin inhibitors, and salicylic acid; phototherapy modalities, including psoralens with ultraviolet A (PUVA) and narrow band ultraviolet B (UVB); and systemic therapies. In moderate-to-severe disease, systemic treatments are usually needed and may include oral agents (retinoids, methotrexate, cyclosporine, and apremilast) or injectables (eg, biologics such as tumor necrosis factor (TNF) inhibitors etanercept, infliximab, and adalimumab) anti-IL-12/23p40 antibody (ustekinumab), IL-17 antagonists (secukinumab, ixekizumab, brodalumab), and anti-IL-23p19 antibody (guselkumab). Many of these treatments are associated with increased risk of adverse events (AEs) such as hepatotoxicity and neutropenia (methotrexate);[10] nephrotoxicity (cyclosporine);[11] depression and weight loss (apremilast);[12] serious infections (cytokine inhibitors);[13,14,15,16] and candidiasis and Crohn's disease (IL-17 antagonists).[16, 17, 18]

Although effective therapeutic options are available, under-treatment or non-treatment of psoriasis has been reported in up to half of surveyed patients (based on absence of treatment and/or dissatisfaction with treatment).[19] Many patients with severe disease are still being managed with only topicals,[4,8] and many patients consider their psoriasis treatment to be inadequate. Accordingly, there remains a need for more effective oral options, when compared with currently available agents, that would improve efficacy responses and increase adherence to treatment.

## 2.1 Study Rationale

BMS-986165 could be a therapeutic option for the treatment of subjects with moderate-to-severe plaque psoriasis based on results of a recently completed 12-week randomized Phase 2, placebo-controlled, parallel-group study with 5 different BMS-986165 treatment arms: 3 mg every

other day (QOD); 3 mg once daily (QD); 3 mg twice daily (BID); 6 mg BID; and 12 mg QD (Study IM011011). Overall, 267 subjects were randomized (44 to 45 subjects per treatment arm) in the Phase 2 study. All BMS-986165 treatment groups, except 3 mg QOD, achieved the primary endpoint of superiority compared with placebo in the proportion of subjects achieving at least a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) after 12 weeks of treatment. Compared with placebo treatment group, in which 6.7% of the subjects achieved PASI 75 response, 38.6% ($P = 0.0003$), 68.9% ($P < 0.0001$), 66.7% ($P < 0.0001$), and 75% ($P < 0.0001$) of subjects treated with 3 mg QD, 3 mg BID, 6 mg BID, and 12 mg QD achieved PASI 75, respectively. The PASI 75 responses plateaued at a dose of 3 mg BID. Also, there was a clinically significant proportion of subjects treated with BMS-986165 achieving an sPGA score of 0 or 1 compared with placebo at Week 12. Compared with the placebo treatment group in which 6.7% of the subjects achieved an sPGA score of 0 or 1, 41.5%, 75.6%, 65.9%, and 75% of the subjects treated with 3 mg QD, 3 mg BID, 6 mg BID, and 12 mg QD achieved an sPGA score of 0 or 1, respectively with responses again plateauing at dose of 3 mg BID. The Phase 3 dose selected (6 mg QD) is expected to demonstrate equivalent efficacy to the 3 mg BID dose. Please refer to [redacted]

This Phase 3 study is designed to confirm the efficacy and safety of BMS-986165 6 mg QD and demonstrate its superiority to a widely used oral agent, apremilast, in a larger global population of subjects with moderate-to-severe plaque psoriasis.

## 2.2 Background

Tyrosine kinase 2 (TYK2) is a nonreceptor tyrosine kinase associated with receptors for the p40-containing cytokines interleukin (IL)-12 and IL 23, as well as the Type I interferon (IFN) receptor, and is required for the activation of their downstream signaling pathways. TYK2 catalyzes the phosphorylation of the intracellular receptor domains and signal transducer and activator of transcription (STAT) proteins resulting in the activation of STAT-dependent transcription and functional responses specific for these cytokines.[20,21,22] Because TYK2-dependent cytokines (eg, Type I IFNs, IL-12, IL-23) are distinct from those dependent on closely related Janus kinase (JAK) family members JAK1/JAK3 (eg, IL-2, IL-15, IL-7) or JAK2 (eg, erythropoietin, thrombopoietin, granulocyte macrophage colony-stimulating factor, a TYK2 inhibitor would be expected to have a highly differentiated profile from inhibitors of other JAK family kinases. TYK2 dependent pathways and the cytokine networks they modulate (eg, IL-23/IL-17, IFNα) have been implicated in the pathophysiology of multiple immune-mediated diseases, including psoriasis, lupus, spondyloarthritides, and Crohn's disease.

BMS-986165 is a potent, highly selective, oral small molecule inhibitor of TYK2. A comprehensive in vitro and in vivo characterization of BMS-986165 has been established and supports the development of this compound in humans. Inhibition of TYK2 is expected to provide therapeutic benefit for subjects with psoriasis for multiple reasons: 1) Many of the pathways in the TYK2 signaling cascade (IL-23 and the downstream mediators IL-17, IL-22, and IFNα) have been implicated in pathogenesis of psoriasis.[7] 2) Biologic agents targeting the IL-17, IL-23p19, and IL-12/23 p40 pathways have been approved for and are highly efficacious in the treatment of

psoriasis. [redacted]

### 2.2.1 Early Clinical Development

The clinical data available to date supporting the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of BMS-986165 are from 5 completed Phase 1 studies in healthy subjects (IM011002, IM011015, IM011016, IM011031, and IM011039) and 1 completed Phase 2 study in adult subjects with moderate-to-severe plaque psoriasis (IM011011).

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

[redacted]

[redacted]

# 3 OBJECTIVES AND ENDPOINTS

**Table 4: Objectives and Endpoints**

| Objective | Endpoint |
|---|---|
| **Primary** | |
| • Assess whether BMS-986165 is superior to placebo at Week 16 in the treatment of subjects with moderate-to-severe plaque psoriasis | • static Physician Global Assessment (sPGA) 0/1 response<br>• Psoriasis Area and Severity Index (PASI) 75 response (defined as a 75% improvement in PASI score from baseline) |
| **Key Secondary** [redacted] | |
| • Assess whether BMS-986165 is superior to apremilast at Week 16 | • sPGA 0/1 response<br>• PASI 75 response<br>• PASI 90 response<br>• sPGA 0 response<br>• PASI 100 response |
| • Assess whether BMS-986165 is superior to apremilast at Week 24 | • sPGA 0/1 response<br>• PASI 75 response<br>• PASI 90 response<br>[redacted] |
| • Assess whether BMS-986165 is superior to placebo over the first 16 weeks of treatment | • sPGA 0/1 response<br>[redacted]<br>• PASI 90 response<br>• sPGA 0 response<br>• PASI 100 response<br>[redacted] |

**Table 4: Objectives and Endpoints**

| Objective | Endpoint |
|---|---|
| • Assess whether BMS-986165 is superior to placebo in scalp psoriasis through Week 16 among subjects with a baseline scalp severity Physician's Global Assessment (ss-PGA) score ≥3 | • ss-PGA 0/1 response<br>[redacted] |
| • Assess whether BMS-986165 is superior to apremilast in scalp psoriasis through Week 16 among subjects with a baseline ss-PGA score ≥3 | • ss-PGA 0/1 response<br>[redacted] |
| • Assess whether BMS-986165 is superior to placebo in nail psoriasis through Week 16 among subjects with a baseline Physician's Global Assessment of Fingernail psoriasis (PGA-F) score ≥3<br>[redacted] | • PGA-F 0/1<br>[redacted] |
| • Assess whether BMS-986165 is superior to placebo in palmoplantar psoriasis through Week 16 among subjects with a baseline palmoplantar Physician's Global Assessment (pp-PGA) score ≥3 | • pp-PGA 0/1 response<br>[redacted] |
| • Evaluate improvement in patient-reported outcomes for BMS-986165 compared with placebo through Week 16<br>• Evaluate improvement in patient-reported outcomes for BMS-986165 compared with apremilast through Week 24 | [redacted] |
| | • PSSD symptom score of 0 (among subjects with a baseline PSSD symptom score ≥ 1)<br>[redacted] |
| | • DLQI 0/1 (among subjects with a baseline DLQI score ≥ 2)<br>[redacted] |

**Table 4: Objectives and Endpoints**

| Objective | Endpoint |
|---|---|
| | [redacted] |
| • Evaluate maintenance and durability of efficacy of BMS-986165 during the randomized withdrawal period through Week 52 among Week 24 PASI 75 responders continuing on treatment compared with those re-randomized to placebo | • Time to relapse until Week 52 |
| | [redacted] |

# 4 STUDY DESIGN

## 4.1 Overall Design

This will be a 52-week, multi-center, randomized double-blind, double-dummy, placebo- and active comparator-controlled study to evaluate the safety and efficacy of BMS-986165 vs placebo and apremilast. The maintenance and durability of BMS-986165 efficacy will also be evaluated. A total of 1000 qualified subjects with moderate-to-severe plaque psoriasis will be enrolled.

The duration of study participation is approximately 60 weeks and will be divided into the following periods: screening (up to 4 weeks), treatment (24 weeks), re-randomization and withdrawal (28 weeks), and follow up (4 weeks).

Physical examinations (PEs), 12-lead electrocardiograms (ECGs), clinical laboratory evaluations, and other assessments will be done at select visits during the study. Subjects in this study will be monitored for AEs. [redacted]

### 4.1.1 Active Comparator-controlled Period (Week 0-24)

#### 4.1.1.1 Screening Period

Subjects will be evaluated during the screening period to ensure that they meet eligibility criteria for this study. A detailed medical history will be done at this time, as well as a complete PE. Psoriasis-related history, which will include length of diagnosis (duration of disease), body surface involvement, and history of systemic treatment, will be assessed here. Depression and suicidality assessments will also be performed. An evaluation for tuberculosis (TB) will be done based on medical history, recent chest imaging, and a QuantiFERON-TB Gold test.

#### 4.1.1.2 Treatment Period

Qualified subjects who have completed the screening procedures and have met the inclusion/exclusion criteria will be randomized on Day 1 in a 2:1:1 ratio, respectively, to one of the following 3 treatment groups:

- BMS-986165 6 mg QD
- Placebo
- Apremilast titrated to 30 mg BID as follows:
    - Day 1: 10 mg tablet in the morning
    - Day 2: 10 mg tablet in the morning and evening
    - Day 3: 10 mg tablet in the morning and 20 mg tablet in the evening
    - Day 4: 20 mg tablet in the morning and the evening
    - Day 5: 20 mg tablet in the morning, and 30 mg tablet in the evening
    - Day 6 and thereafter: 30 mg tablet in the morning and the evening

Dummy tablets (placebo to the BMS-986165 6 mg tablet, placebo to apremilast 30 mg tablet BID, and placebo to apremilast 10 mg, 20 mg, and 30 mg during titration) will be administered to the subjects to maintain blinding. Additional details are provided in Section 6.1.

Randomization should not occur until at least 8 days after the screening visit to allow collection of PSSD data during screening in order to calculate a baseline PSSD score. Randomization will be stratified by geographic region (US and rest of world), previous biologic use for psoriasis, psoriatic arthritis or other inflammatory disease (yes/no), and body weight (≥90 kg and <90 kg). As this is designed to be a global study across multiple countries, randomization in each country will be targeted to approximately 35% or less of the total sample size. This change is being implemented to achieve geographical representation across countries and to minimize the potential for any single country to have a disproportionate impact on the overall efficacy and/or safety profile.

#### 4.1.1.3 Week 16

The coprimary endpoints (sPGA 0/1 and PASI 75) will be assessed at Week 16. Subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD at Week 16. Subjects who

are receiving BMS-986165 6 mg QD or apremilast 30 mg BID will continue the same treatment through Week 24.

### 4.1.2 Randomized Withdrawal and Maintenance Period (Week 24-52)

The Randomized Withdrawal and Maintenance Period will start at Week 24 and continue to Week 52. The subjects who had been in the placebo arm and switched to BMS-986165 6 mg QD at Week 16 will continue this treatment until Week 52.

#### 4.1.2.1 Week 24

At Week 24, subjects originally randomized to BMS-986165 6 mg QD who do not achieve PASI 75 response will continue to receive BMS-986165 6 mg QD in a blinded manner. Subjects who achieve PASI 75 response will be re-randomized in a blinded manner to one of the following 2 treatment groups in a 1:1 ratio:

- BMS-986165 6 mg QD
- Placebo

If the subjects who were re-randomized to placebo experience a relapse as defined below at any visit during this period, they will be switched back in a blinded manner to BMS-986165 6 mg QD until the end of the maintenance period (Week 52). Relapse will be defined as at least a 50% loss of Week 24 PASI percent improvement from baseline.

Subjects originally randomized to apremilast who achieve PASI 75 response will be switched in a blinded manner to placebo. If the subject experiences a relapse at any visit during this period, the subject will be treated with BMS-986165 6 mg QD until the end of the maintenance period (Week 52). Subjects receiving apremilast who do not achieve PASI 75 response at Week 24 will be switched to BMS-986165 6 mg QD.

During the assessment at Week 24, a subject who has an sPGA ≥ 3 [redacted] may be treated with restricted topicals/shampoos as described in Section 6.7.1 at the investigator's discretion. These treatments may be only initiated at Week 24, and not at subsequent time points. A subject who is initiated on these treatments at Week 24 may use them as needed per the investigator's judgment through Week 52.

#### 4.1.2.2 Week 52 and Follow-up Period

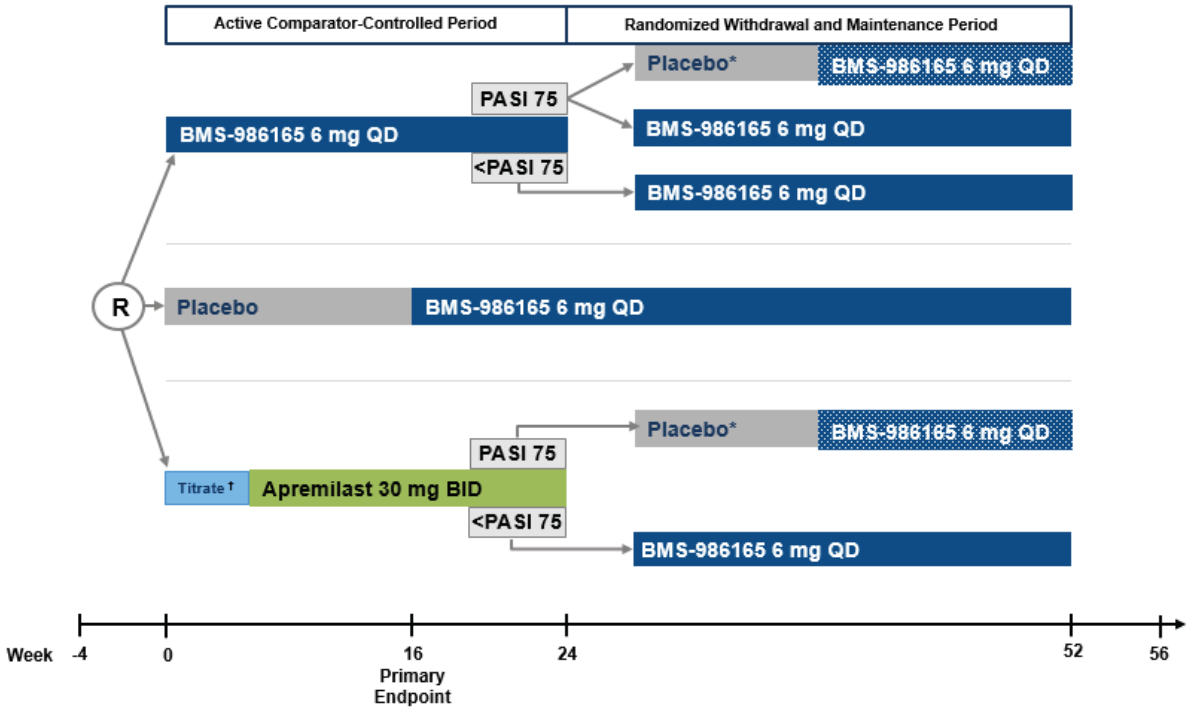
The follow-up period is a 4-week window after the Week 52 visit, unless the subject rolls over into the long-term extension. All subjects (excluding those in the long-term extension) should be off treatment after the Week 52 visit. Subjects will be encouraged to report any serious adverse events (SAEs) or AEs experienced during this time.

Subjects who discontinue study treatment early should remain in the study for protocol-specified procedures (please refer to Section 7.1 for more details).

Subjects completing 52 weeks of treatment will be offered the opportunity to roll over to a separate long-term extension study (≥2 years) where they will be treated with BMS-986165 6 mg QD.

The study design schematic is presented in Figure 1.

**Figure 1: Study Design Schematic**




*Upon relapse (at least a 50% loss of Week 24 PASI percent improvement from baseline), subjects will be switched to BMS-986165 6 mg QD.
†Apremilast is titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing as described in Section 4.1.1.2
Abbreviations: BID = twice daily; PASI = Psoriasis Area and Severity Index; QD = once daily; R = randomize

The coprimary endpoints will be evaluated at Week 16. The duration of the study for each subject will be up to 52 weeks on treatment, and 4 additional weeks for safety follow-up.

### *4.1.3 Data Monitoring Committee and Other External Committees*

#### *4.1.3.1 Data Monitoring Committee*

An external data monitoring committee (DMC) with multi-disciplinary representation will be established to evaluate on a periodic basis AEs, laboratory measurements, and safety assessments to ensure the ongoing safety of study subjects. An independent reporting statistician not involved in the conduct of the study will be designated by [redacted] to provide the DMC with essential safety data during the study.

The DMC responsibilities, authorities, and procedures will be documented and followed according to the DMC charter.

#### *4.1.3.2 Infection Adjudication Committee*

An independent Infection Adjudication Committee, composed of individuals with relevant expertise, will blindly review and adjudicate infection AEs, such as opportunistic infections, influenza, herpes zoster, and TB, reported in the study per criteria specified in a separate charter.

Additional information about these infections may be collected on the case report form in order to characterize and understand them. The Adjudication Committee members will be blinded to the treatment assignment of subjects. The structure, responsibilities, and procedures of the Adjudication Committee will be outlined in a charter. The Adjudication Committee is distinct from the DMC and Adjudication Committee members will not be investigators on the study.

#### *4.1.3.3 CV Adjudication Committee*

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

#### *4.1.3.4 Suicidal Ideation and Behavior Adjudication Committee*

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

### 4.2 Number of Subjects

Approximately 1000 qualified subjects will be randomized in a 2:1:1 ratio to BMS-986165 6 mg QD, apremilast 30 mg BID, and placebo, respectively. Sample size considerations are described in Section 9.1.

### 4.3 End of Study Definition

The duration of study participation for individual subjects is expected to be up to 60 weeks (420 days), which includes screening (up to 4 weeks), treatment (52 weeks), and follow-up (up to 4 weeks) periods.

The start of the trial is defined as first visit for first subject screened. The end of the trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities (Section 1.3) for the last subject. Study completion is defined as the final date on which data were or are expected to be collected (Week 56 for collection of potential SAEs).

## 4.4 Scientific Rationale for Study Design

This Phase 3 study will be conducted in a population of subjects with stable moderate-to-severe plaque psoriasis who are candidates for systemic psoriasis therapy. This study is designed to confirm the efficacy and safety of BMS-986165 compared with placebo and apremilast in achieving sPGA of 0/1 and PASI 75 at Week 16. The sPGA and PASI 75 are standard measures in clinical trials of demonstrating efficacy of systemic psoriasis treatments. This study will also examine the efficacy durability after re-randomized withdrawal at Week 24 in subjects who had achieved PASI 75 in the BMS-986165 treatment arm. A placebo arm is included in this study for a short duration of 16 weeks to provide a control for the natural fluctuation of psoriasis activity that may occur and to provide a safety standard for comparison. Subjects in the placebo arm will be switched to BMS-986165 at Week 16 to provide them psoriasis treatment after the endpoints are collected. Apremilast is included as the active control in this study as it is an approved, widely used, oral daily medication for psoriasis. Week 16 was chosen as it would allow enough time for BMS-986165 as well as apremilast to treat psoriasis. In addition, prior apremilast registrational trials had reported psoriasis-related outcomes at Week 16 as their primary endpoints. Randomized withdrawal at Week 24 through Week 52 is considered enough time to assess the efficacy maintenance and durability of BMS-986165 in subjects who had achieved a PASI 75 at Week 24.

# 5 STUDY POPULATION

Eligibility criteria for this study have been carefully considered to ensure 1) selection of appropriate subjects with psoriasis, 2) safety of the study subjects, and 3) the results of the study can be used for regulatory filing and other purposes. It is imperative that subjects fully meet all eligibility criteria.

All screening and randomization evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

## 5.1 Inclusion Criteria

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

1) **Signed Written Informed Consent**
   a) Subjects must be willing to participate in the study and sign the informed consent form (ICF)
2) **Type of Subject and Target Disease Characteristics**
   a) Men and women diagnosed with stable plaque psoriasis for 6 months or more. Stable psoriasis is defined as no morphology changes or significant flares of disease activity in the opinion of the investigator.
   b) Deemed by the investigator to be a candidate for phototherapy or systemic therapy
   c) ≥10% of BSA involvement at screening visit and Day 1
   d) Psoriasis Area and Severity Index (PASI) score ≥12, and static Physician's Global Assessment (sPGA) ≥3 at screening visit and Day 1
3) **Age and Reproductive Status**
   a) Men and women aged ≥18 years at the time of screening visit
   b) Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening visit, and a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [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 must agree to use correctly a highly effective method(s) of contraception for the duration of treatment (52 weeks) with study drug(s) BMS-986165 plus 5 half-lives of study drug (3 days) plus 30 days (duration of ovulatory cycle) for a total of 33 days post-treatment completion (total of 33 days after last dose of study drug). WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, but must still undergo pregnancy testing as described in this protocol
   e) Male subjects who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (APPENDIX 4) for the duration of treatment with study treatment(s) plus 5 half-lives of the study treatment (3 days) for a total of 3 days post-treatment completion. In addition, male subjects must be willing to refrain from sperm donation during this time

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 4), which have a failure rate of < 1% when used consistently and correctly.

## 5.2 Exclusion Criteria

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

**1) Target Disease Exceptions**

a) Has non-plaque psoriasis (ie, guttate, inverse, pustular, erythrodermic, or drug-induced psoriasis) at screening or Day 1

**2) Infectious/Immune-related Exclusions**

a) History or evidence of outpatient active infection and/or febrile illness within 7 days prior to Day 1

b) History of serious bacterial, fungal, or viral infection requiring hospitalization and intravenous (IV) antimicrobial treatment within 60 days prior to Day 1

c) Any untreated bacterial infection within 60 days prior to Day 1

d) Any ongoing evidence of chronic, bacterial infection (eg, chronic pyelonephritis, chronic osteomyelitis, chronic bronchiectasis)

e) Any history of proven infection of a joint prosthesis in which the prosthesis was not removed or replaced, or received antibiotics for suspected infection of a joint prosthesis in which the prosthesis was not removed or replaced

f) Received live vaccines within 60 days prior to Day 1, or plans to receive a live vaccine during the study, or within 60 days after completing study treatment

g) Presence of herpes zoster lesions at screening or Day 1

h) History of serious herpes zoster or serious herpes simplex infection which includes, but is not limited to, any episode of disseminated herpes simplex, multidermatomal herpes zoster, herpes encephalitis, ophthalmic herpes, or recurrent herpes zoster (recurrent is defined as 2 episodes within 2 years)

i) Evidence of, or test positive for, hepatitis B virus (HBV) at screening. Positive hepatitis B lab testing is defined as 1) Positive Hepatitis B Surface Ag (HBsAg+) **OR** 2) Presence of Hepatitis B Virus DNA **OR** 3) Positive anti-hepatitis B core antibody without concurrent positive hepatitis B surface antibody (HBcAb+ and HBsAb-)

j) Evidence of, or test positive for, hepatitis C virus (HCV) at screening. A positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti-HCV Ab), **AND** 2) positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction)

k) Positive for human immunodeficiency virus by antibody testing (HIV-1 and -2 Ab) at screening

**l)** Any history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the subject's immune status (eg, history of opportunistic infections [eg, *Pneumocystis jirovecii* pneumonia, histoplasmosis, or coccidioidomycosis], history of splenectomy, primary immunodeficiency)

**3) Any of the following TB criteria:**

a) History of active TB prior to screening visit, regardless of completion of adequate treatment

b) Signs or symptoms of active TB (eg, fever, cough, night sweats, and weight loss) during screening as judged by the investigator

c) Any imaging of the chest (eg, chest x-ray, chest computed tomography [CT] scan) obtained during the screening period, or anytime within 6 months prior to screening with documentation, showing evidence of current active or history of active pulmonary TB

d) Latent TB infection (LTBI) defined as positive IFN gamma release assay (IGRA), by QuantiFERON-TB Gold testing at screening, in the absence of clinical manifestations

Note: Subject is eligible if (i) there are no current signs or symptoms of active TB **AND** (ii) subject has received adequate documented treatment for LTBI within 5 years of screening **OR** has initiated prophylactic treatment for LTBI per local guidelines and is rescreened after 1 month of treatment. To continue in the study, subject must agree to complete a locally-recommended course of treatment for LTBI. Use of rifampin, however, is not recommended as it can reduce efficacy of apremilast used as a comparator in this trial

Note: An IGRA test that is indeterminate must be retested for confirmation. If the second test is again indeterminate, the subject will be excluded from the study. If the retest is positive, the subject should be treated as having LTBI. If the retest is negative, subject may be eligible provided no other exclusion criteria for TB are met

**4) Medical History and Concurrent Diseases**

a) Any major surgery within 8 weeks prior to Day 1, or any planned surgery for the first 52 weeks of the study

b) Has donated blood >500 mL within 4 weeks prior to Day 1, or plans to donate blood during the course of the study

c) Drug or alcohol abuse, as determined by the investigator, within 6 months prior to Day 1

d) Medical marijuana or prescription marijuana taken for medicinal reasons

e) Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal (GI), endocrine, pulmonary, psychiatric, neurologic, immunologic, or local active infection/infectious illness) that, in the investigator's judgment or after consultation with the medical monitor, will substantially increase the risk to the subject if he or she participates in the study

f) Unstable cardiovascular disease, defined as a recent clinical cardiovascular event (eg, unstable angina, myocardial infarction, stroke, rapid atrial fibrillation) in the last 3 months prior to screening, or a cardiac hospitalization (eg, revascularization procedure, pacemaker implantation) within 3 months prior to screening

g) Has uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) >160 mm Hg or diastolic BP >100 mm Hg

Note: Determined by 2 consecutive elevated readings. If an initial BP reading exceeds this limit, the BP may be repeated once after the subject has rested sitting for ≥10 minutes. If the repeat value is less than the criterion limits, the second value may be accepted

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

i) Has cancer or 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, or carcinoma of cervix in situ that has been treated with no evidence of recurrence)

j) Any uncontrolled neuropsychiatric illness judged as clinically significant by the investigator during screening or at Day 1

**OR**

Any lifetime history of suicidal ideation, suicidal behavior, or suicidal attempts by medical history or by electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) documentation, or by answering "yes" to Question 4 or 5 for suicidal ideation on the eC-SSRS at screening or at Day 1, or is clinically deemed to have a suicide risk by the investigator

k) Prior exposure to investigational product (ie, BMS-986165 or apremilast)

l) If the subject has received biologics previously, the following exclusion criteria for washout will apply:

i) Antibodies to IL-12, IL-17, or IL-23 (eg, ustekinumab, secukinumab, tildrakizumab, ixekizumab, or guselkumab) within 6 months of Day 1

ii) TNF inhibitor(s) (eg, etanercept, adalimumab, infliximab, certolizumab) within 2 months of Day 1

iii) Agents that modulate integrin pathways to impact lymphocyte trafficking (eg, natalizumab), or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, or visilizumab) within 3 months of Day 1

iv) Rituximab within 6 months of Day 1

m) Has received systemic non-biologic psoriasis medications and/or any systemic immunosuppressants therapy (including, but not limited to, methotrexate, azathioprine, cyclosporine, JAK inhibitors, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, or fumaric acid derivatives) within 4 weeks prior to Day 1

n) Has used leflunomide within 6 months prior to Day 1

o) Has used opioid analgesics within 4 weeks prior to Day 1

p) Has received lithium, antimalarials, or intramuscular (IM) gold within 4 weeks of the first administration of any study medication

q) Has used any strong CYP450 inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin) within 4 weeks prior to Day 1

r) Has received phototherapy (including either oral and topical PUVA light therapy, ultraviolet B [UVB] or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to Day 1

s) Has used topical medications/treatments that could affect psoriasis evaluation (including, but not limited to, high potency corticosteroids (WHO Classes I-V), >3% salicylic acid, urea, alpha- or beta-hydroxyl acids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, and tacrolimus) within 2 weeks prior to Day 1

Note: Low potency topical steroids (WHO Class VI and VII) are permitted on the palms, soles, face, and intertriginous areas but should not be used within 24 hours prior to any study visit. Bland emollients (defined as emollients without urea or alpha or beta hydroxy acids or other ingredients which are pharmaceutically active) are allowed on all body regions but should not be used within 24 hours prior to any study visit

t) Use of shampoos that contain corticosteroids, coal tar, >3% salicylic acid, or vitamin D3 analogues within 2 weeks prior to Day 1

u) Has received an experimental antibody or experimental 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) prior to Day 1 **OR** is currently enrolled in an investigational study

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

**5) Physical and Laboratory Evaluations**

a) At Screening

i) Absolute WBC count <3000/$mm^3$

ii) Absolute lymphocyte count <500/$mm^3$

iii) Absolute neutrophil count <1000/$mm^3$

iv) Platelet count <100,000/$mm^3$

v) Hemoglobin <9 g/dL

vi) ALT and/or AST >3 × upper limit of normal (ULN)

vii) Total, unconjugated, and/or conjugated bilirubin >2 × ULN

viii) Thyroid-stimulating hormone (TSH) outside the normal reference range

**AND**

Free T4 (thyroxine) or T3 (triiodothyronine) outside the normal reference range

b) ECG abnormalities that are considered clinically significant and would pose an unacceptable risk to the subject if participating in the study

c) Renal impairment based on an estimated glomerular filtration rate (eGFR) <45 mL/min

d) Inability to be venipunctured and/or tolerate venous access

e) Any other significant laboratory abnormalities that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study

**6) Allergies and Adverse Drug Reactions**

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

**7) 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 BMS approval is required).

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

c) Inability to comply with restrictions and prohibited activities/treatments as listed in the study protocol

d) Site personnel or their immediate family

e) Any contraindications listed in the country-specific label for apremilast

## 5.3 Lifestyle Restrictions

General skin care measures (with above restrictions for topical treatments) that are standard for patients with plaque psoriasis are permitted. Subjects should avoid excessive sun exposure and avoid risks that are known to provoke flare of psoriasis.

### 5.3.1 *Meals and Dietary Restrictions*

Study treatment may be taken without regard to meals; however, subjects are required to fast for a minimum of 10 hours before visits on which fasting lipid samples [redacted] will be drawn. Details are provided in Section 8.5.

### *5.3.2 Caffeine, Alcohol, and Tobacco*

No restrictions are required; however, extensive use of caffeine, alcohol, and tobacco should be avoided.

### *5.3.3 Activity*

No restrictions are required; however, unusual physical exertion should be avoided during the study.

## 5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized in the study for any reason. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated

Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal set of screen failure information includes date of consent, demography, screen failure details (ie, eligibility criteria that the subject did not meet), and any serious AEs during the screening period.

### *5.4.1 Retesting During Screening or Rescreening*

For laboratory parameters that initially do not meet eligibility requirements, a single retest within the 28-day screening period is permitted before subject is declared a screen failure. This is 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.

The study permits the rescreening (after the end of the initial 28-day screening period) of a subject who discontinues the study as a pretreatment failure (ie, the subject fails to meet eligibility criteria and has not been treated). The subject must be reconsented and will be assigned a new identification number, and a full screening visit must be performed again. A subject can only be rescreened 1 time (ie, if the subject fails 1 rescreening attempt, no additional rescreening is allowed). Depending on the timing of rescreening, repeat chest imaging may not be required. Duration of existing treatments and required discontinuation periods shall be considered relative to the new screening visit and/or randomization.

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

## 6 TREATMENT

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

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following: BMS-986165, placebo, and apremilast.

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.

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. Table 5 shows the study treatments for Protocol IM011047.

**Table 5: Study Treatments for IM011047**

| Product Description / Class and Dosage Form | Potency | IP/Non-IMP | Blinded or Open Label | Packaging / Appearance | Storage Conditions (per label) |
|---|---|---|---|---|---|
| BMS-986165 tablet | 6 mg | IP | Blinded | Bottle | Store at 15 to 25°C; Store in a tightly closed container; Protect from light |
| Placebo tablet to match BMS-986165 6 mg | n/a | IP | Blinded | Bottle | Store at 15 to 25°C; Store in a tightly closed container; Protect from light |
| Apremilast tablet | 10 mg* | IP | Blinded | Blister card | Store tablets below 30°C (86°F). Store in original container |
| Placebo tablet to match apremilast 10 mg | n/a | IP | Blinded | Blister card | Store tablets below 30°C (86°F). Store in original container |
| Apremilast tablet | 20 mg† | IP | Blinded | Blister card | Store tablets below 30°C (86°F). Store in original container |
| Placebo tablet to match apremilast 20 mg | n/a | IP | Blinded | Blister card | Store tablets below 30°C (86°F). Store in original container |
| Apremilast tablet | 30 mg‡ | IP | Blinded | Bottle | Store tablets below 30°C (86°F). Store in original container |
| Placebo tablet to match apremilast 30 mg | n/a | IP | Blinded | Bottle | Store tablets below 30°C (86°F). Store in original container |

IP = investigational product; IMP = investigational medicinal product; n/a = not applicable

*Used for titration Day 1 through Day 3 morning dose
†Used for titration Day 3 evening dose through Day 5 morning dose
‡From Day 5 evening dose onwards.

## 6.1 Treatments Administered

Study treatment will be administered as described in Section 4.1.1.2. The selection and timing of dose for each subject is as follows:

**Table 6: Selection and Timing of Dose**

| Study Treatment | Unit dose strength(s)/Dosage level(s) | Dosage formulation Frequency of Administration | Route of Administration |
|---|---|---|---|
| 6 mg QD BMS-986165 | 6 mg | 1 active tablet QD in the morning; 1 placebo titration kit* then 2 apremilast placebo (1 tablet in the morning, 1 tablet in the evening) | oral |
| 30 mg BID apremilast | 30 mg | 1 active titration kit* then 1 active morning and evening and 1 BMS-986165 placebo QD in the morning | oral |
| Placebo BID | n/a | 1 placebo apremilast titration kit* then 2 apremilast placebo (1 tablet in the morning, 1 tablet in the evening) and 1 BMS-986165 placebo QD in the morning | oral |

Abbreviations: BID = twice daily; n/a = not applicable; QD = once daily

*Titration kit described in Section 6.1.1.

### *6.1.1 Titration Kit for Active and Placebo Apremilast*

Apremilast will be titrated over 5 days to a maintenance dose of 30 mg BID. To maintain the blind between subjects receiving apremilast and BMS-986165 during the titration period, active apremilast and matching apremilast placebo tablets will be provided. This will be supplied in an 18-day titration kit as follows:

One 10 mg tablet in the morning on Day 1; two 10 mg tablets (one in the morning, one in the evening) on Day 2; one 10 mg tablet in the morning and one 20 mg tablet in the evening on Day 3; two 20 mg tablets (one tablet in the morning, one tablet in the evening) on Day 4; one 20 mg tablet in the morning and one 30 mg tablet in the evening on Day 5; one 30 mg tablet in the morning and one 30 mg tablet in the evening for each Day 6 through Day 18.

## 6.2 Method of Treatment Assignment

Before the study is initiated, each user (at investigative sites) will receive log-in information and directions on how to access the interactive response technology (IRT) system. At the time of the screening visit, immediately after informed consent is obtained and before any study-related procedures are performed, the investigative site will access the enrollment option of the IRT system for assignment of a subject number for all subjects, including subjects not subsequently randomized or treated. The subject number is assigned sequentially by the system and will be unique across all sites. All enrolled subjects will be assigned sequential subject numbers. The

subject number will not be used for any other subject. If a subject is rescreened, they will be given a new identification number.

At Week 0 (Day 1), subjects who meet all criteria for enrollment at Screening and Day 1 will be centrally randomized in a 2:1:1 ratio to BMS-986165 6 mg QD, placebo, or apremilast 30 mg BID as determined by a computer-generated randomization schedule using IRT. The randomization lists will be generated by the IRT vendor using a permuted block design within each combination of stratum level. The randomization in this study will be stratified by geographic region geographic region (US and rest of world), previous biologic use for psoriasis, psoriatic arthritis or other inflammatory disease (yes/no), and body weight (≥90 kg and <90 kg). As this is designed to be a global study across multiple countries, randomization in each country will be targeted to approximately 35% or less of the total sample size. This change is being implemented to achieve geographical representation across countries and to minimize the potential for any single country to have a disproportionate impact on the overall efficacy and/or safety profile.

After all inclusion/exclusion criteria have been met for a subject, the investigative site will access the IRT on Day 1 for the purposes of randomizing a subject. A treatment group will be assigned by IRT based on the above-described randomization schedule and each subject will be assigned a unique randomization number. In addition, a unique kit number will be assigned to the subject corresponding to the treatment assignment.

At the Week 0 and Week 2 visits, a kit with a 2-week supply of study treatment is provided. At all subsequent visits, kits will contain adequate study treatment for a 4-week supply. At subsequent visits, when new treatment kits are to be dispensed, the investigative site will access the IRT to obtain the kit number to assign to the subject. Study treatment will be dispensed at study visits as shown in the Schedule of Activities (Section 1.3).

At Week 16, subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD.

At Week 24, subjects originally randomized to BMS-986165 6 mg QD who do not achieve PASI 75 will continue to receive BMS-986165 6 mg QD in a blinded manner. Subjects who achieve PASI 75 response will be re-randomized in a blinded manner to either BMS-986165 6 mg QD or placebo. Subjects re-randomized to placebo who experience a relapse at a subsequent visit will be switched back onto BMS-986165 6 mg QD in a blinded manner. The investigative site and other study personnel will not be provided with the PASI 75 scores at these visits.

At Week 24, subjects originally randomized to apremilast 30 mg BID who do not achieve PASI 75 response will be switched in a blinded manner to BMS-986165 6 mg QD while subjects who achieve PASI 75 response at Week 24 will be switched in a blinded manner to placebo. If a relapse occurs at a subsequent visit, they will be switched in a blinded manner to BMS-986165 6 mg QD. The investigative site and other study personnel will not be provided with the PASI 75 scores at these visits.

### 6.2.1 Method of Study Treatment Assignment at Week 24 and Subsequent Visits Impacted by COVID-19-related Issues

At Week 24, when COVID-19-related issues result in the subject visit being missed or conducted remotely, the study treatment assigned by the IRT system will not be determined by the PASI 75 response, because PASI assessments will not be done. The study treatment assigned by the IRT system will be defaulted to BMS-986165 6 mg QD for the duration of the study.

For all subsequent visits post Week 24, when COVID-19-related issues result in the subject visit being missed or conducted remotely, the study treatment assigned by the IRT system will not be determined by the PASI relapse response, because PASI assessments will not be done. Study treatment assignment will be done as per the following:

- Missed visits: the study treatment assigned by the IRT system will be the study treatment assigned at the previous visit
- Visits conducted remotely: the study treatment assigned by the IRT system will be defaulted to BMS-986165 6 mg QD for the duration of the study

## 6.3 Blinding

### 6.3.1 Maintaining the Blind

Blinded treatment assignments will be managed using IRT.

All tablets are identical in appearance and will be supplied in blister cards or bottles with each daily dose made up of the appropriate combination of active and/or placebo tablets to provide the correct treatment, as shown in Table 5. Investigative site staff, Sponsor and designee personnel, and subjects and their families will remain blinded to treatment assignments. [redacted]

### 6.3.2 Circumstances for 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, ie, 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 investigator 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 case of an emergency, the investigator has unrestricted access to randomization information via IRT and is capable of breaking the blind through the IRT system without prior approval from the sponsor. After the unblinding, the investigator shall notify the medical monitor and/or study director. The method of unblinding for emergency purposes is described in the IRT manual. Subject and unblinded treatment information and the reason for the blind being broken must be recorded on the appropriate study status page of the electronic case report form (eCRF). After unblinding via IRT, the investigator shall notify the medical monitor.

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 must be discussed with the medical monitor prior to unblinding.

## 6.4 Dosage Modification

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

## 6.5 Preparation/Handling/Storage/Accountability

The 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.

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

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

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

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

### *6.5.1 Retained Samples for Bioavailability/Bioequivalence*

Not applicable.

## 6.6 Treatment Compliance

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

## 6.7 Concomitant Therapy

### *6.7.1 Prohibited and/or Restricted Treatments*

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

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

**2)** Any concurrent use of strong CYP450 inducers according to the US package insert for apremilast as it may reduce apremilast efficacy. Examples include rifampin, phenobarbital, carbamazepine, and phenytoin, unless it is considered necessary for the subject's welfare and/or treatment of an AE/SAE.

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

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

**5)** Phototherapy; use of tanning booths or therapeutic sunbathing.

**6)** Any use of biologic medications (eg, adalimumab, etanercept, infliximab, ustekinumab).

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

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

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

**9)** Any topical medications/treatments, which are used for any indication, that could affect psoriasis evaluation (including, but not limited to, high potency corticosteroids (WHO Classes I-V), >3% salicylic acid, urea, alpha- or beta-hydroxyl acids, anthralin, calcipotriene, vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, and tacrolimus).

Exception: The following topical treatments may be initiated only at Week 24 per investigator's discretion in subjects who have [redacted] (See Section 4.1.2.1):

- High potency corticosteroids (WHO Classes I-V), >3% salicylic acid, urea, alpha- or beta-hydroxyl acids, anthralin, calcipotriene, vitamin D derivatives, retinoids, tazarotene.

Note: Low potency topical steroids (WHO Classes VI and VII) are permitted on the palms, soles, face, and intertriginous areas but should not be used within 24 hours prior to any study

visit. Bland emollients (defined as emollients without urea or alpha or beta hydroxy acids or other ingredients which are pharmaceutically active) are allowed on all body regions but should not be used within 24 hours prior to any study visit.

**10)** Any medicated shampoos that contain corticosteroids, coal tar, >3% salicylic acid, or vitamin D3 analogues.

Exception: The above shampoos may be initiated only at Week 24 per investigator's discretion in subjects who have [redacted] (See Section 4.1.2.1):

**11)** Live vaccination

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

The investigator should contact and confirm agreement with the medical monitor prior to the administration of any concomitant medications.

### *6.7.2 Permitted Concomitant Medications*

Stable doses of concomitant medication for chronic medical conditions, except for psoriasis, are permitted as long as neither the medication nor the medical condition meet exclusion criteria as detailed in Section 5.2. Dose adjustments of these medications should be avoided during the study unless clinically indicated. If a dose adjustment of these medications should occur, they must be recorded on the Concomitant medications eCRF or the Procedures and Significant non-drug therapies eCRF. The investigator should instruct the subject to notify the study site about any new treatments he/she takes after the start of the study treatment. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts study treatment must be listed on the Concomitant medications eCRF or the Procedures and Significant non-drug therapies eCRF.

Note: Low potency topical steroids (WHO Classes VI and VII) are permitted on the palms, soles, face, and intertriginous areas but should not be used within 24 hours prior to any study visit. Bland emollients (defined as emollients without urea or alpha or beta-hydroxy acids or other ingredients which are pharmaceutically active) are allowed on all body regions but should not be used within 24 hours prior to any study visit.

### *6.7.3 Rescue Medications*

At Week 24, a subject who has an sPGA [redacted] may be treated with restricted topicals or shampoos, respectively, at the investigator's discretion (see Section 6.7.1). These treatments may be only initiated at Week 24, and not at subsequent time points. A subject who is initiated on these treatments at Week 24 may use them as needed per the investigator's judgment through Week 52.

## 6.8 Treatment After the End of the Study

At the end of the study, the investigator should ensure that subjects continue to receive appropriate standard of care to treat the condition under study.

In addition, for subjects who continue to demonstrate clinical benefit, BMS may continue to provide study treatment via a rollover extension study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS.

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

# 7 DISCONTINUATION CRITERIA

## 7.1 Discontinuation from Study Treatment

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

- Subject requests to stop study treatment. Subjects who discontinue study treatment early should remain in the study for protocol-specified 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 subject to provide this information.
- Any clinically significant AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject. If treatment is discontinued due to an AE, the AE eCRF must be completed to show that the AE caused discontinuation
- eGFR <45 mL/min on repeat assessment within 7 days
- Abnormal liver tests suggestive of drug-induced liver injury (DILI), as defined in Section 8.2.8 or if the investigator believes that it is in the best interest of the subject
- Subject reports suicidal ideation, suicidal behavior, or suicide attempts at any time after randomization, or documents suicidal ideation by answering “Yes” to Question 4 or 5 on the eC-SSRS, or documents suicidal behavior on the eC-SSRS at any time during the study. The subject should then be immediately referred to a mental health professional for evaluation of suicide risk
- The subject develops a malignancy, with the exception of a subject who develops non-melanoma skin cancer who may continue in the study at the discretion of the investigator
- Pregnancy, positive pregnancy test, or subject expresses an interest in becoming pregnant (refer to Section 8.2.6)
- Subject develops active TB during the study or prematurely discontinues treatment for LTBI, or subject is noncompliant with LTBI therapy (refer to Section 8.4.4)
- Termination of the study or program by BMS

- Unblinding of a subject's treatment assignment for any reason (emergency or nonemergency)
- Inability or failure to comply with protocol requirements in the opinion of the investigator
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All subjects who discontinue BMS-986165 should comply with protocol-specified follow-up procedures as outlined in Section 1.3. 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 (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). Replacement of subjects is not permitted.

If study treatment is discontinued 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 eCRF page.

### *7.1.1 Temporary Discontinuation of Study Medication*

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

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

### *7.1.2 Post-Study Treatment Follow-Up*

Post-treatment follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcomes and/or survival follow-up data as required and in line with Section 4 until death or the conclusion of the study.

Subjects who discontinue study treatment should be encouraged to undergo all study-related visits for the full treatment period in order to support the final efficacy and safety analysis.

## 7.2 Discontinuation from the Study

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures specified in Section 1.3. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information.

- Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.

- The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate 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.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

### 7.3 Lost to Follow-up

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

## 8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 1.3) and described in Section 4.1.
- Protocol waivers or exemptions are not allowed.
- All significant safety concerns must be discussed with the medical monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria before randomization. Randomization should not occur until at least 8 days after the screening visit to allow collection of PSSD data during screening in order to calculate a baseline PSSD score. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline

purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

- For several assessments, appropriate training will be provided to investigators and designated personnel at sites. Only those individuals trained and certified to perform these assessments will be performing them during the study.

## 8.1 Efficacy Assessments

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

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

### *8.1.1 Investigator-administered Assessments*

#### *8.1.1.1 static Physician's Global Assessment (sPGA)*

The sPGA is a 5-point scale of an average assessment of all psoriatic lesions based on erythema, scale, and induration.[24] The sPGA measure determines psoriasis severity at a single point in time (without taking into account the baseline disease condition) as clear (0), almost clear (1), mild (2), moderate (3), or severe (4). sPGA assessments should be performed by a trained physician (eg, 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 5).

#### *8.1.1.2 Psoriasis Area and Severity Index (PASI)*

The PASI is a measure of the average redness, thickness, and scaliness of psoriatic skin lesions (each graded on a 0 -4 scale), weighted by the area of involvement (head, arms, trunk to groin, and legs to top of buttocks).[25] 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 the baseline value. The PASI 75, PASI 90, and PASI 100 are defined similarly. BMS will host a training session prior to initiation of the study to demonstrate proper PASI scoring. PASI assessments should be performed by a trained physician (dermatologist) or appropriately trained investigator who is experienced in the assessment of psoriasis patients (see APPENDIX 6).

#### *8.1.1.3 Body Surface Area (BSA)*

Measurement of psoriasis body surface area involvement is estimated using the handprint method with the size of a subject's handprint (including fingers and thumb) representing 1% of body

surface area involved.[26,27,28] 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.

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

For this assessment in subjects with scalp involvement,[29] scalp lesions are evaluated in terms of clinical signs of redness, thickness, and scaliness and scored on the following 5-point ss-PGA scale:

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

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

[redacted]

#### 8.1.1.6 Physician's Global Assessment-Fingernails (PGA-F)

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

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

The PGA-F will be performed only in subjects with psoriatic fingernail involvement to assess severity and subsequent improvement. An example is provided in APPENDIX 9. The PGA-F should be performed by a dermatologist or appropriately trained investigator who is experienced in the assessment of psoriasis patients.

[redacted]

[redacted]

#### 8.1.1.8 Palmoplantar PGA (pp-PGA)

This measure will be used for subjects with palmoplantar (including the finger and toe surfaces) involvement at baseline.[33] The pp-PGA uses a 5-point (0-4) scale: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe (see APPENDIX 11). The pp-PGA should be performed by a dermatologist or appropriately trained investigator who is experienced in the assessment of psoriasis patients.

[redacted]

### 8.1.2 Subject-reported Assessments

#### 8.1.2.1 Psoriasis Symptoms and Signs Diary (PSSD)

The PSSD is an 11-item subject-reported instrument that assesses severity of symptoms and subject-observed signs commonly associated in plaque psoriasis.[35,36] It has been shown to be reliable and valid in measuring symptoms and signs of subjects with moderate-to-severe plaque psoriasis in the clinic and has strong psychometric properties in assessing treatment effects in clinical trials.[37] The PSSD assesses severity of 5 symptoms (itch, pain, stinging, burning, skin tightness) and 6 subject-observed signs (skin dryness, cracking, scaling, shedding or flaking, redness, bleeding) using 0 to10 numerical ratings. The severity of each item is rated on an 11-point numeric rating scale ranging from 0 (absent) to 10 (worst imaginable). Two versions of the PSSD were developed, one with a 24-hour recall period (PSSD-24h) and one with a 7-day recall period. The PSSD-24h will be administered daily in this trial to avoid recall bias with a longer recall period (see APPENDIX 13).

#### 8.1.2.2 Dermatology Life Quality Index (DLQI)

The DLQI[38] is a subject-reported quality of life index which consists of 10 questions concerning symptoms and feelings, daily activities, leisure, work, school, personal relationships, and treatment during the last week. Each question is scored on a scale of 0 to 3 by a tick box: 0 - “not at all,” 1 –

"a little," 2 – "a lot," or 3 – "very much." The scores are summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment) (see APPENDIX 14).

[redacted]

[redacted]

#### 8.1.2.8 Psoriatic Arthritis Screening and Evaluation (PASE) Questionnaire

The psoriatic arthritis screening and evaluation (PASE) questionnaire will be administered at screening in subjects with peripheral joint complaints. The PASE questionnaire is a self-administered tool that is used to screen for psoriatic arthritis among subjects who have psoriasis. The PASE questionnaire consists of 15 questions subdivided into 7 questions focusing on symptoms of psoriatic arthritis, and 8 questions focusing on the impact of psoriatic arthritis on function. Each question is scored on a 1 to 5 scale, with a maximum score of 75. A score of 47 or above has been shown to distinguish between psoriatic arthritis and non-psoriatic arthritis.[44] This questionnaire is only intended to be a screening tool for psoriatic arthritis and does not replace a comprehensive musculoskeletal exam performed by a rheumatologist. The PASE questionnaire should take 6 to 10 minutes to complete and is only done at screening (see APPENDIX 20).

## 8.2 Adverse Events

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

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

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

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

### 8.2.1 Adverse Events of Interest

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

information about certain skin-related AEs, infection AEs, CK elevation, and malignancy may be collected on the case report form in order to better characterize and understand them.

### 8.2.2 Time Period and Frequency for Collecting AE and SAE Information

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

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

All SAEs must be collected from the date of subject's written consent until 30 days after the final dose of the study drug or subject's participation in the study if the last scheduled visit occurs at a later time. Monitoring for SAEs will occur at every study visit.

- The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure. Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in APPENDIX 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

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

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

### 8.2.3 Method of Detecting AEs and SAEs

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

### 8.2.4 Follow-up of AEs and SAEs

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

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

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

### 8.2.5 Regulatory Reporting Requirements for SAEs

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

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

### 8.2.6 Pregnancy

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

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

Any pregnancy that occurs in a female partner of a male study subject should be reported to [redacted] Drug Safety. In order for Sponsor or designee 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.

### 8.2.7 Laboratory Test Result Abnormalities

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

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

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

### *8.2.8 Potential Drug-Induced Liver Injury (DILI)*

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

Potential drug-induced liver injury is defined as:

**1)** Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation > 3 times ULN

**AND**

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

**AND**

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

### *8.2.9 Other Safety Considerations*

Any significant worsening of a pre-existing medical condition noted during interim or final PE, ECG, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

## 8.3 Overdose

For this study, taking more than 2 days' worth of study treatment within a 24-hour time period will be considered an overdose.

In the event of an overdose the investigator should:

**1)** Contact the medical monitor immediately

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

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the subject.

## 8.4 Safety

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

### 8.4.1 Physical Examinations

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

### 8.4.2 Vital signs

Refer to Schedule of Activities (Section 1.3).

### 8.4.3 Electrocardiograms

A 12-lead electrocardiogram will be performed at the visits indicated in the Schedule of Activities. The subject will remain supine for 5 to 10 minutes prior to the ECG and must have their lab work done after the tracing so that the ECG results remain as accurate as possible. The ECG results will be read by the primary study investigator or a designee.

### 8.4.4 Tuberculosis Screening and Chest Imaging

Chest imaging results and PE are part of the process to assess a subject's eligibility, as outlined in Section 1.3 and as defined in exclusion criterion 3.c (Section 5.2). Chest imaging (eg, chest x-ray, chest CT scan) at the screening visit is required if not already performed and documented within 6 months of obtaining written informed consent. A subject must not have active signs or symptoms of TB, as judged by the investigator, to be eligible for the study.

In addition to a complete PE and medical history to evaluate exposure to TB, all subjects will have a screening test, an IGRA (eg, QuantiFERON®-TB Gold) performed centrally. If unable to obtain central laboratory results, an IGRA test could be obtained locally, after consultation with the [redacted] medical monitor. A subject with an indeterminate IGRA test result must be retested for confirmation. If the second result is again indeterminate, the subject will be excluded from the study. If the second result is positive, the subject should be considered as having LTBI provided there are no signs or symptoms of active TB. If the second result is negative, the subject may be eligible provided no other exclusion criterion for TB is met.

### 8.4.5 Clinical Safety Laboratory Assessments

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

| **Hematology** | |
|---|---|
| Hemoglobin (Hgb)<br>Hematocrit (Hct)<br>White Blood Cell Count, including differential<br>Platelet Count | |
| **Chemistry** | |
| AST<br>ALT<br>Total Bilirubin | Total Protein<br>Albumin<br>Sodium |

| | |
|---|---|
| Direct Bilirubin (if total bilirubin > ULN)<br>Alkaline Phosphatase<br>Lactate Dehydrogenase (LDH)<br>Creatinine<br>Blood Urea Nitrogen (BUN)<br>Uric Acid<br>Glucose (fasting at some visits) | Potassium<br>Chloride<br>Calcium<br>Phosphorus<br>Creatine Kinase (CK)*<br>Estimated Glomerular Filtration Rate (eGFR) |
| **Urinalysis** | |
| Protein<br>Glucose<br>Blood<br>Leukocyte Esterase<br>Specific Gravity<br>pH<br>Microscopic Examination (reflex if abnormal) | |
| **Lipid Panel** | |
| Cholesterol (total)<br>High Density Lipoprotein (HDL)<br>Low Density Lipoprotein (LDL)<br>Triglycerides | |
| **Infectious Serologies** | |
| Hepatitis C Antibody with reflex to Hepatitis C RNA if positive<br>Hepatitis B Surface Antigen (HBsAg)<br>Hepatitis B Surface Antibody (HBsAb)<br>Hepatitis B Core Antibody (HBcAb)<br>Hepatitis B DNA Viral Load (HBV DNA)<br>HIV-1 and -2 antibody | |
| **Other Analyses** | |
| Pregnancy test (WOCBP only: serum hCG test at screening, followed by urine hCG test every 4 weeks)<br>Follicle-stimulating Hormone (FSH) (to confirm menopausal status [see APPENDIX 4], at screening)<br>Hemoglobin A1C<br>Thyroid-Stimulating Hormone (TSH)<br>• If TSH above normal reference range, test free T4; if TSH below normal range, test free T4 & T3<br>High-Sensitivity C Reactive Protein (hs-CRP)<br><br>Serum Immunoglobulins (IgM, IgG, IgA, IgE) | |

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

#### *8.4.5.1 Estimated Glomerular Filtration Rate (eGFR)*

Glomerular filtration rate will be estimated using the Modification of Diet in Renal Disease (MDRD) equation at screening and during the study at select visits.

The MDRD equation is as follows:[45]

$$eGFR = 175 \times \text{standardized } SCr^{-1.154} \times age^{-0.203} \times 1.212 \text{ [if black] or } 0.742 \text{ [if female]}$$

Note: GFR is expressed as mL/min/1.73 $m^2$ of body surface area and SCr (serum creatinine) is expressed in mg/dL.

Subjects with an eGFR <45mL/min will be excluded from participation

### 8.4.6 Depression Monitoring

Depression will be monitored by administration of the Eight-item Patient Health Questionnaire (PHQ-8) at screening and during visits as outlined in Section 1.3.

#### 8.4.6.1 Eight-item Patient Health Questionnaire (PHQ-8)

The PHQ-8 is established as a valid diagnostic and severity measure for depressive disorders in large clinical studies.[46] Each of the 8 questions is based on a 2-week recall and scored on a scale of 0 to 3 by a tick box as: Not at All, Several Days, More than Half the Days, and Nearly Every Day. A score of ≥ 10 is suggestive of moderate depressive symptoms (see APPENDIX 21).[47] If a subject scores ≥ 15 on the PHQ-8 during the study, the investigator will review the situation and refer the subject to a mental health professional if deemed necessary.

### 8.4.7 Suicidal Ideation and Behavior (SIB) Monitoring

Subjects in this clinical trial will be monitored for suicidal ideation and behavior by the eC-SSRS (Section 8.4.7.1) at the visits outlined in the Schedule of Activities (Section 1.3). Subjects who answer "yes" to Questions 4 or 5 which indicates a suicidal ideation severity level of 4 or 5 or document suicidal behavior or suicidal attempts on the eC-SSRS will have their treatments discontinued and be immediately referred to a mental health professional for further evaluation. In addition, family members or caregivers of the subjects will be instructed to immediately report any suicidal ideation, suicidal behavior, or suicide attempt to the investigator.

#### 8.4.7.1 electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) is a computer-automated, patient-reported version of the C-SSRS instrument that defines 11 categories of suicidal ideation and behavior events.[48,49,50] The categories are as follows:

- Suicidal ideation
  1. Passive
  2. Active: Nonspecific (no method, intent, or plan)
  3. Active: Method, but no intent or plan
  4. Active: Method and intent, but no plan
  5. Active: Method, intent, and plan
- Suicidal behavior
  1. Completed suicide
  2. Suicide attempt
  3. Interrupted attempt
  4. Aborted attempt

5. Preparatory actions toward imminent suicidal behaviors

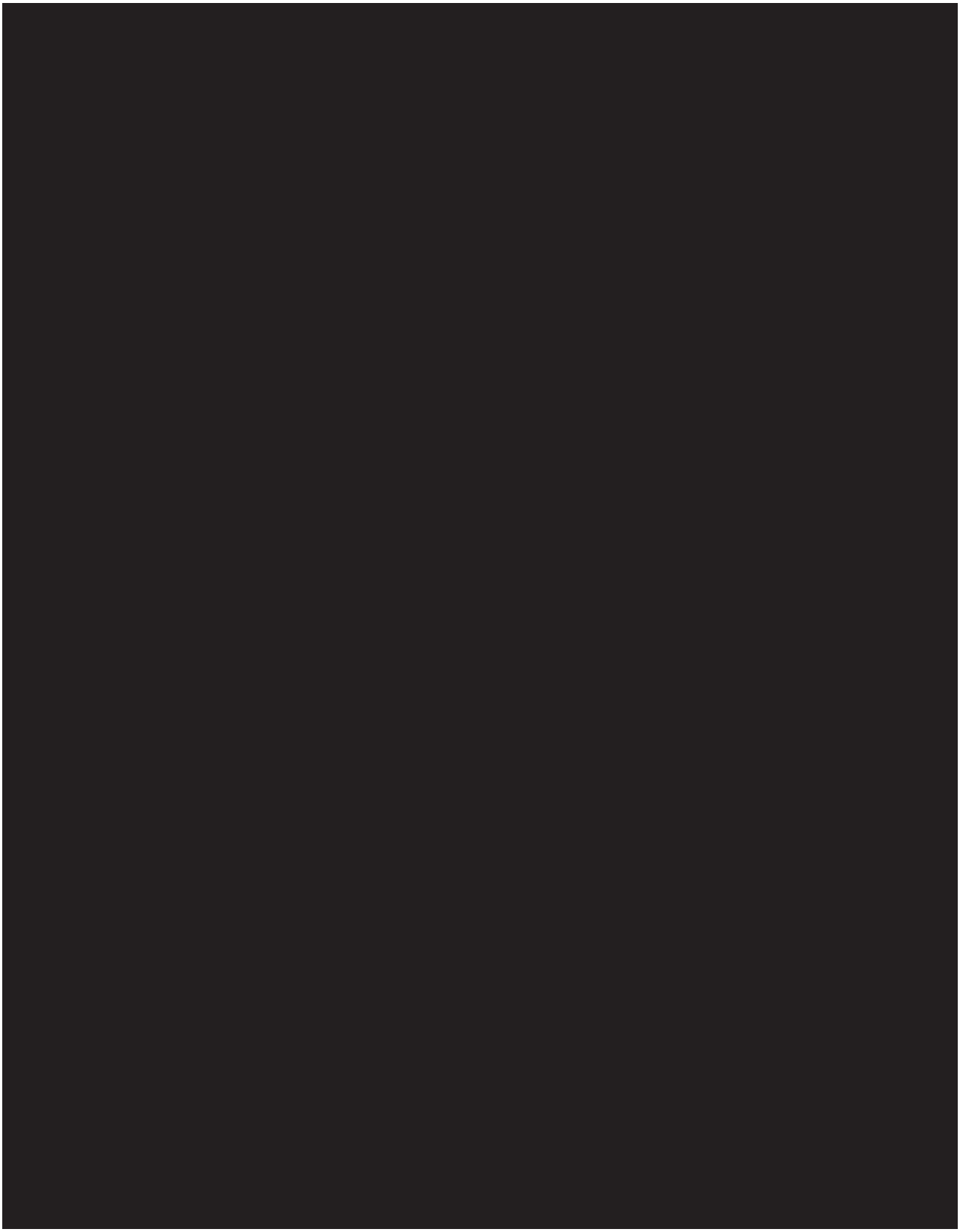
- Self-injurious behavior, no suicidal intent

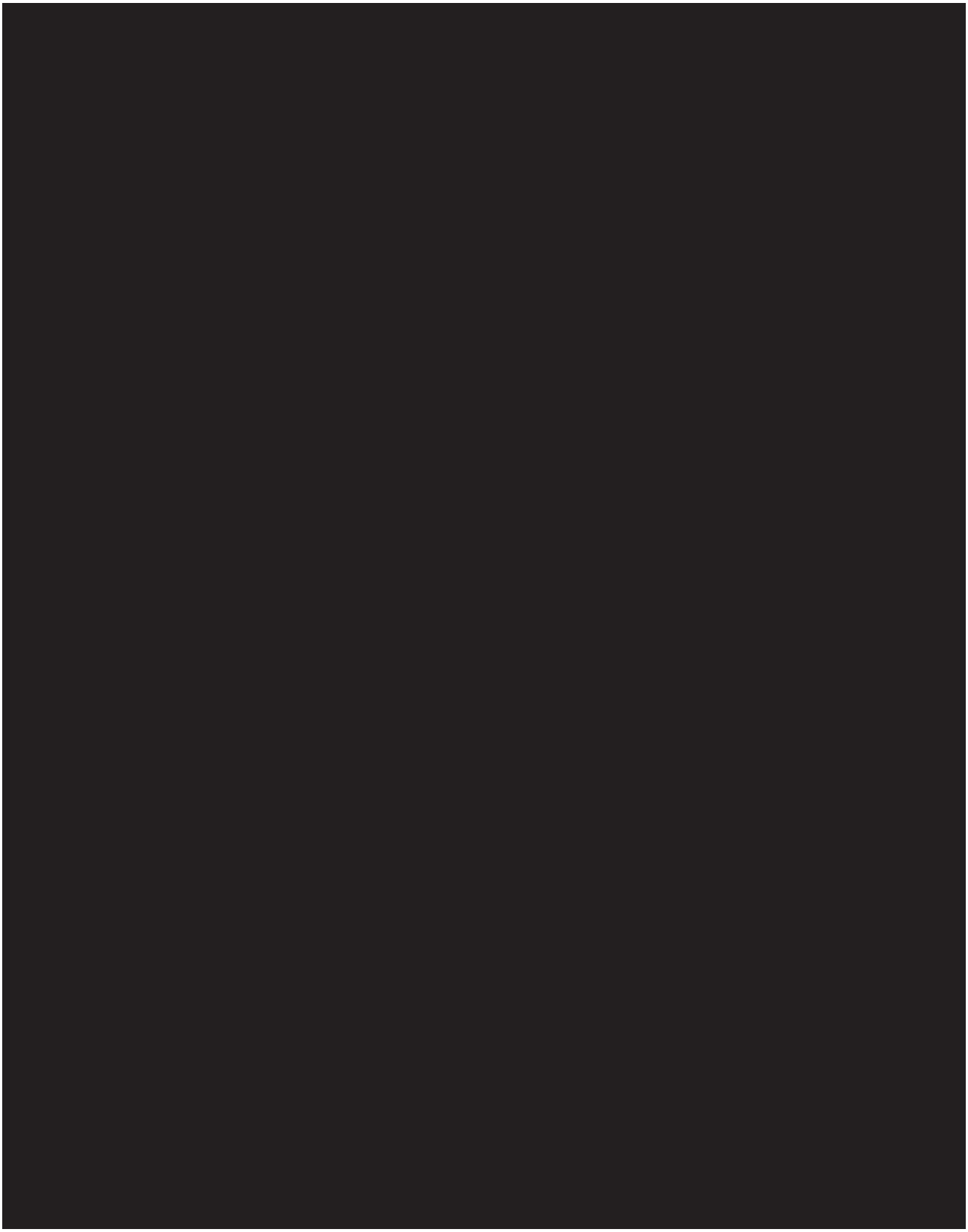
APPENDIX 22 provides definitions of these categories.[51]

### 8.4.8 Imaging Safety Assessment

Not applicable.

[redacted]





[redacted]

## 8.7 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

[redacted]

[redacted]

## 9.2 Populations for Analyses

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

**Enrolled Population:** All subjects who sign informed consent.

**Full Analysis Set (FAS):** All subjects who were randomized to receive assigned study treatment. Following the intent-to-treat principle, subjects will be analyzed according to the treatment group assigned at randomization. The FAS will be the primary efficacy analysis population.

**Per Protocol Set (PPS):** A subset of the FAS who are compliant with study treatment and who do not have any relevant protocol deviations that may impact the coprimary efficacy endpoint assessments (Section 9.6.3). The PPS will be analyzed for the coprimary endpoint comparisons according to the treatment assigned at randomization.

**Randomized Withdrawal Population:** Defined as all Week 24 responder subjects who are re-randomized and received at least one dose of study treatment during the randomized withdrawal and maintenance period. Subjects will be analyzed according to the treatment assigned at Week 24.

**As-treated Population:** All randomized subjects who take at least one dose of study treatment. Subjects will be analyzed according to treatment received. The As-treated population will be for safety analyses.

[redacted]

## 9.3 Endpoints

### *9.3.1 Primary Endpoints*

The coprimary efficacy endpoints for BMS-986165 compared to placebo at Week 16 are defined as:

- sPGA 0/1 response assessed as a proportion of subjects with a sPGA score of 0 or 1

- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score

### 9.3.2 Secondary Endpoints

#### 9.3.2.1 Key Secondary Endpoints for Comparisons to Placebo

The key secondary endpoints for BMS-986165 compared to placebo at Week 16 are defined as:

- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score
- PASI 100 response assessed as a proportion of subjects who achieve a 100% improvement from baseline in the PASI score
- sPGA 0 response assessed as a proportion of subjects with a sPGA score of 0
- Change from baseline in PSSD symptom score
- PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score $\geq 1$
- ss-PGA 0/1 assessed as a proportion of subjects with a ss-PGA score 0 or 1 among subjects with a baseline ss-PGA score $\geq 3$
- DLQI 0/1 assessed as a proportion of subjects with a DLQI score of 0 or 1 among subjects with a baseline DLQI score $\geq 2$
- PGA-F 0/1 assessed as a proportion of subjects with a PGA-F score of 0 or 1 among subjects with a baseline PGA-F score $\geq 3$
- pp-PGA 0/1 assessed as a proportion of subjects with a pp-PGA score of 0 or 1 among subjects with a baseline pp-PGA score $\geq 3$

An additional key secondary endpoint to assess the maintenance and durability of efficacy of BMS-986165 during the randomized withdrawal period through Week 52 among Week 24 PASI 75 responders compared with re-randomized placebo is defined as:

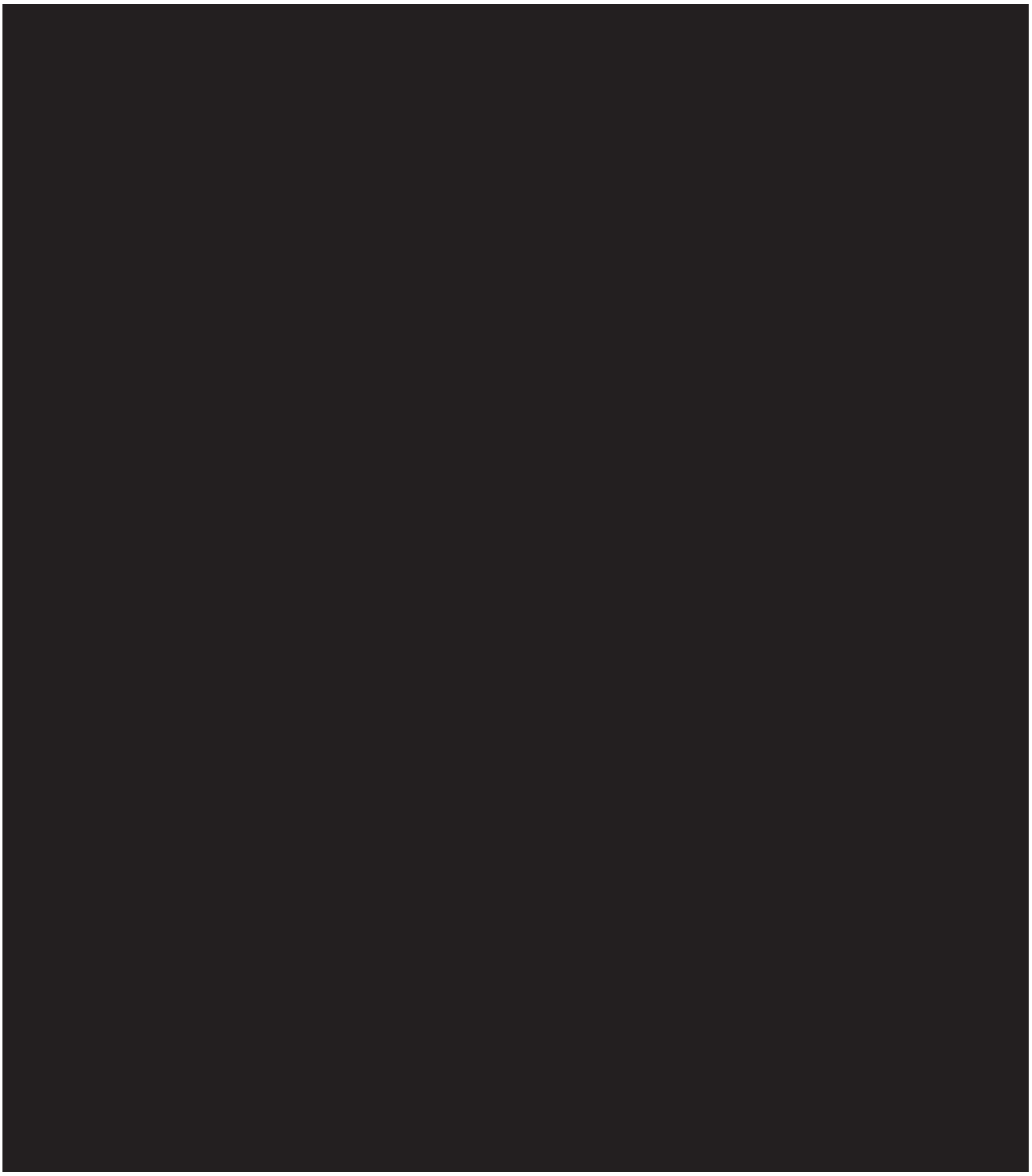
- Time to relapse until Week 52

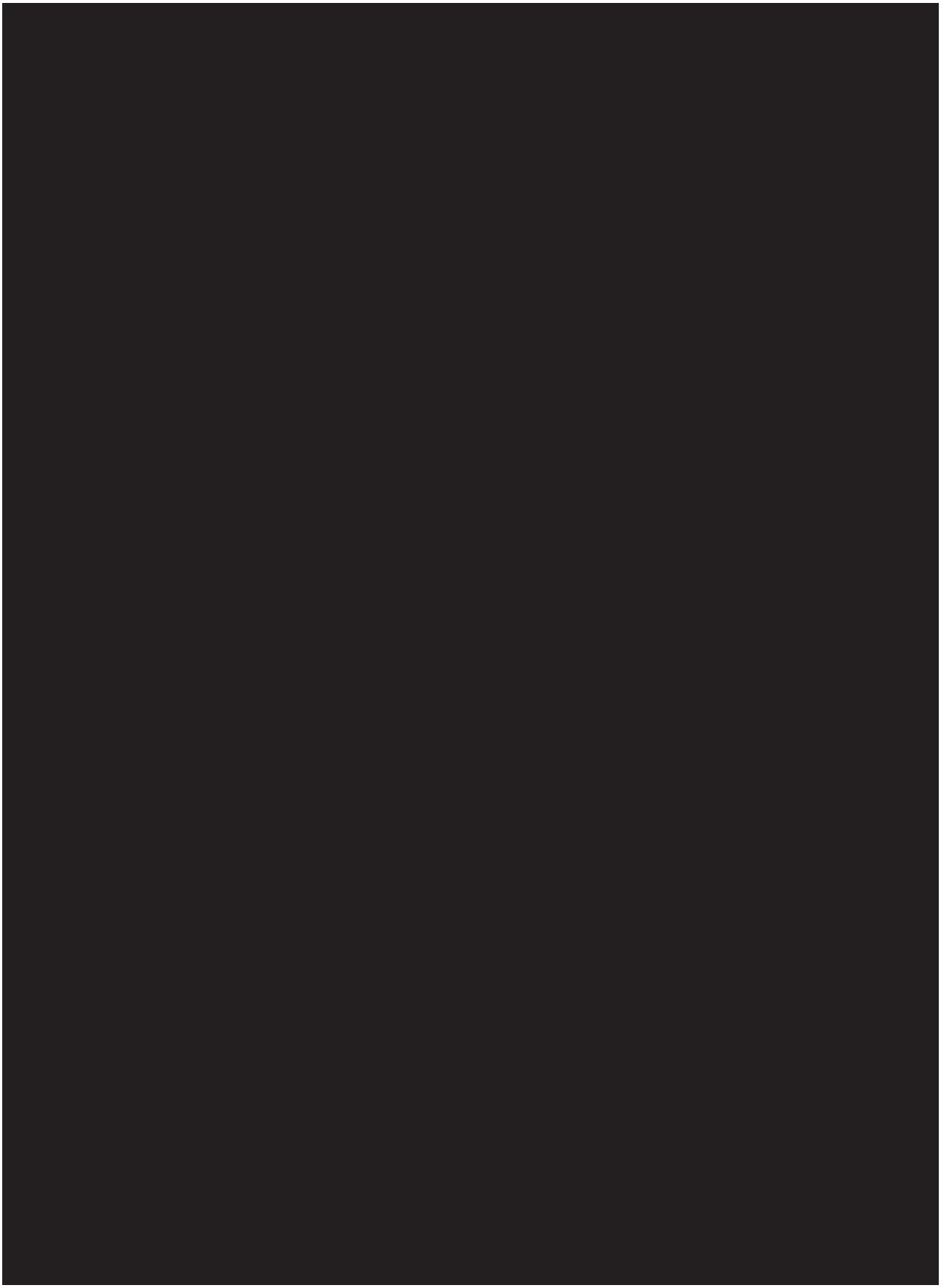
#### 9.3.2.2 Key Secondary Endpoints for Comparisons to Apremilast

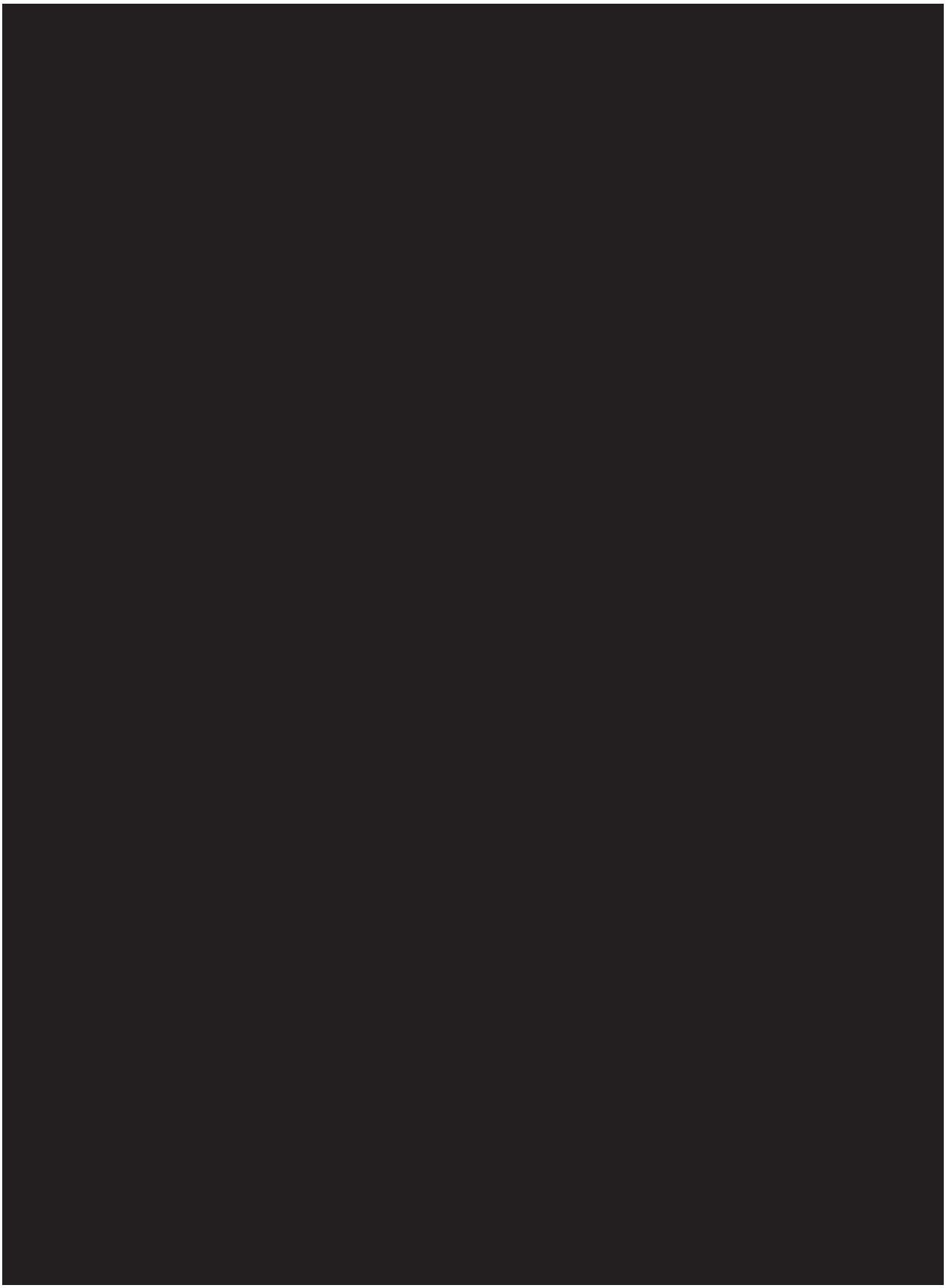
The key secondary endpoints for BMS-986165 compared to apremilast at Week 16 are defined as:

- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score
- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score
- PASI 100 response assessed as a proportion of subjects who achieve a 100% improvement from baseline in the PASI score
- sPGA 0/1 response assessed as a proportion of subjects with a sPGA score of 0 or 1

- sPGA 0 response assessed as a proportion of subjects with a sPGA score of 0
- Change from baseline in PSSD symptom score
- PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥ 1
- ss-PGA 0/1 assessed as a proportion of subjects with a ss-PGA score 0 or 1 among subjects with a baseline ss-PGA score ≥ 3







[redacted]

## 9.4 Efficacy Analyses

Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified. Efficacy variables will be summarized for all visits in which the variable is assessed. Complete details of the planned analyses will be documented in the statistical analysis plan and finalized before database lock.

During the active-controlled comparator period data will be presented for the following treatments:

- BMS-986165 6 mg QD
- Apremilast 30 mg BID
- Placebo

For the randomized withdrawal and maintenance period data will be presented for the following treatments for assessment of maintenance and durability of re-randomized Week 24 PASI 75 responders originally randomized to BMS-986165 6 mg QD:

- BMS-986165 6 mg QD
- Placebo

For other summaries of the randomized withdrawal and maintenance period data will be presented for the following treatments:

- All BMS-986165 6 mg QD (all subjects exposed to BMS-986165 6 mg QD; includes subjects on placebo during the randomized withdrawal and maintenance period that switched)
- BMS-986165 6 mg QD (responders/nonresponders)
- BMS-986165 6 mg QD→Placebo
- Placebo-BMS-986165 6 mg QD (starting from Week 16 rather than Week 24)
- Apremilast 30 mg BID→Placebo

- Apremilast 30 mg BID→BMS-986165 6 mg QD

### 9.4.1 Coprimary Endpoint Analyses

The analysis model for the coprimary efficacy endpoints, sPGA 0/1 and PASI 75 (responder / non-responder) at Week 16, will use stratified Cochran-Mantel-Haenszel (CMH) tests stratified by geographic region (US and rest of world), previous biologic use for psoriasis, psoriatic arthritis or other inflammatory disease (yes/no), and body weight (≥90 kg and <90 kg) to compare the response rates of BMS-986165 6 mg QD to placebo using the Week 16 data of the FAS. If expected cell counts are not sufficient for each strata level, then strata levels will be combined for the analysis. The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the /odds in placebo group) and the corresponding 2-sided 95% confidence interval (CI) will be provided. Estimates of proportions and their 2-sided 95% CIs will be provided.

#### 9.4.1.1 Imputation Methods for Coprimary Endpoints

Non-responder imputation (NRI) will be used for coprimary efficacy endpoints for subjects who discontinue study or treatment of study prior to Week 16, start a protocol prohibited medication/therapy that could improve psoriasis during the first 16 weeks of treatment, or who have otherwise missing endpoint data at the specified timepoint. NRI will the primary method of imputation for the coprimary efficacy endpoints.

#### 9.4.1.2 Sensitivity Analyses for the Coprimary Endpoints

The following imputation methods will be used in sensitivity analyses of the coprimary efficacy endpoints:

- Last observation carried forward (LOCF) for subjects with missing values at Week 16
- For subjects with missing values at Week 16, LOCF will be used for placebo subjects. NRI will be used for BMS-986165 6 mg QD subjects. This will include subjects who discontinue early, start a protocol prohibited medication/therapy prior to Week 16 that could improve psoriasis, or who have otherwise missing endpoint data at Week 16

#### 9.4.1.3 Supportive Analyses for the Coprimary Endpoints

The coprimary efficacy endpoints will be analyzed using the Week 16 data of the PPS using the analysis described in Section 9.4.1 and the imputation methods described in Section 9.4.1.1.

Additionally, the coprimary efficacy endpoints for the FAS will be analyzed with a logistic regression model with treatment, geographic region, prior biologic treatment use, and body weight strata. Proportions and 2-sided 95% confidence intervals will be provided.

#### 9.4.1.4 Subgroup Analyses for the Coprimary Endpoints

Subgroup analyses will be conducted for the coprimary efficacy endpoints for the FAS using the analysis described in Section 9.4.1 and the imputation methods described in Section 9.4.1.2. Subgroups to be evaluated may include the following:

- Gender
- Age categories (< 65; ≥ 65)

- Race
- Body weight categories (< 90 kg; ≥ 90 kg)
- Prior biologic use (yes/no)
- Prior systemic treatment of psoriasis (yes/no)
- Geographic region (per stratification factor; US or rest of world)

### 9.4.2 Secondary Endpoint Analyses

The analysis model for the binary secondary endpoints will use stratified CMH tests stratified by geographic region (US and rest of world), prior biologic treatment use (yes/no), and body weight (≥90 kg and <90 kg) to compare the response rates of BMS-986165 6 mg QD to placebo or apremilast for the FAS. If expected cell counts are not sufficient for each strata level, then strata levels will be combined for the analysis. The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the /odds in placebo group or active comparator group) and the corresponding 2-sided 95% CI will be provided.

The analysis model for continuous secondary endpoints will use analysis of covariance (ANCOVA) with treatment, geographic region (US and rest of world), prior biologic treatment use (yes/no), and body weight (≥90 kg and <90 kg) as fixed effects. The baseline value will be added into the model as a covariate. Treatment differences based on least-squares (LS) means and the corresponding 2-sided 95% CIs will be provided for the difference between BMS-986165 6 mg QD and placebo or active comparator depending on the endpoint being assessed.

#### 9.4.2.1 Imputation Methods for Secondary Endpoints

NRI will be applied to the analyses of binary secondary efficacy endpoints for subjects who discontinue early, start a protocol prohibited medication/therapy that could improve psoriasis, or who have otherwise missing endpoint data at the specified timepoint.

For continuous secondary efficacy endpoints, baseline observation carried forward (BOCF) will be used for subjects who discontinue study treatment due to:

- Lack of efficacy
- Adverse events

Additionally, BOCF will be used for subjects who start a protocol prohibited medication/therapy that could improve psoriasis. LOCF will be used for all other missing data.

[redacted]

### *9.4.4 Time-to-Relapse Endpoint*

The Kaplan-Meier product limit method will be used to estimate the distribution curves for time-to-relapse during the Randomized Withdrawal and Maintenance Period. Relapse is defined as the first loss of 50% or greater of the PASI percent improvement at Week 24 any time during the Randomized Withdrawal and Maintenance Period. Treatment comparisons of subjects re-randomized at Week 24 to BMS-986165 6 mg QD or placebo will be performed using the log-rank test stratified by geographic region (US and rest of world), prior biologic treatment use (yes/no), and body weight (≥90 kg and <90 kg).

## 9.5 Safety Analyses

Safety data will be analyzed for AEs, SAEs, laboratory analytes, vital signs, ECGs, and suicidality and depression. Safety will be summarized using the As-treated population for the active

comparator-controlled period, randomized withdrawal period, and overall. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

During the active comparator-controlled period, data will be presented for the following treatments:

- BMS-986165 6 mg QD
- Apremilast 30 mg BID
- Placebo

For the randomized withdrawal and maintenance period data will be presented for the following treatments for assessment of maintenance and durability of re-randomized Week 24 PASI 75 responders originally randomized to BMS-986165 6 mg QD:

- BMS-986165 6 mg QD
- Placebo

For other summaries of the randomized withdrawal and maintenance period data will be presented for the following treatments:

- All BMS-986165 6 mg QD (all subjects exposed to BMS-986165 6 mg QD; includes subjects on placebo during the randomized withdrawal and maintenance period that switched)
- BMS-986165 6 mg QD (responders/nonresponders)
- BMS-986165 6 mg QD-Placebo
- Placebo-BMS-986165 6 mg QD (starting from Week 16 rather than Week 24)
- Apremilast 30 mg BID-Placebo
- Apremilast 30 mg BID-BMS-986165 6 mg QD

### 9.5.1 Adverse Events

Treatment-emergent adverse events (TEAEs), SAEs, deaths, AEs leading to study treatment discontinuation, AEs by maximum severity, and AEs by relationship will be summarized by the MedDRA system organ class and preferred term. All TEAEs as well as AEIs, and each AE adjudicated category (ie, infections, cardiovascular, and suicidal ideation/behavior) will also be summarized by preferred term sorted by decreasing frequency.

### 9.5.2 Vital Signs and ECGs

Vital signs and ECGS will be summarized as raw, change from baseline, and change from maximum postbaseline value. Incidence of abnormal ECG findings will also be summarized.

### 9.5.3 Clinical Laboratory Tests

Laboratory analytes will be summarized as raw, change from baseline, and change from maximum postbaseline value. Incidence of abnormal, high, or low values will be summarized.

### 9.5.4 Suicidality and Depression Assessments

Suicidality and depression will be assessed using eC-SSRS and PHQ-8. Data will be summarized, as applicable.

## 9.6 Other Analyses

### 9.6.1 Demographics and Baseline Data

Demographics and baseline data will be summarized by treatment for each applicable analysis population. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

### 9.6.2 Prior and Concomitant Medications

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

### 9.6.3 Relevant Protocol Deviations

Relevant protocol deviations are deviations that can have an impact on the primary efficacy endpoints. The impact of relevant protocol deviations on the primary efficacy results will be assessed by excluding subjects from the FAS to define the PPS in supportive analyses of the primary efficacy endpoints. Relevant protocol deviations to be considered regarding exclusion of subjects from the FAS will include the following:

- Subject randomized but did not take any study treatment
- Subject failed to meet any study inclusion criteria but was randomized to receive study treatment
- Subject met a study exclusion criterion which may have an impact on the coprimary efficacy endpoints but was randomized to receive study treatment
- Subject non-compliant with study treatment within the first 16 weeks of treatment; defined as <80% compliant with study treatment
- Subject took prohibited concomitant medication prior to Week 16
- Subject received treatment different to intended treatment at any visit prior to Week 16

All subjects with relevant protocol deviations will be identified prior to database lock. Relevant protocol deviations will be summarized by treatment group and deviation category for the FAS population.

[redacted]

## 9.7 Interim Analyses

No interim analysis is currently planned.

## 9.8 Statistical Impacts Due to COVID-19

### *9.8.1 Impact on Efficacy Endpoints*

There are no COVID-19-related impacts to the Week 16 efficacy endpoints as all subjects remaining in the trial completed the Week 16 visit prior to COVID-19 site restrictions. Efficacy endpoints involving Week 24 and later visits may be impacted by COVID-19 in the form of missing data and/or a treatment assignment defaulting to BMS-986165.

Censoring rules will be applied to the PASI 75 time-to-relapse endpoint for re-randomized subjects due to the following COVID-19-related issues post Week 24:

- Subject study treatment assignment was defaulted to BMS-986165 because they had a remote safety monitoring visit due to COVID-19 and efficacy assessments were not performed. The subject will be censored at the time of the remote visit if relapse had not been observed already;
- Subject has missing visit(s) (ie, efficacy assessments not performed) after Week 24 and assuming relapse was not observed prior to missed visit(s):
    - If the subject returns at a later visit and is found to have relapsed, midpoint imputation will be used to determine time-to-relapse (ie, midpoint of the censoring interval).
    - If the subject returns at a later visit and has not relapsed, then the subject will continue to be evaluated for relapse.
    - If the subject is discontinued from study treatment, then the subject will be censored at the time of study treatment discontinuation.

Sensitivity analyses for time-to-relapse may be performed with additional details provided in the statistical analysis plan prior to database lock.

Data handling due to COVID-19-related issues for other efficacy endpoints [redacted] will be described in the statistical analysis plan prior to database lock.

### 9.8.2 Impact on Safety Variables

No modifications are planned for the analysis of safety data due to COVID-19-related issues. There will not be any additional safety data handling considerations for missing data or treatment interruptions due to COVID-19.

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## 11 APPENDICES

## APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

| Term | Definition |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| AE | adverse event |
| AEI | adverse event of interest |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| Anti-HCV | hepatitis C virus antibody |
| [redacted] | [redacted] |
| AST | aspartate aminotransferase |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| BID | twice daily |
| BMS | Bristol-Myers Squibb |
| BSA | body surface area |
| BUN | blood urea nitrogen |
| [redacted] | [redacted] |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| Cmax | maximum plasma concentration |
| CMH | Cochran-Mantel-Haenszel |
| CK | creatine kinase |
| CT | computed tomography |
| [redacted] | [redacted] |
| CYP450 | cytochrome P450 |
| [redacted] | [redacted] |
| DILI | drug-induced liver injury |
| DLQI | Dermatology Life Quality Index |

| Term | Definition |
|---|---|
| DMC | Data Monitoring Committee |
| DNA | deoxyribonucleic acid |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eC-SSRS | electronic Columbia-Suicide Severity Rating Scale |
| eGFR | Estimated Glomerular Filtration Rate |
| [redacted] | [redacted] |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| GI | gastrointestinal |
| [redacted] | [redacted] |
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| hCG | human chorionic gonadotropin |
| Hct | hematocrit |
| HCV | hepatitis C virus |
| HDL | high density lipoprotein |
| Hgb | hemoglobin |
| HIV | human immunodeficiency virus |
| hs-CRP | high-sensitivity C-reactive protein |
| IB | Investigator Brochure |
| [redacted] | [redacted] |
| ICF | informed consent form |
| IEC | Independent Ethics Committee |
| IFN | interferon |
| IFNγ | interferon gamma |

| Term | Definition |
|---|---|
| IGRA | interferon gamma release assay |
| IL | interleukin |
| IM | intramuscular |
| IMP | investigational medicinal product |
| IP | investigational product |
| IRT | interactive response technology |
| ITT | intent-to-treat |
| IV | intravenous |
| JAK | Janus kinase |
| LDH | lactate dehydrogenase |
| LDL | low density lipoprotein |
| LTBI | latent tuberculosis infection |
| MACE | Major Adverse Cardiovascular Events |
| MedDRA | Medical Dictionary for Regulatory Activities |
| [redacted] | [redacted] |
| NRI | non-responder imputation |
| PASE | psoriatic arthritis screening and evaluation |
| PASI | Psoriasis Area and Severity Index |
| PD | pharmacodynamics |
| PE | physical examination |
| PHQ-8 | Eight-Item Patient Health Questionnaire |
| PK | pharmacokinetics |
| [redacted] | [redacted] |
| pp-PGA | palmoplantar Physician's Global Assessment |
| PsA | psoriatic arthritis |
| PSSD | Psoriasis Symptoms and Signs Diary |
| [redacted] | [redacted] |
| QD | once daily |
| QOD | every other day |
| PGA-F | Physician Global Assessment- Fingernails |

| Term | Definition |
|---|---|
| PUVA | Psoralens with ultraviolet A |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| [redacted] | [redacted] |
| SIB | Suicidal Ideation and Behavior |
| sPGA | static Physician Global Assessment |
| ss-PGA | scalp specific Physician's Global Assessment |
| STAT | signal transducer and activator of transcription |
| TB | tuberculosis |
| T4 | thyroxine |
| T3 | triiodothyronine |
| [redacted] | [redacted] |
| TSH | thyroid-stimulating hormone |
| TNF | tumor necrosis factor |
| TYK2 | tyrosine kinase 2 |
| ULN | upper limit of normal |
| UVB | ultraviolet B |
| [redacted] | [redacted] |
| WOCBP | women of childbearing potential |

# APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

## Regulatory and Ethical Considerations

### Good Clinical Practice

This study will be conducted in accordance with:

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

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

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

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

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

### Institutional Review Board/Independent Ethics Committee

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

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

### Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

**Financial Disclosure**

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

**Informed Consent Process**

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

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

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form 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 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 and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

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

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

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

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

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

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

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

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

**Source Documents**

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

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

**Study Treatment Records**

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

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

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

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

**Case Report Forms**

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

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

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

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

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

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

**Monitoring**

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

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

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

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

**Records Retention**

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

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

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

**Return of Study Treatment**

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

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

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

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

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

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

**Clinical Study Report and Publications**

A Signatory Investigator must be selected to sign the CSR.

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

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

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

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

## Adverse Events

**Adverse Event Definition:**

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

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

**Events Meeting the AE Definition**

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

**Events NOT Meeting the AE Definition**

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

**DEFINITION OF SAE**

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

## Serious Adverse Events

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

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

## Evaluating AEs and SAEs

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

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

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

All SAEs must be followed to resolution or stabilization.

## Reporting of SAEs to Sponsor or Designee

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

SAEs must be recorded on the SAE Report Form. For studies capturing SAEs through electronic data capture (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.

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

**SAE Email Address:** [redacted]

**SAE Fax Number:**

**Americas:** [redacted]

**Europe/East Asia Pacific:** [redacted]

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

**Americas:** [redacted]

**Europe/East Asia Pacific:** [redacted]

# APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

## DEFINITIONS

### Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming 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 subject's medical records, medical examination, or medical history interview.

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

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

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

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

## CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILD BEARING POTENTIAL

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**<br>*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]<br>– oral<br>– intravaginal<br>– transdermal |
| • Progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |
| **Highly Effective Methods That Are User Independent** |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b]<br>• Intrauterine device (IUD)[c]<br>• Intrauterine hormone-releasing system (IUS)[c]<br>• Bilateral tubal occlusion |
| • Vasectomized partner<br>*A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* |

- Sexual abstinence

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

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

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

[c] Intrauterine 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)<br>• Withdrawal(coitus interruptus).<br>• Spermicide only<br>• Lactation amenorrhea method (LAM) |

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

Male subjects 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 subjects are required to use a condom for study duration and until the end of relevant systemic exposure defined as 3 days after the end of treatment in the male subject.
- 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 subject.
- Male subjects 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 for 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 8.2.6 and APPENDIX 3.

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

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

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

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

Physician's Static Global Assessment based upon above Total Average

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

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

# APPENDIX 6 PSORIASIS AREA AND SEVERITY INDEX (PASI)

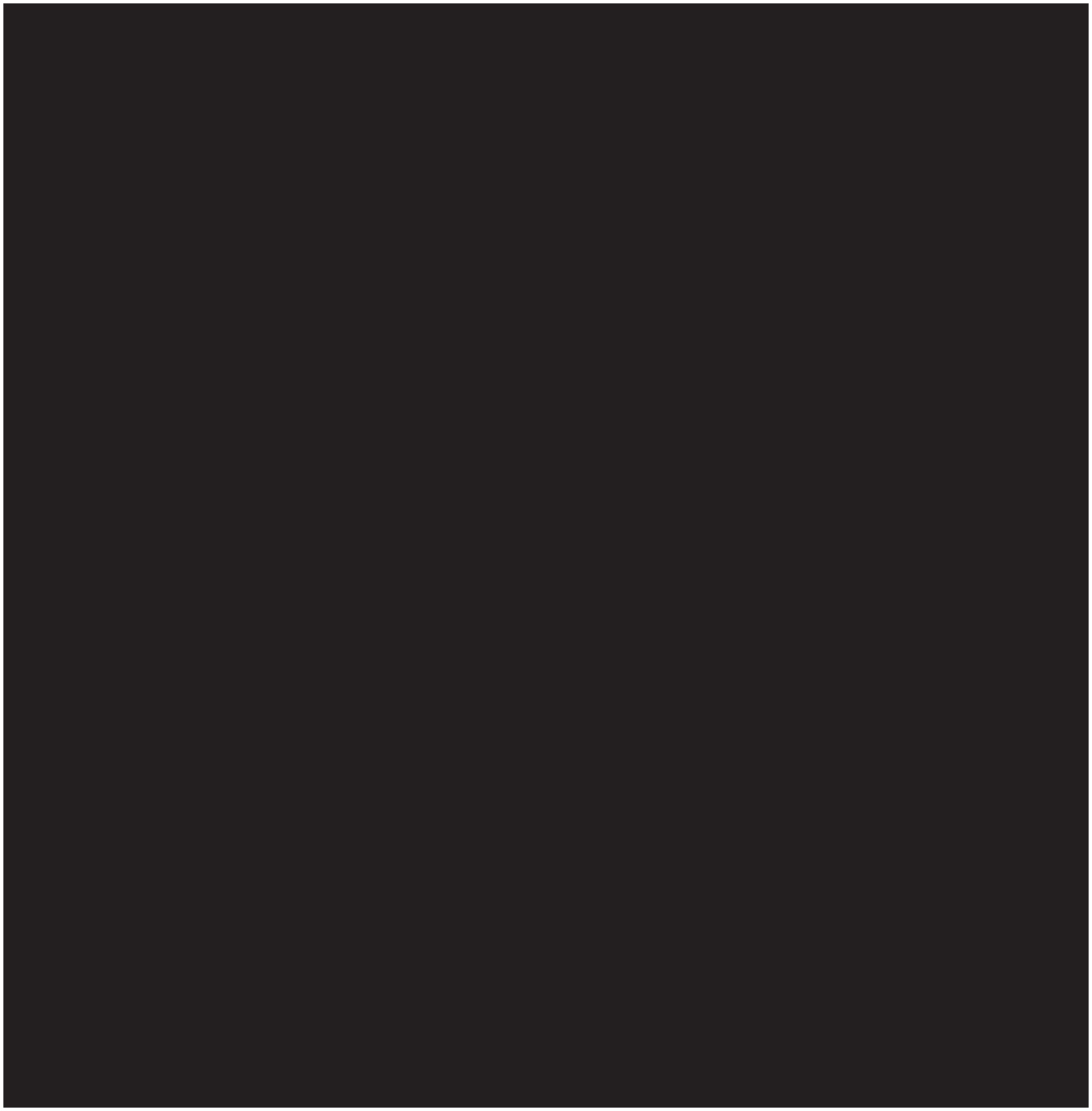
Psoriasis Area and Severity Index (PASI); a quantitative rating scale for measuring the severity of psoriatic lesions based on area coverage and plaque appearance. Please complete **all** sections of the table below.

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

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

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

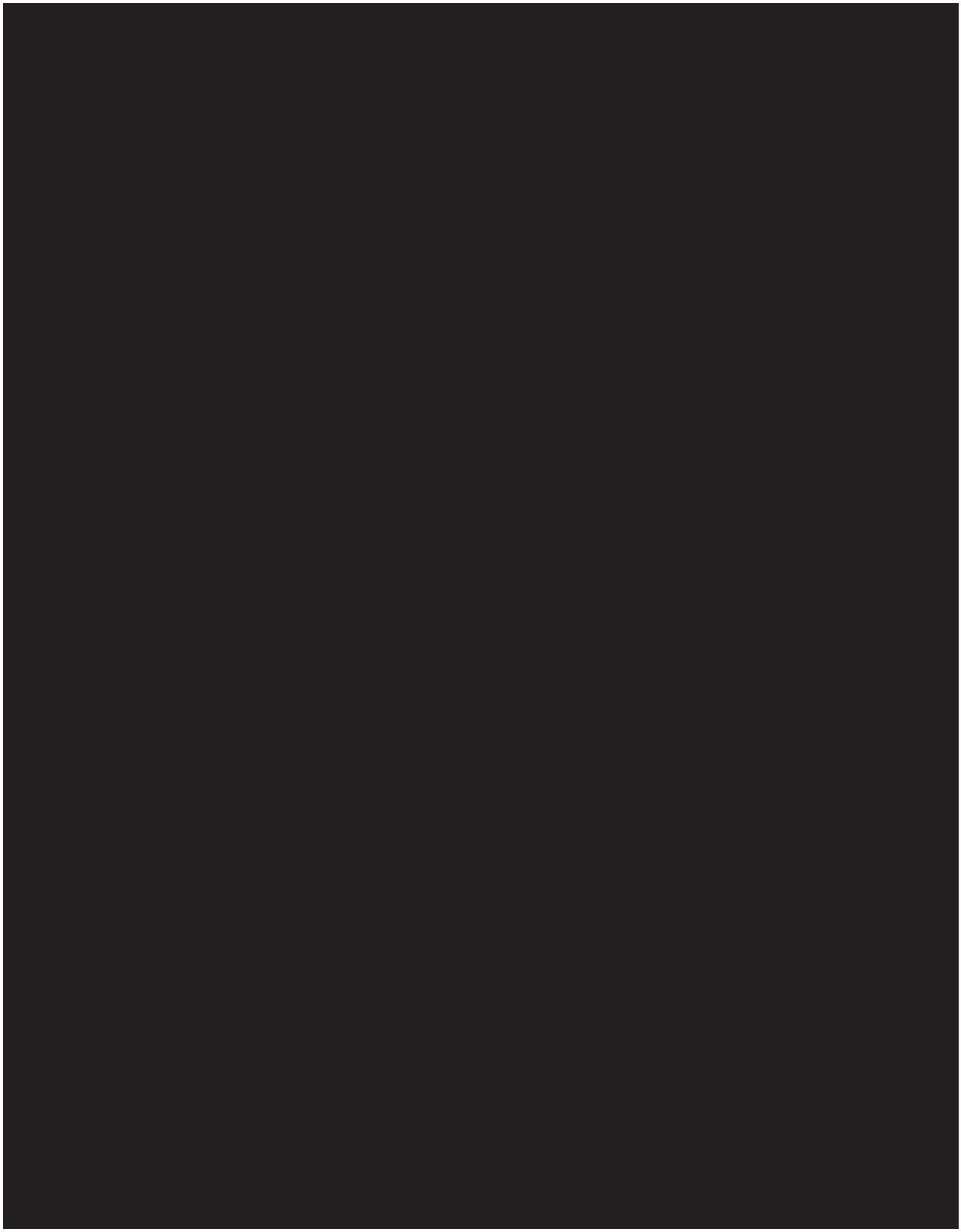
| Score | Category | Description |
|---|---|---|
| 0 | Absence of Disease | No evidence of redness, no evidence of thickness, and no evidence of scaliness on the scalp |
| 1 | Very Mild Disease | The overall clinical picture consists of flat lesions with barely perceptible erythema, with or without a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

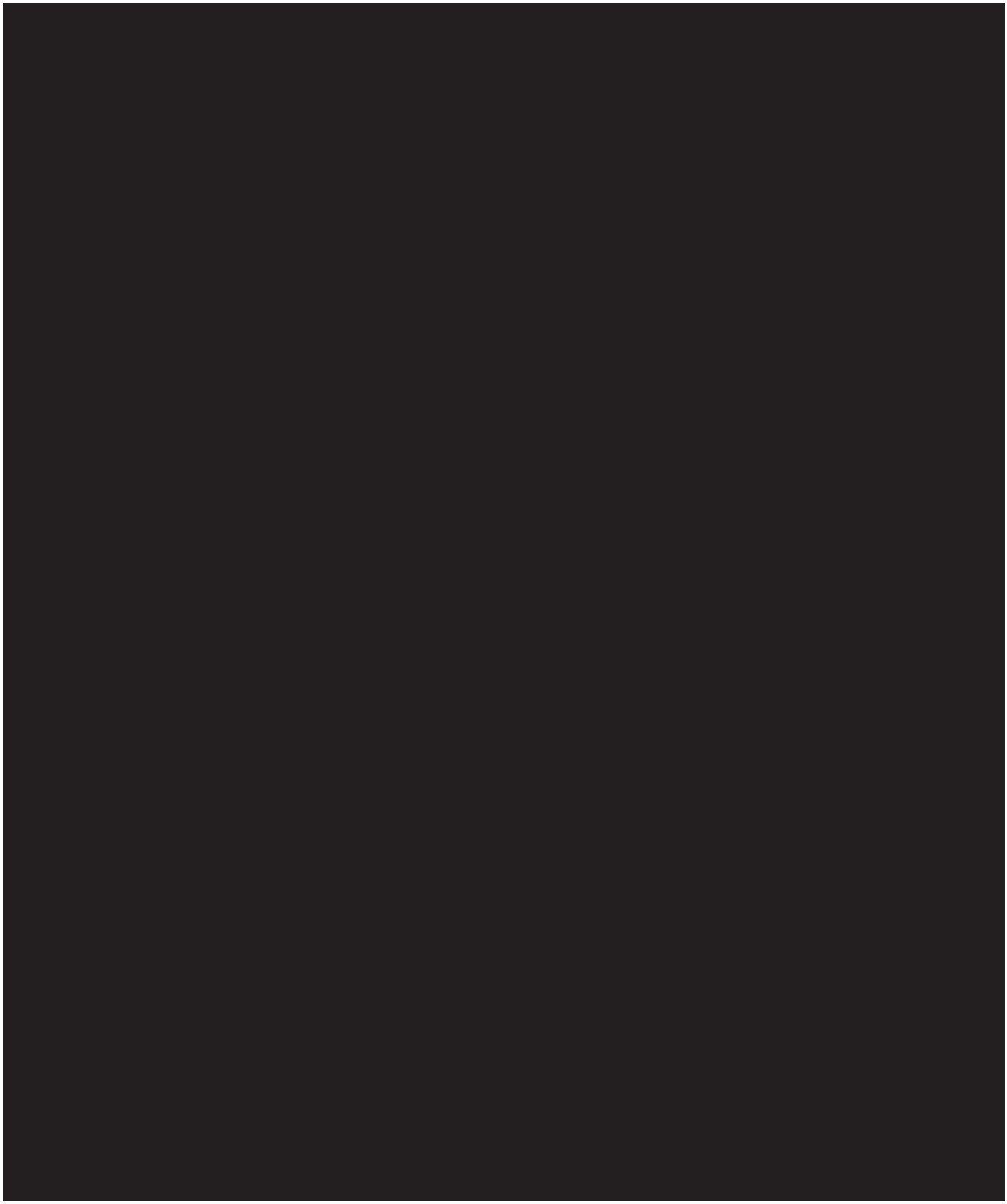


# APPENDIX 9 PHYSICIAN'S GLOBAL ASSESSMENT-FINGERNAILS (PGA-F)

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

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

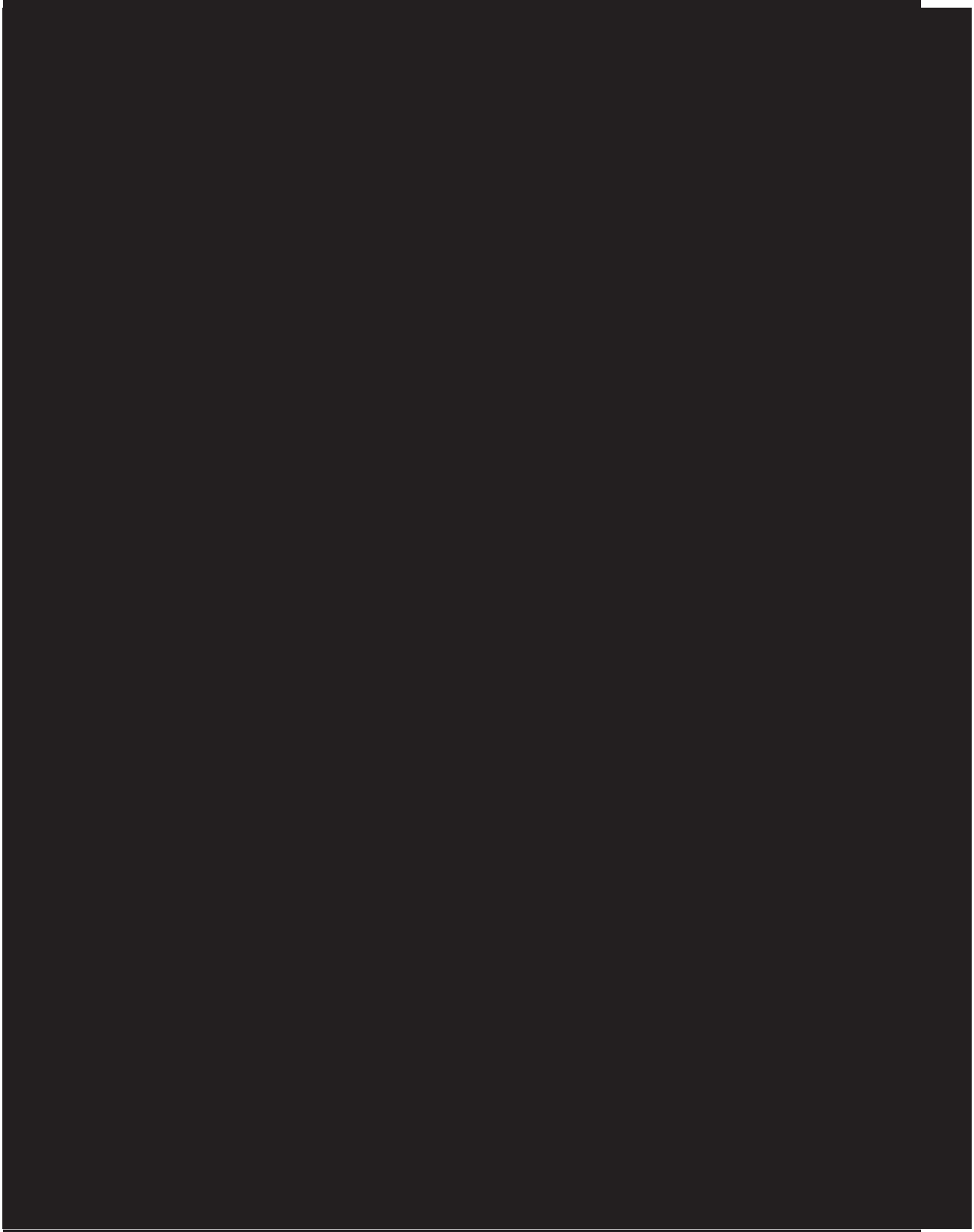




# APPENDIX 11 PALMOPLANTAR PSORIASIS PHYSICIAN'S GLOBAL ASSESSMENT (pp-PGA)

Palmoplantar (including finger and toe surfaces) psoriasis lesions are evaluated by the investigator based on overall severity, then scored on the following 5-point scale:

| Score | Category | Description |
|---|---|---|
| 0 | Clear | No signs of plaque psoriasis |
| 1 | Almost Clear | Just perceptible erythema and just perceptible scaling |
| 2 | Mild | Light pink erythema, with minimal scaling with or without pustules |
| 3 | Moderate | Dull red, clearly distinguishable erythema with diffuse scaling, some thickening of the skin, with or without fissures, with or without pustule formation |
| 4 | Severe | Deep, dark red erythema with obvious and diffuse scaling and thickening as well as numerous fissures with or without pustule formation |



# APPENDIX 13 PSORIASIS SYMPTOMS AND SIGNS DIARY (PSSD)

Please answer each question to the best of your ability. There are no right or wrong answers. Please pay close attention to the time period of interest. These questions ask you to think about the **past 24 hours**. **Please complete the diary at the same time every day.**

Individuals with psoriasis may experience a range of symptoms. Please indicate how severe each of the following skin symptoms was in the **past 24 hours**. Please select only one number for each item on the 0 to 10 scale (0=Absent and 10= Worst imaginable).

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Rate the severity of itch in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 2. Rate the severity of dryness in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 3. Rate the severity of cracking in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 4. Rate the severity of skin tightness in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 5. Rate the severity of scaling (build-up of skin) in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 6. Rate the severity of shedding or flaking in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 7. Rate the severity of redness in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 8. Rate the severity of bleeding in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 9. Rate the severity of burning in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 10. Rate the severity of stinging in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |
| 11. Rate the severity of pain from your psoriasis lesions in the past 24 hours. | 0 Absent | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 Worst imaginable |

# APPENDIX 14 DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: Date: Score:

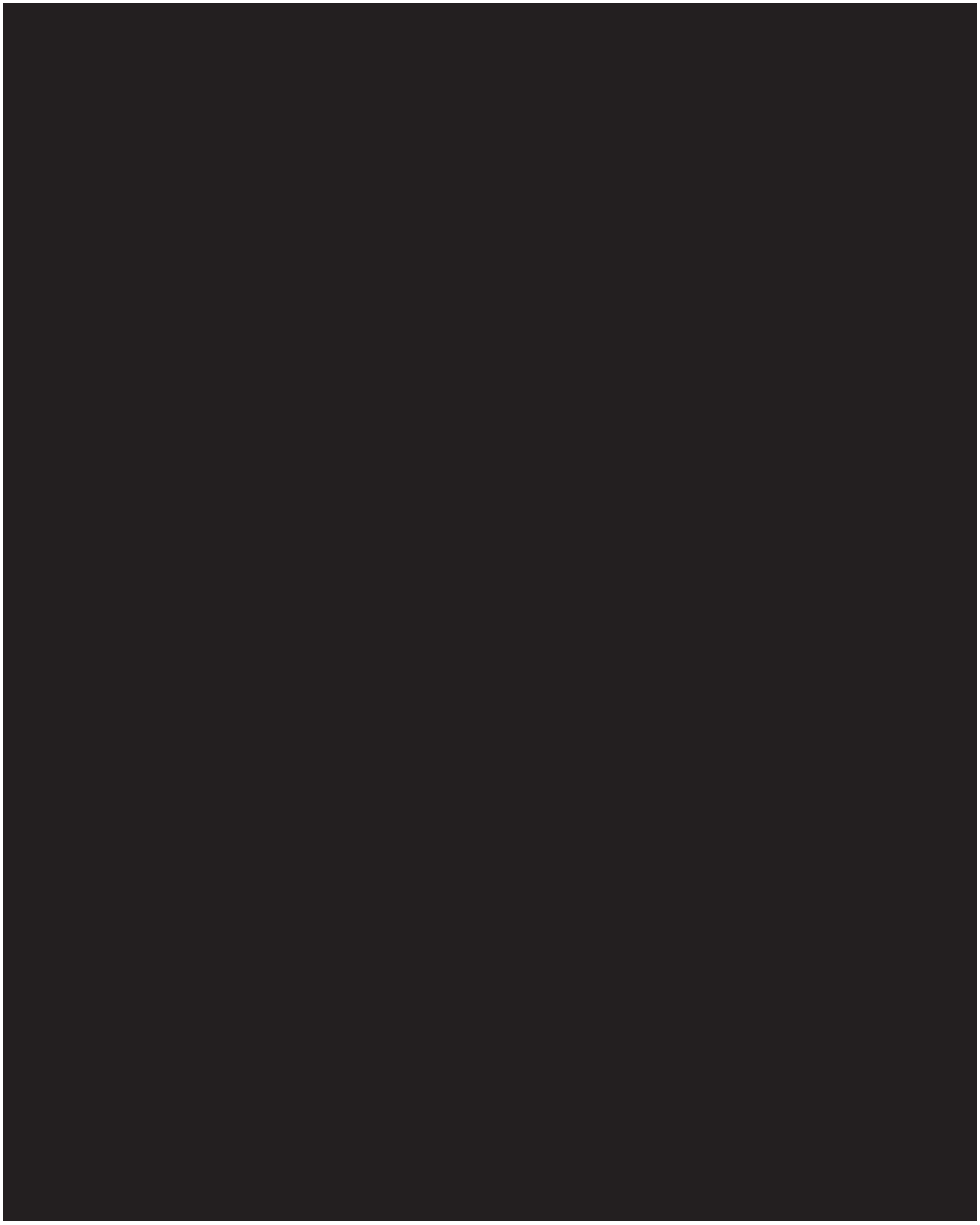
Name: Diagnosis:

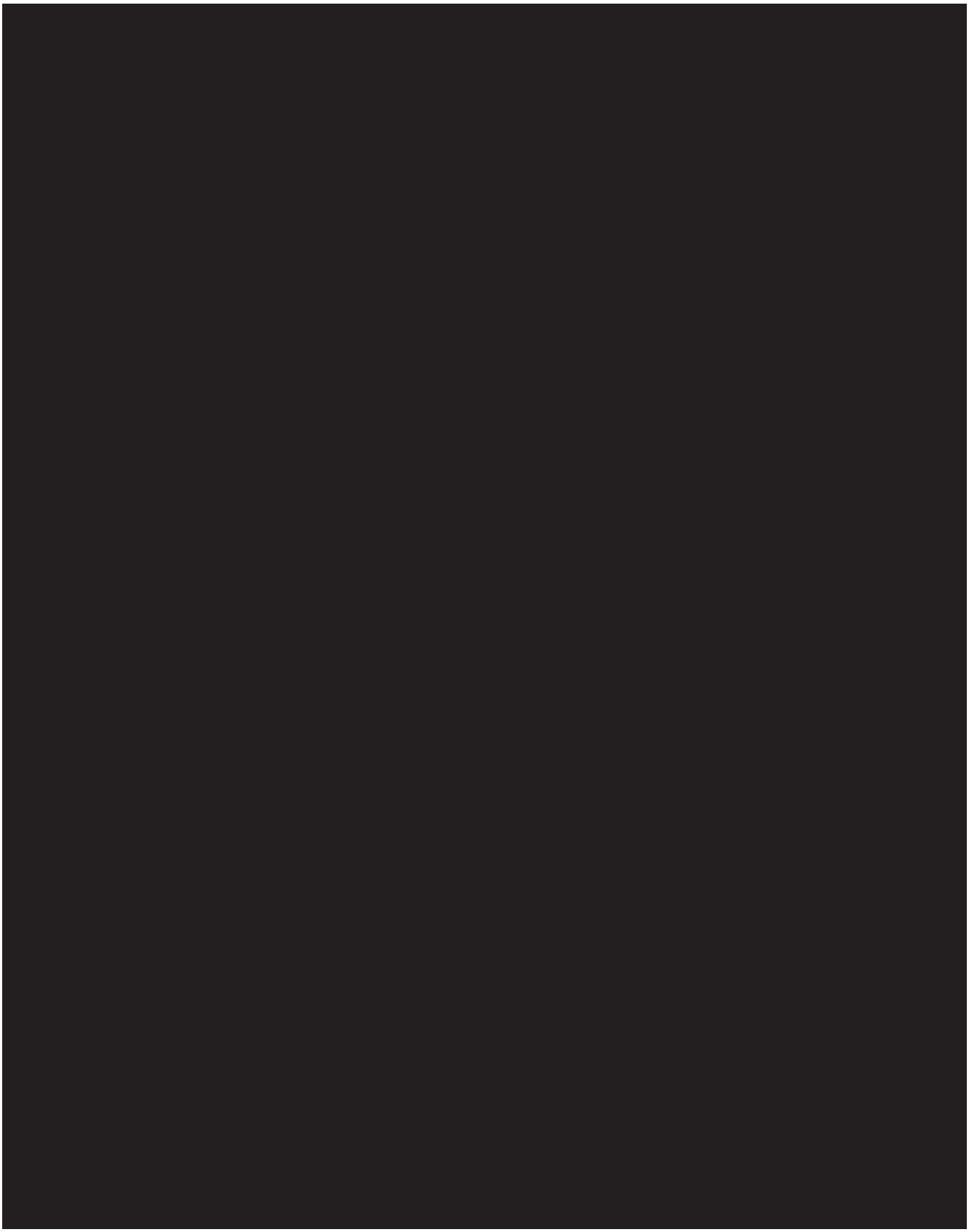
Address:

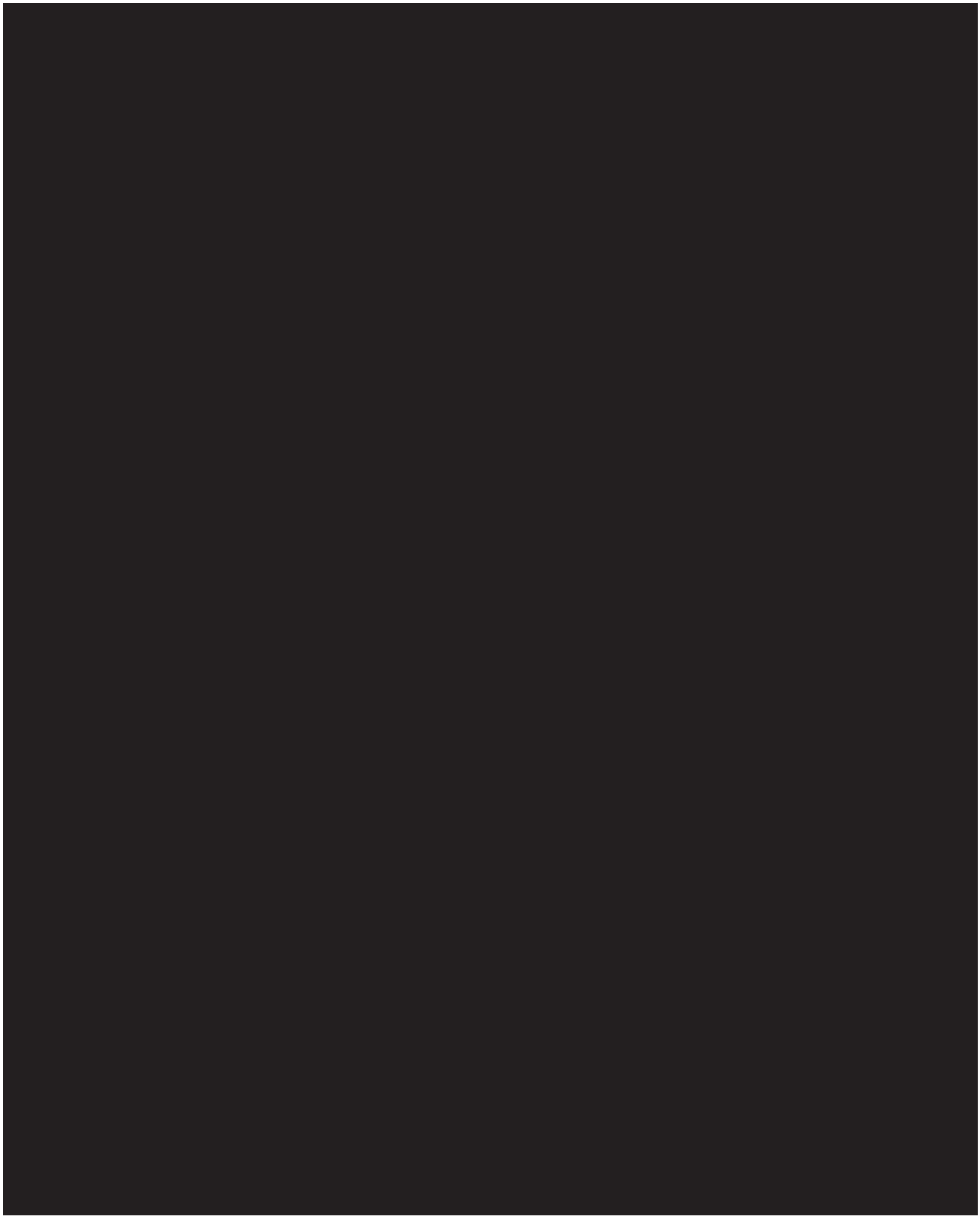
**The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.**

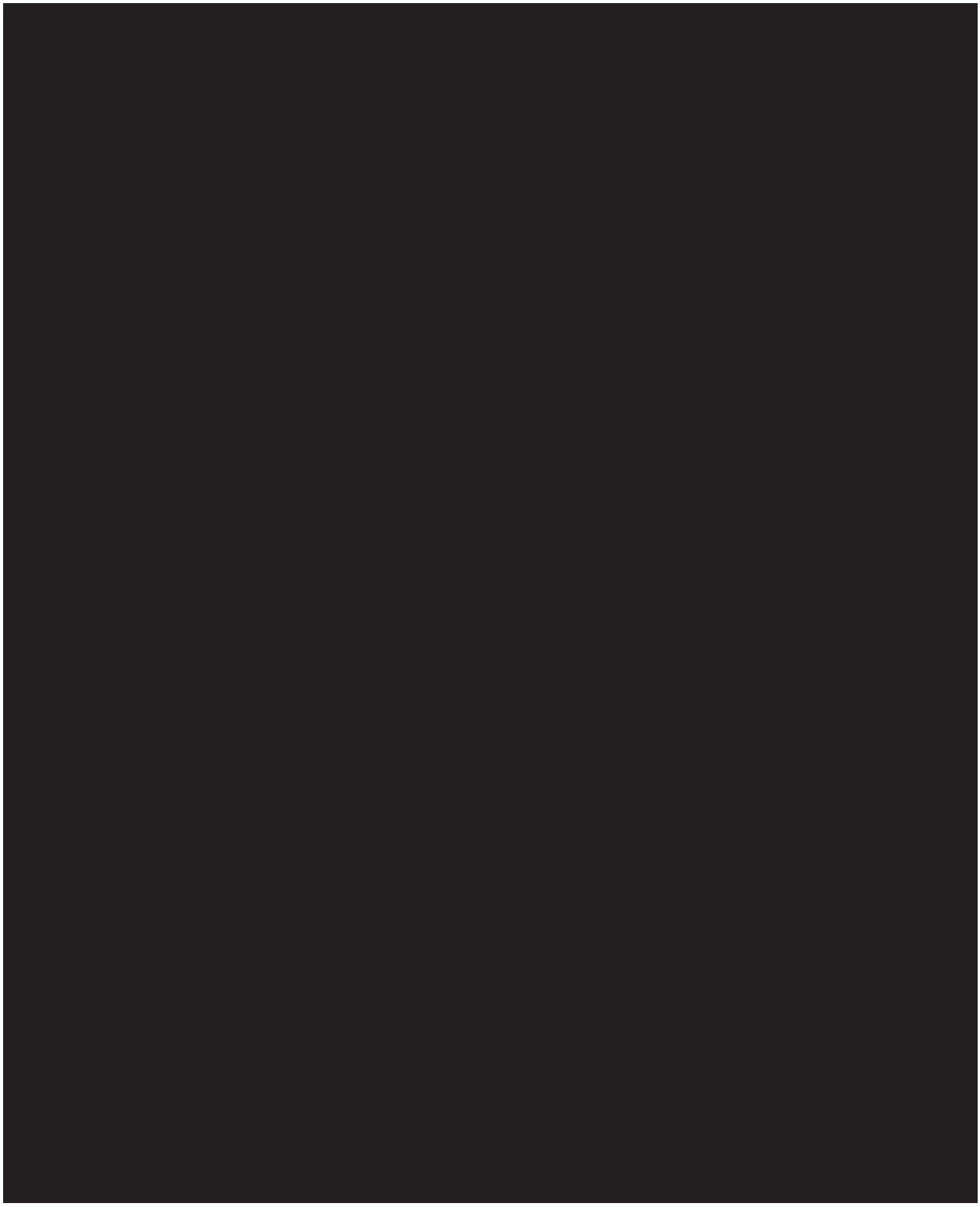
| | | | | |
|---|---|---|---|---|
| 1. | Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been? | Very much<br>A lot<br>A little<br>Not at all | ☐<br>☐<br>☐<br>☐ | |
| 2. | Over the last week, how **embarrassed** or **self-conscious** have you been because of your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

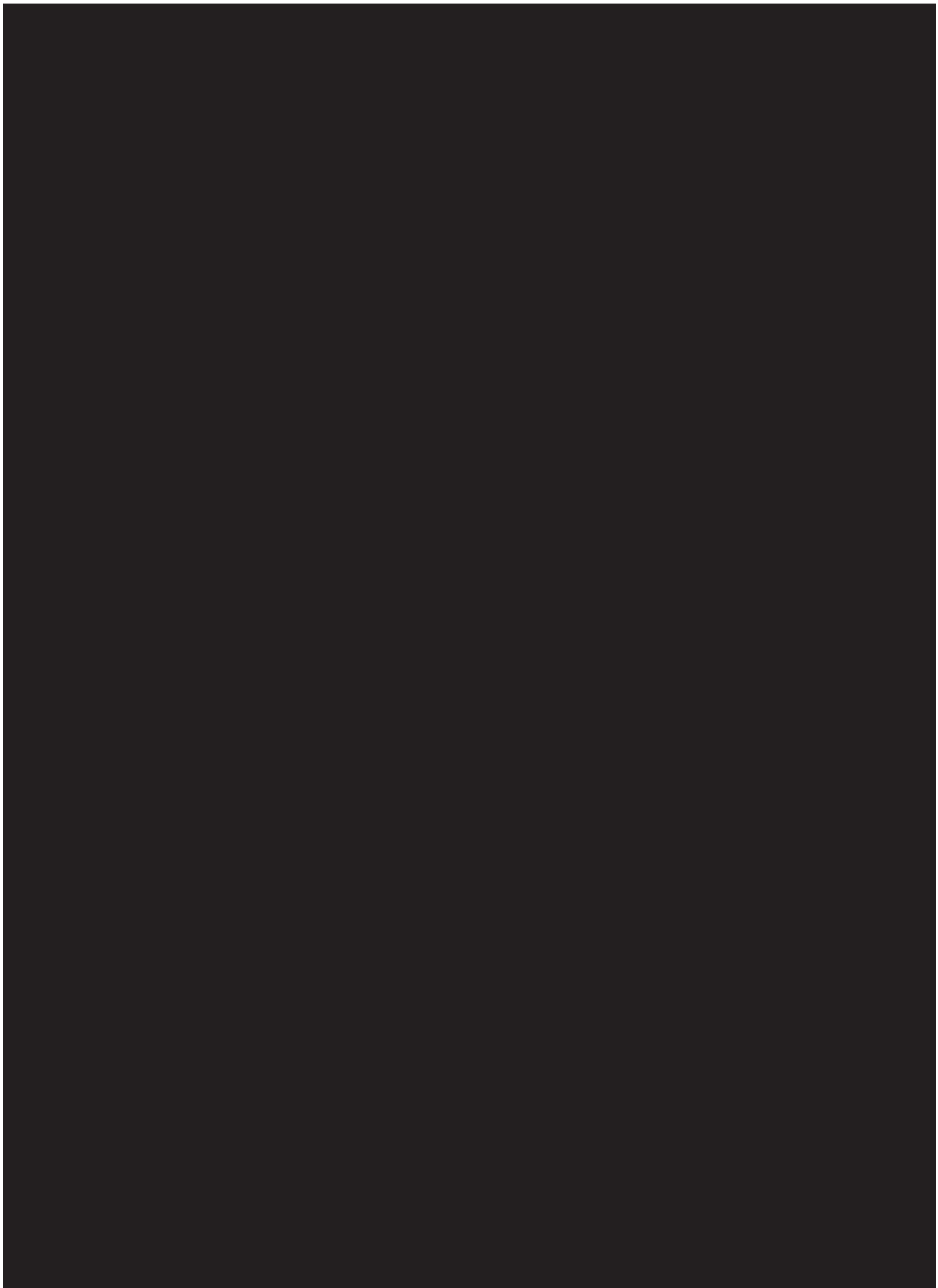
**Please check you have answered EVERY question. Thank you**

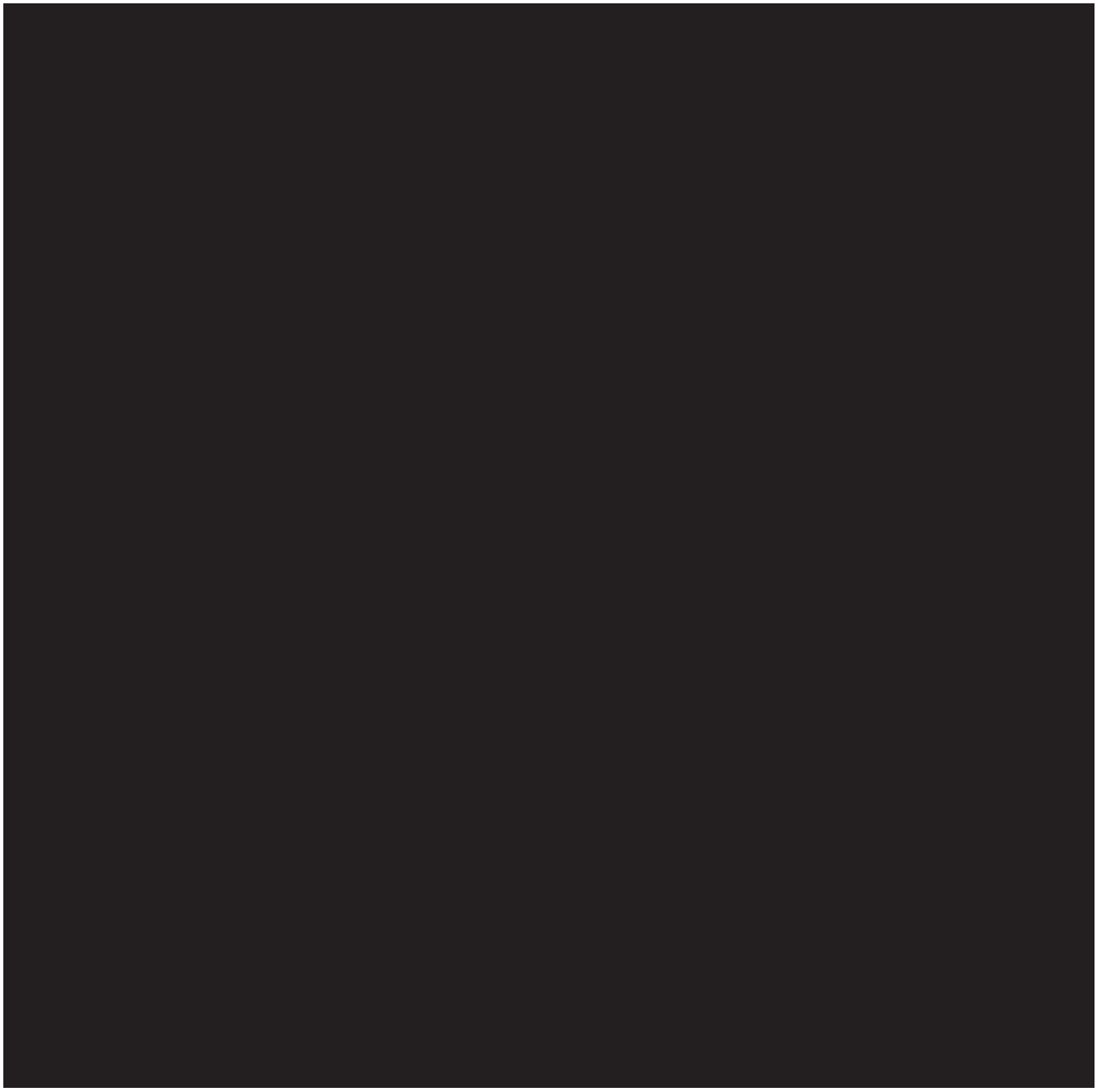


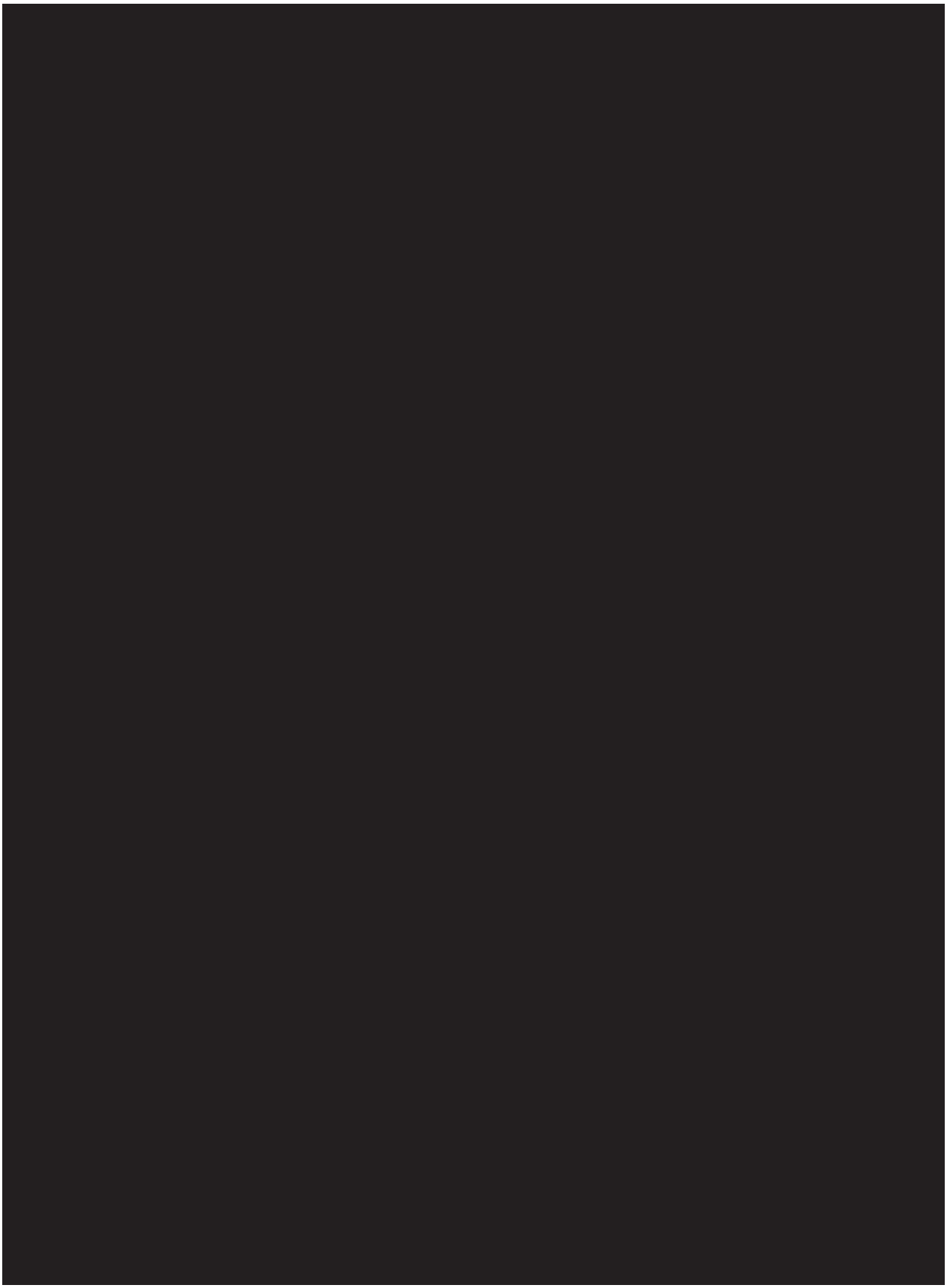


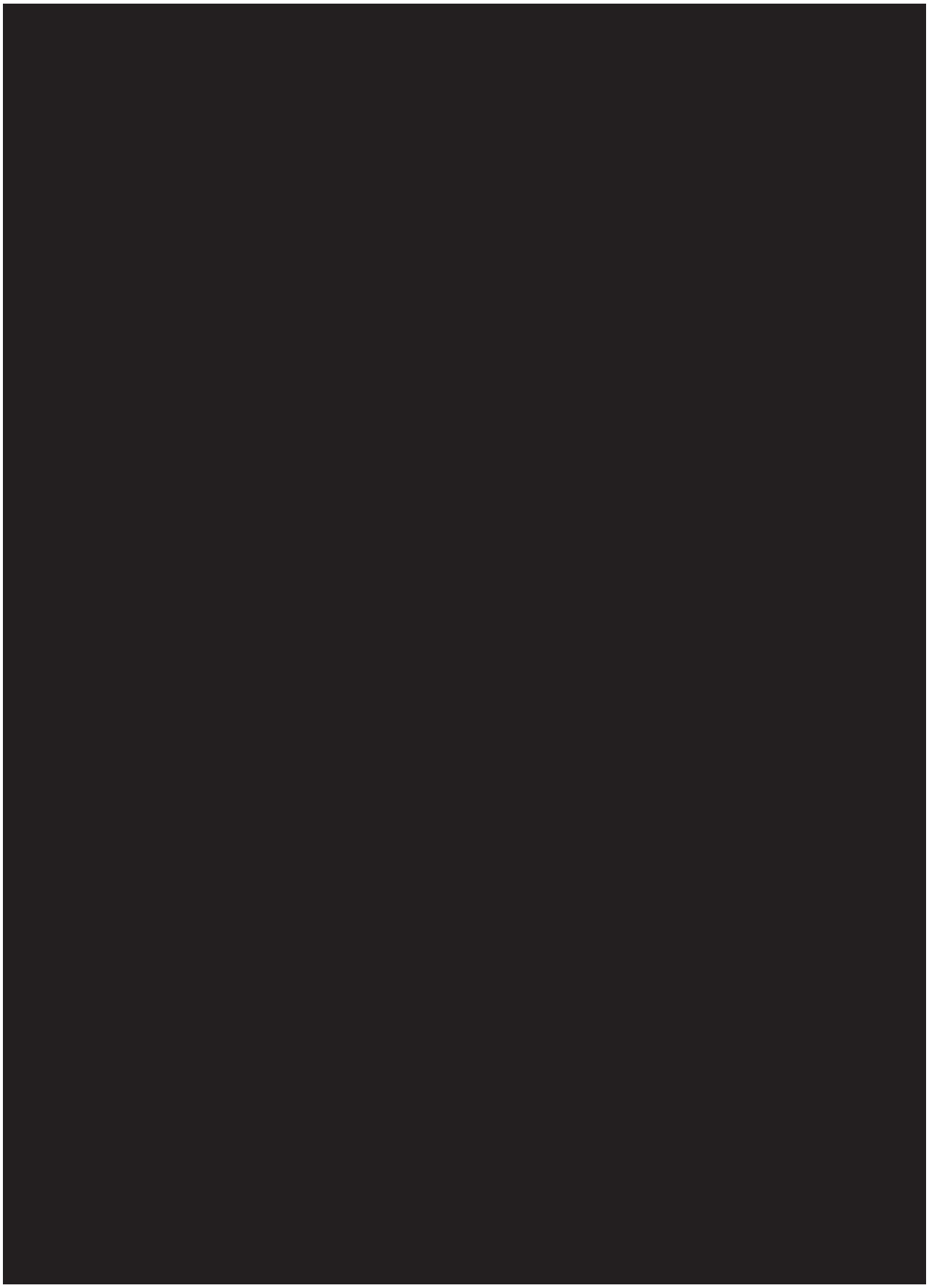












# APPENDIX 20 PSORIATIC ARTHRITIS SCREENING AND EVALUATION (PASE) QUESTIONNAIRE

Please circle or mark **ONLY ONE** of the five choices on the following 15 questions. The answers to these questions will help us better understand your symptoms. This should take about 5-6 minutes to complete. Thank you for your time.

| **Symptoms sub-scale** | **Strongly Disagree** | **Disagree** | **Neutral** | **Agree** | **Strongly Agree** |
|---|---|---|---|---|---|
| 1. I feel tired for most of the day | **1** | **2** | **3** | **4** | **5** |
| 2. My joints hurt | **1** | **2** | **3** | **4** | **5** |
| 3. My back hurts | **1** | **2** | **3** | **4** | **5** |
| 4. My joints become swollen | **1** | **2** | **3** | **4** | **5** |
| 5. My joints feel 'hot' | **1** | **2** | **3** | **4** | **5** |
| 6. Occasionally, an entire finger or toe becomes swollen, making it look like a 'sausage' | **1** | **2** | **3** | **4** | **5** |
| 7. I have noticed that the pain in my joints moves from one joint to another, eg, my wrist will hurt for a few days then my knee will hurt and so on. | **1** | **2** | **3** | **4** | **5** |
| **SYMPTOM SCORE (Max 35)** | Add scores for questions 1-7 and write in box A | | | | A. |
| **Function sub-scale** | **Strongly Disagree** | **Disagree** | **Neutral** | **Agree** | **Strongly Agree** |
| 8. I feel that my joint problems have affected my ability to work | **1** | **2** | **3** | **4** | **5** |
| 9. My joint problems have affected my ability to care for myself, eg, getting dressed or brushing my teeth | **1** | **2** | **3** | **4** | **5** |
| 10. I have had trouble wearing rings on my fingers or my watch | **1** | **2** | **3** | **4** | **5** |
| 11. I have had trouble getting into or out of a car | **1** | **2** | **3** | **4** | **5** |
| 12. I am unable to be as active as I used to be | **1** | **2** | **3** | **4** | **5** |
| 13. I feel stiff for more than 2 hours after waking up in the morning | **1** | **2** | **3** | **4** | **5** |
| 14. The morning is the worst time of day for me | **1** | **2** | **3** | **4** | **5** |
| 15. It takes me a few minutes to get moving to the best of my ability, any time of the day | **1** | **2** | **3** | **4** | **5** |
| **FUNCTION SCORE (Max 40)** | Add scores for questions 8-15 and write in box B | | | | B. |
| **TOTAL PASE SCORE (Max 75)** | Add scores in boxes A and B and write in box C | | | | C. |

# APPENDIX 21 EIGHT ITEM PATIENT HEALTH QUESTIONNAIRE (PHQ-8)

The eight-item Patient Health Questionnaire depression scale is established as a valid self-administered diagnostic and severity measure for depressive disorders. It consists of 8 different questions, with an answer scale from 0-3. The overall score is determined by adding up each of the individual answers from each question.
Scoring interpretation is as follows: 0-4 no significant depressive symptoms, 5-9 mild depressive symptoms, 10-14 moderate depressive symptoms, 15-19 moderately severe depressive symptoms, and 20-24 severe depressive symptoms

**Over the last 2 weeks, how often have you been bothered by any of the following problems?**

| | Not at all | Several Days | More than half the days | Nearly every day |
|---|---|---|---|---|
| 1. Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| 2. Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| 3. Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| 4. Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| 5. Poor appetite or over eating | 0 | 1 | 2 | 3 |
| 6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down | 0 | 1 | 2 | 3 |
| 7. Trouble concentrating on things, such as reading the newspaper, or watching television | 0 | 1 | 2 | 3 |
| 8. Moving or speaking so slowly that other people could have noticed? Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |

Total Score:

# APPENDIX 22 SUICIDAL IDEATION AND BEHAVIOR CATEGORIES AND DEFINITIONS

## Suicidal Ideation

### Passive suicidal ideation: wish to be dead

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

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

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

### Active suicidal ideation: method, but no intent or plan

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

### Active suicidal ideation: method and intent, but no plan

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

### Active suicidal ideation: method, intent, and plan

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

## Suicidal Behavior

### Completed suicide

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

### Suicide attempt

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

**Interrupted suicide attempt**

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

**Aborted suicide attempt**

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

**Preparatory acts toward imminent suicidal behaviors**

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

**Self-Injurious Behavior Without Suicidal Intent**

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

# Statistical Analysis Plan

| | |
|---|---|
| **Sponsor:** | Bristol-Myers Squibb |
| **Protocol No:** | IM011047 |
| [redacted] | |
| **Version Date:** | 21-May-2020 |
| **Version No.:** | 7.0 |

| | |
|---|---|
| **Title:** | A Multi-Center, Randomized, Double-Blind, Placebo- and Active Comparator-controlled Phase 3 Study with Randomized Withdrawal and Retreatment to Evaluate the Efficacy to Evaluate the Efficacy and Safety of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis |
| [redacted] | |
| **SAP No.** | 2.0 |





Approved v2.0 [redacted]

# Approvals

| [redacted] Author | |
|---|---|
| [redacted] Title: | [redacted] |
| Signature /Date: | |

| [redacted] Approvals | |
|---|---|
| [redacted] Title: | [redacted] |
| Signature /Date: | |

| BMS Approvals | |
|---|---|
| [redacted] | [redacted] |
| Signature /Date | |
| [redacted] | |
| Signature /Date: | |

# Table of Contents

# Abbreviations

| Glossary of Abbreviations: | |
|---|---|
| AE | Adverse event |
| AEI | Adverse event of interest |
| ANCOVA | Analysis of covariance |
| [redacted] | [redacted] |
| ATC | Anatomic Therapeutic Classification |
| BID | Twice daily |
| BSA | Body surface area |
| CI | Confidence interval |
| CK | Creatine kinase |
| CMH | Cochran-Mantel-Haenszel |
| CRF | Case Report Form |
| CSP | Clinical Safety Program |
| CSR | Clinical Study Report |
| CTCAE | Controlled Terminology Criteria for Adverse Events |
| DLQI | Dermatology Life Quality Index |
| DMC | Data Monitoring Committee |
| EAIR | Exposure-adjusted incidence rate |
| ECG | Electrocardiogram |
| eC-SSRS | Electronic Columbia-Suicide Severity Rating Scale |
| [redacted] | [redacted] |
| FAS | Full analysis set |
| [redacted] | [redacted] |
| IL | Interleukin |
| IRS | Independent Reporting Statistician |
| IRT | Interactive Response Technology |
| ITT | Intention-to-treat |
| LOCF | Last observation carried forward |
| LS | Least-squares |
| MAR | Missing at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mBOCF | Modified baseline observation carried forward |
| MI | Multiple imputation |

| Glossary of Abbreviations: | |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| NRI | Nonresponder imputation |
| PASE | Psoriatic arthritis screening and evaluation |
| PASI | Psoriasis Area and Severity Index |
| [redacted] | [redacted] |
| PDGD | Protocol deviation guidance document |
| PGA-F | Physician Global Assessment-Fingernails |
| PHQ-8 | Eight-Item Patient Health Questionnaire |
| [redacted] | [redacted] |
| PP | Per-protocol |
| [redacted] | [redacted] |
| pp-PGA | Palmoplantar Physician's Global Assessment |
| PPS | Per-protocol set |
| PSSD | Psoriasis Symptoms and Signs Diary |
| [redacted] | [redacted] |
| QD | Once daily |
| QoL | Quality of Life |
| QTcB | QT interval corrected using Bazett's formula |
| QTcF | QT interval corrected using Fridericia's formula |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| [redacted] | [redacted] |
| sPGA | static Physician Global Assessment |
| ss-PGA | Scalp specific Physician's Global Assessment |
| TEAE | Treatment-emergent adverse event |
| TFLs | Tables, figures, and listings |
| [redacted] | [redacted] |

# 1.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under BMS Protocol IM011047.

The SAP outlines the following:

- Study design
- Study objectives
- Endpoints and assessments
- Analysis sets
- Statistical methodology
- Conventions and definitions

The SAP should be read in conjunction with the study protocol and case report form (CRF) according to the version on Page 1 of this document. Any further changes to the protocol or CRF may necessitate updates to the SAP. Changes following approval of the first version of the SAP will be tracked in the SAP Change Log and a final version of the updated SAP will be approved prior to final database lock.

# 2.0 Study Description

## 2.1 Study Design

This is a 52-week, multi-center, randomized, double-blind, double-dummy, placebo- and active comparator-controlled study with randomized withdrawal and retreatment to evaluate the safety and efficacy of BMS-986165 vs placebo and apremilast. A total of 1000 qualified subjects with moderate-to-severe plaque psoriasis will be enrolled.
Following a screening period of up to 4 weeks, qualified subjects who have completed the screening procedures and have met the inclusion/exclusion criteria will be randomized in a blinded manner in a 2:1:1 ratio via interactive response technology (IRT) to one of the following 3 treatment groups:

- BMS-986165 6 mg once daily (QD)
- Placebo
- Apremilast titrated to 30 mg twice daily (BID) as follows:
    - Day 1: 10 mg tablet in the morning
    - Day 2: 10 mg tablet in the morning and evening
    - Day 3: 10 mg tablet in the morning and 20 mg tablet in the evening
    - Day 4: 20 mg tablet in the morning and the evening
    - Day 5: 20 mg tablet in the morning and 30 mg tablet in the evening
    - Day 6 and thereafter: 30 mg tablet in the morning and the evening

Dummy tablets (placebo for the BMS-986165 6 mg tablet, placebo for apremilast 30 mg tablet BID, and placebo for apremilast 10 mg, 20 mg, 30 mg during titration) will be administered to the subjects to maintain blinding in a double-dummy fashion.

**Week 16**
The coprimary endpoints, static Physician Global Assessment (sPGA) 0/1 and Psoriasis Area and Severity Index (PASI) 75 will be assessed at Week 16. Subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD at Week 16. Subjects who are randomized to BMS-986165 6 mg QD or apremilast will continue on this treatment regimen in a blinded manner.

**Week 24**
The randomized withdrawal and maintenance period will start at Week 24 and continue to Week 52. At Week 24, subjects originally randomized to BMS-986165 6 mg QD who do not achieve PASI 75 response will continue to receive BMS-986165 6 mg QD in a blinded manner. Subjects who achieve PASI 75

response will be re-randomized in a blinded manner to one of the following 2 treatment groups in a 1:1 ratio:

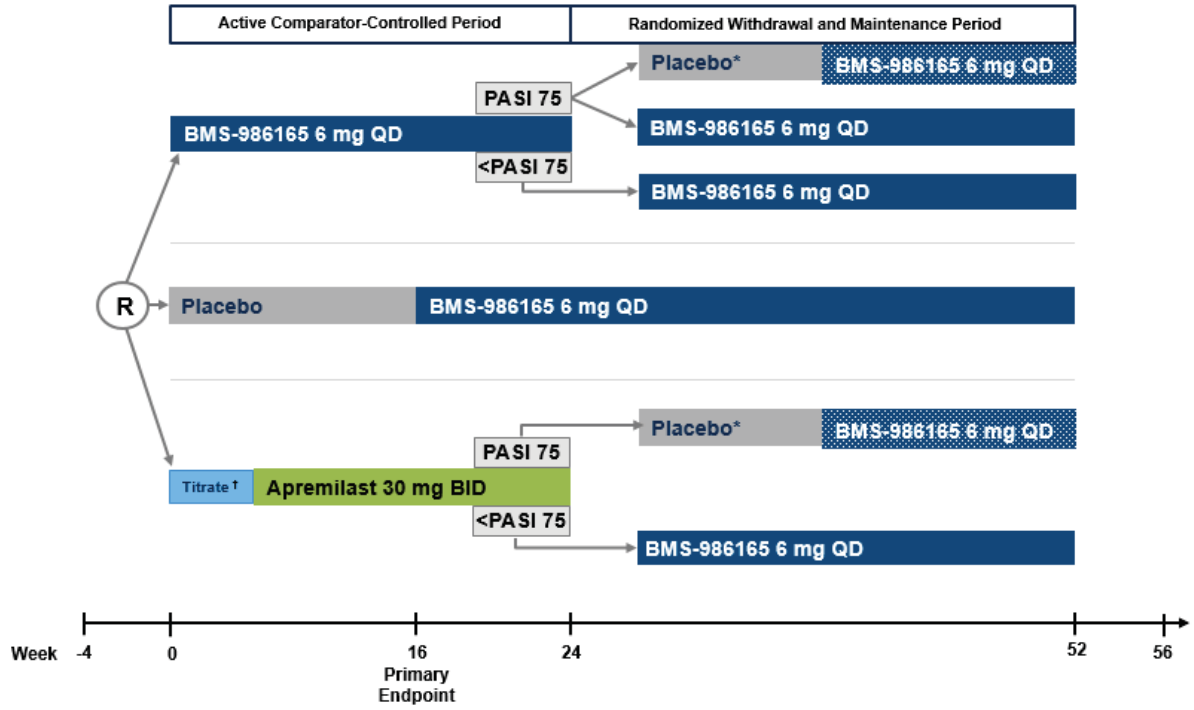
- BMS-986165 6 mg QD
- Placebo

If the subjects who were re-randomized to placebo experience a relapse as defined below at any visit during this period, they will be switched back in a blinded manner to BMS-986165 6 mg QD until the end of the maintenance period (Week 52). Relapse will be defined as at least a 50% loss of Week 24 PASI percent improvement from baseline.

Subjects originally randomized to apremilast who achieve PASI 75 response will be switched in a blinded manner to placebo. If the subject experiences a relapse at any visit during this period, the subject will be treated with BMS-986165 6 mg QD until the end of the maintenance period (Week 52). Subjects receiving apremilast who do not achieve PASI 75 response at Week 24 will be switched to BMS-986165 6 mg QD.During the Week 24 assessment, a subject who has an sPGA ≥3 or ss-PGA≥3 may be treated with restricted topicals/shampoos as described in the protocol (Section 6.7.1). These treatments may only be initiated at Week 24, and not at subsequent time points. A subject who is provided these treatments at Week 24 may use them as needed per the investigator's judgement through Week 52.

The duration of study participation is approximately 60 weeks and will be divided into the following periods: Screening (up to 4 weeks), Treatment (52 weeks), and Follow-up (4 weeks). A schedule of assessments can be found in the protocol. A study design schematic is provided in Figure 1.

Figure 1: Study Design Schematic




[redacted]

## 2.3 Treatment Assignment and Randomization

At Week 0 (Day 1), subjects who have met all criteria for enrollment will be centrally randomized by a computer-generated randomization schedule in a 2:1:1 ratio to the following treatments:

- BMS-986165 6 mg QD
- Placebo
- Apremilast 30 mg BID (titrated)

The randomization lists were generated by the IRT vendor using a permuted block design within each stratum combination level. Randomization will be stratified by geographic region (U.S. and Rest of World),

previous biologic use (for psoriasis, psoriatic arthritis, or other inflammatory disease only; yes/no), and body weight (≥90 kg and <90 kg).

A treatment group will be assigned by IRT based on the above-described randomization schedule and each subject will be assigned a unique randomization number. In addition, a kit (container) number will be assigned to the subject by the IRT each time study treatment is dispensed. Dummy tablets (placebo to the BMS-986165 6 mg tablet and placebo to apremilast) will be administered to the subjects to maintain blinding.

At Week 16, subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD.

At Week 24, subjects originally randomized to BMS-986165 6 mg QD who do not achieve PASI 75 will continue to receive BMS-986165 6 mg QD in a blinded manner. Subjects who achieve PASI 75 response will be re-randomized in a blinded manner in a 1:1 ratio to the following treatments:

- BMS-986165 6 mg QD
- Placebo

Subjects re-randomized to placebo who experience a relapse at a subsequent visit will be switched back onto BMS-986165 6 mg QD in a blinded manner. The investigative site and other study personnel will not have knowledge of the PASI 75 scores at these visits and will therefore remain blinded.

At Week 24, subjects originally randomized to apremilast who do not achieve a PASI 75 response will be switched in a blinded manner to BMS-986165 6 mg QD. Subjects originally randomized to apremilast who achieve PASI 75 response at Week 24 will be switched \ in a blinded manner in a 1:1 ratio to the following treatments:

- Apremilast 30 mg BID
- Placebo

The investigative site and other study personnel will not have knowledge of the PASI 75 score at this visit and will therefore remain blinded.

Subjects re-randomized to placebo from apremilast treatment who experience a relapse as defined above at a subsequent visit will be switched to BMS-986165 6 mg QD in a blinded manner. The investigative site and other study personnel will not have knowledge of the PASI 75 scores at these visits and will therefore remain blinded.

## 2.4 Unblinding Information

The Data Monitoring Committee (DMC) provides oversight of safety considerations throughout the study. A separate unblinded team, comprised of an unblinded Independent Reporting Statistician (IRS) and unblinded programmer(s), will produce output for the DMC using masked treatments. Treatment decodes may only be requested by the DMC Chair and will be provided by the IRS. Data summaries and listings will be transmitted via a secure portal by the IRS to only the DMC members. Additional details regarding the DMC process and unblinding are provided in the DMC charter.

[redacted]

## 2.5 Changes in Statistical Considerations from the Protocol

The following is a list of the important changes in the SAP from the Statistical Considerations section in the protocol:

- The hierarchical testing order for the key secondary endpoints has been updated and two separate hierarchies have been provided, one for US submission and one for ex-US submission (see Tables 1 and 2 in Sec. 6.1.3). The update to the hierarchies are due to emerging information from clinical

trials conducted with other agents recently approved for the treatment of psoriasis. The hierarchies presented in the document supersede the one that is in the protocol.

- Key secondary endpoints were added for the comparison of BMS-986165 to apremilast for sPGA 0/1, PASI 75, and PASI 90 at Week 24.
- Imputation methods were updated to remove the prohibited medication/therapy criteria for binary and continuous endpoints.
- The Full Analysis Set was changed from “all subjects who were randomized to receive assigned study treatment” in the protocol to “all subjects who are randomized”.
- The list of relevant protocol deviations provided in the protocol was updated for determination of the Per Protocol population.
- Logistic regression analyses for binary endpoints were removed as these are similar to the CMH analyses.

# 3.0 **Objectives**

## 3.1 Primary Objective

- Assess whether BMS-986165 is superior to placebo at Week 16 in the treatment of subjects with moderate-to-severe plaque psoriasis

## 3.2 Secondary [redacted] Objectives

- Assess whether BMS-986165 is superior to apremilast at Week 16
- Assess whether BMS-986165 is superior to apremilast at Week 24
- Assess whether BMS-986165 is superior to placebo over the first 16 weeks of treatment
- Assess whether BMS-986165 is superior to placebo in scalp psoriasis through Week 16 in those subjects who have baseline scalp severity Physician’s Global Assessment (ss-PGA) score ≥3
- Assess whether BMS-986165 is superior to apremilast in scalp psoriasis through Week 16 in those subjects who have baseline ss-PGA score ≥3
- Assess whether BMS-986165 is superior to placebo in nail psoriasis through Week 16 in those subjects who have baseline Physician’s Global Assessment-Fingernail (PGA-F) psoriasis score ≥3
- [redacted]
- Assess whether BMS-986165 is superior to placebo in palmoplantar psoriasis through Week 16 in those subjects who have baseline palmoplantar Physician’s Global Assessment (pp-PGA) score ≥3
- Evaluate improvement in patient-reported outcomes for BMS-986165 compared with placebo through Week 16
- Evaluate improvement in patient-reported outcomes for BMS-986165 compared with apremilast through Week 24
- Evaluate maintenance and durability of efficacy of BMS-986165 during the randomized withdrawal period through Week 52 among Week 24 PASI 75 responders continuing on treatment compared with those re-randomized to placebo

# 4.0 Outcomes

The description of assessments for efficacy and safety can be found in Section 8 of the protocol. The calculation of key measures are provided in Section 8.2 of the SAP.

## 4.1 Efficacy

### 4.1.1 Primary Endpoint(s)

The coprimary endpoints for BMS-986165 compared to placebo at Week 16 are defined as:

- sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least a 2-point improvement from baseline
- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score

### 4.1.2 Secondary Endpoint(s)

#### 4.1.2.1 Key Secondary Endpoints for Comparisons to Placebo

The key secondary efficacy endpoints for BMS-986165 compared to placebo at Week 16 are defined as:

- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in PASI score
- sPGA 0 response assessed as a proportion of subjects with an sPGA score of 0
- Scalp specific Physician's Global Assessment (ss-PGA) 0/1 assessed as a proportion of subjects with a ss-PGA score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA score ≥3
- PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥1
- PASI 100 response assessed as a proportion of subjects who achieve a 100% improvement from baseline in PASI score
- Physician Global Assessment-Fingernails (PGA-F) 0/1 assessed as a proportion of subjects with a PGA-F score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline PGA-F score ≥3
- DLQI 0/1 assessed as a proportion of subjects with a DLQI score of 0 or 1 among subjects with a baseline DLQI score ≥2 (Ex-US submission only)

An additional key secondary endpoint to assess the maintenance and durability of efficacy of BMS-986165 during the randomized withdrawal period through Week 52 among Week 24 PASI 75 responders compared with re-randomized placebo is defined as:

- Time-to-relapse (where relapse is defined as ≥ 50% loss of Week 24 PASI percent improvement from baseline) until Week 52 for Week 24 BMS-986165 PASI 75 responders (Ex-US submission only)

#### 4.1.2.2 Key Secondary Endpoints for Comparisons to Apremilast

The key secondary endpoints for BMS-986165 compared to apremilast at Week 16 are defined as:

- sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least a 2-point improvement from baseline
- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score

- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score
- Change from baseline in PSSD symptom score
- ss-PGA 0/1 assessed as a proportion of subjects with a ss-PGA score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA score ≥3
- sPGA 0 response assessed as a proportion of subjects with an sPGA score of 0
- PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥1

The key secondary endpoints for BMS-986165 compared to apremilast at Week 24 are defined as:

- sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least a 2-point improvement from baseline at Week 24
- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score at Week 24
- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score at Week 24

[redacted]

[redacted]

[redacted]

[redacted]

## 4.2 Safety

The safety outcomes include the following:

- Adverse events (AEs)
    - Treatment-emergent adverse events (TEAEs) – defined as:
        - AEs which occur after the first dose of study treatment through 30 days after the final dose of the study treatment or subject's participation in the study if the last scheduled visit occurs at a later time.
    - Treatment-emergent adverse events of interest (AEIs) for the following events:
        - Skin-related AEs
        - Infection AEs, including influenza
        - CK elevation (evaluated as lab toxicity grade 2 or higher)
        - Malignancy
    - SAEs
    - Deaths
- Clinical laboratory parameters
    - Absolute and change from baseline values
    - Laboratory abnormalities (as determined by Controlled Terminology Criteria for Adverse Events [CTCAE v5.0] grading) presented as the worst postbaseline toxicity group
    - Shifts from baseline
    - Potential drug induced liver injury (DILI) is defined as a subject who meets the following criteria:
        - 1) ALT or AST elevation >3 times ULN

        AND

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

        AND

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

- ALT or AST elevation >5 times ULN

- Vital signs
  - Absolute and change from baseline values
  - Marked abnormalities defined by the below categories:
    - Heart rate:
      - Value > 100 and change from baseline > 30
      - Value < 55 and change from baseline < -15
    - Systolic blood pressure:
      - Value > 140 and change from baseline > 20
      - Value < 90 and change from baseline < -20
    - Diastolic blood pressure:
      - Value > 90 and change from baseline > 10
      - Value < 55 and change from baseline < -10

- Electrocardiograms (ECGs)
  - Absolute and change from baseline values
  - Marked abnormalities defined by the below categories:
    - QT interval corrected using Fridericia's formula (QTcF):
      - 450 -< 480 msec
      - 480 -< 500 msec
      - ≥ 500 msec
      - 30 < change from baseline ≤ 60 msec
      - Change from baseline > 60 msec
      - Males: < 450 msec, ≥ 450 msec
      - Females: < 470 msec, ≥ 470 msec
    - PR interval ≥ 200 msec
    - QRS interval ≥ 200 msec

In cases where the QT interval is corrected using Bazett's (QTcB) formula is captured instead of QTcF, then QTcB will be converted to QTcF for analyses.

- Eight-Item Patient Health Questionnaire (PHQ-8) total score
  - Absolute and change from baseline values
  - Shifts from baseline scores

- Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)
  - ~~o~~ Suicidal ideation and suicidal behavior responses by visit
  - Shifts from baseline to postbaseline value for suicidal ideation and suicidal behavior
  - Worst postbaseline value for suicidal ideation and behavior

[redacted]

# 5.0 Populations for Analyses

The following analysis sets will be used in the summary and analysis of study data:

- **Enrolled population**: All subjects who sign informed consent.
- **Full Analysis Set (FAS)**: All subjects who are randomized. Following the intent-to-treat (ITT) principle, subjects will be analyzed according to the treatment group assigned at randomization. The FAS will be the primary efficacy analysis population.
- **Per Protocol Set (PPS)**: A subset of the FAS who are compliant with study treatment and who do not have any relevant protocol deviations that may impact the coprimary efficacy endpoint assessments. The PPS will be analyzed according to the treatment assigned at randomization. The PPS will be a supportive efficacy analysis population and only the co-primary endpoints will be analyzed using this set.
- **As-treated population**: All randomized subjects who take at least one dose of study treatment. Subjects will be analyzed according to treatment received.
- [redacted]
- [redacted]

## 5.1 Relevant Protocol Deviations

Relevant protocol deviations are deviations that can have an impact on the primary efficacy endpoints. The impact of relevant protocol deviations on the primary efficacy results will be assessed by excluding subjects from the FAS to define the PPS in supportive analyses of the primary efficacy endpoints. Relevant protocol deviations to be considered regarding exclusion of subjects from the FAS will include the following:

- Randomized but did not take any study treatment
- No postbaseline PASI or sPGA
- Baseline BSA involvement < 10%
- Baseline PASI score < 12
- Baseline sPGA < 3
- Did not have non-plaque psoriasis at baseline
- Poor compliance to study medication within the first 16 weeks of treatment, <75% compliant with study treatment
- Failure to adhere to prohibited concomitant medication restrictions as described below:
    - Investigational drug or placebo taken outside of the study any time between Day 1 and the Week 16 assessment
    - Phototherapy within 4 weeks prior to the Week 16 assessment
    - Biologic medications (eg, adalimumab, etanercept, infliximab, ustekinumab) any time between Day 1 and the Week 16 assessment
    - Oral psoriasis medications any time between Day 1 and the Week 16 assessment
    - Oral corticosteroids (unless for the treatment of an adverse event) within 4 weeks prior to the Week 16 assessment
    - Topical medications/treatments that could affect psoriasis evaluations within 2 weeks prior to the Week 16 assessment
    - Medicated shampoos within 2 weeks prior to the Week 16 assessment
- Subject received treatment that was different than intended treatment at any visit prior to Week 16.

All subjects with relevant protocol deviations will be identified prior to database lock and unblinding of treatment assignment with the exception of subjects where actual treatment received is different than randomized treatment which will be determined after treatment unblinding. Relevant protocol deviations will be summarized by treatment group and deviation category for the FAS population.

# 6.0 **Statistical Analyses**

Descriptive summaries and analyses will be presented for data captured throughout the study using the following treatment groups.

During the first 16 weeks of treatment, summaries will be provided for the following treatment groups:

- BMS-986165 6 mg QD
- Apremilast
- Placebo

During the first 24 weeks of treatment, summaries will be provided for the following treatment groups:

- BMS-986165 6 mg QD (subjects continuously taking BMS-986165 6 mg QD)
- Apremilast

Summaries of all subjects exposed to BMS-986165 6 mg QD will also be provided as applicable. Adverse events will be summarized using exposure-adjusted incidence rates (EAIR) for these summaries.

Additionally, certain data for BMS-986165 Week 24 PASI 75 responders who have been re-randomized will be summarized by re-randomized treatment. Additional summary may be defined later.

## 6.1 Efficacy Analyses

All efficacy analyses will be performed using the FAS, unless otherwise specified.

Tests of significance of BMS-986165 6 mg QD vs. placebo for the coprimary endpoints will be two-sided with a significance level of 0.05. Both coprimary endpoints need to demonstrate statistical significance to result in a successful study.

The key secondary endpoints will be tested with a two-sided significance level of 0.025 to compare BMS-986165 6mg QD vs. placebo and vs. apremilast. A hierarchical testing approach will be used for testing of key secondary endpoints (see Section 6.1.3). Two-sided 95% confidence intervals (CIs) will be provided for all efficacy estimates. [redacted]

Coprimary and key secondary efficacy endpoints will be displayed graphically by treatment group and visit, as applicable. All efficacy endpoints will be summarized descriptively.

The stratified levels are provided below:

- US/PRIOR USE/< 90 KG
- US/PRIOR USE/>=90 KG
- US/NAÏVE/<90 KG
- US/NAÏVE/>=90 KG
- ROW/PRIOR USE/< 90 KG
- ROW/PRIOR USE/>=90 KG
- ROW/NAÏVE/<90 KG
- ROW/NAÏVE/>=90 KG

### 6.1.1 Primary Endpoints

#### 6.1.1.1 Primary Analysis

Analysis Model

A stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare the sPGA 0/1 response rates at Week 16 between BMS-986165 6 mg QD and placebo using the stratification factors from IRT specified in Section 6.1. The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the odds in the placebo group) and the corresponding 2-sided 95% CIs and p-values will be reported. Additionally, treatment differences in proportions and the 95% CI for the treatment difference will be provided. The common treatment difference in proportion with the confidence interval, common odds ratio with the confidence interval and p-value will be estimated by the Mantel-Haenszel method consistently.

A similar analysis will be performed to compare the PASI 75 response rates at Week 16 between BMS-986165 6mg QD and placebo.

Imputation Methodology

Non-responder imputation (NRI) will be used for coprimary efficacy endpoints for subjects who:

- Discontinue treatment or study prior to Week 16
- Have missing Week 16 endpoint data for any reason

NRI will be used as the primary method of imputation for the coprimary efficacy endpoints.

### 6.1.1.2 Sensitivity Analyses

As a method to assess the sensitivity of the primary imputation method for the coprimary endpoints, further imputation methods will be used to impute Week 16 data in subjects who:

- Discontinue treatment or study prior to Week 16
- Have missing Week 16 endpoint data for any reason

The coprimary endpoints will be analyzed using the primary analysis method for each sensitivity imputation method described below:

Last Observation Carried Forward (LOCF)

The last observed post-baseline value will be carried forward and used as the Week 16 value. Subjects without a post-baseline will be considered a nonresponder.

LOCF and NRI

Subjects randomized to the placebo group will have the endpoint value imputed using LOCF (post-baseline). If a placebo subject does not have a post-baseline values, they will be considered a nonresponder. Subjects randomized to BMS-986165 6 mg QD will have their endpoint value imputed using the NRI methodology.

Tipping Point Analysis

Tipping point analysis will further be used to assess the robustness of the primary study results. Different number of events between treatment groups will be assessed until the study conclusion is changed. Each imputed value is initially imputed as a responder. The imputed values in the placebo group will remain as responders while the BMS-986165 imputed values are replaced as a nonresponders one at a time, therefore changing the number of events between groups. Once all imputed values in the BMS-986165 group have been replaced with nonresponders values, the data will reset to where the BMS-986165 group imputed values are all responders and one by one the imputed values in the placebo group are replaced with a nonresponder until all placebo are nonresponders and all BMS-986165 are responders. Furthermore, every pair of imputations between the placebo and BMS-986165 groups will be assessed similarly, creating a matrix of possible patterns.

At each iteration, the statistical analysis is assessed, and the direction of the analysis is recorded. A graph will be provided to identify at what point to which the difference in events cause a direction shift in study results. The tipping point analyses will be based on a two-sample chi-square test approach rather than a stratified CMH test approach for simplicity of the analysis.

Figure 1: Example of Tipping Point Analysis Direction Boundary

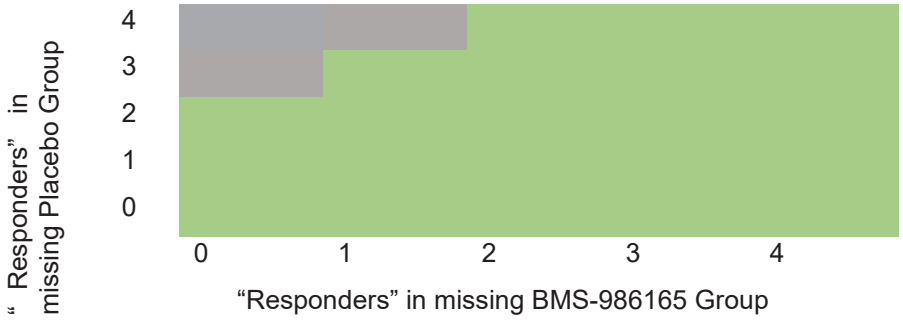



Figure 1 represents an example of the tipping-point analysis for all subjects with missing primary efficacy endpoint (responder/non-responder) in BMS-986165 group (N=5) and placebo group (n=5). Gray cells represent pairs where the statistical analysis resulted in non-significance. Green cells represent pairs where the statistical analysis resulted in significant difference between groups. The tipping-point boundary is where the green cells become gray.

Multiple Imputation

Multiple imputation (MI) will be used for sensitivity analyses for each of the coprimary efficacy endpoints, PASI 75 response at Week 16 and sPGA 0/1 response at Week 16. Multiple imputation of missing data for PASI 75 response and sPGA 0/1 response will be performed by fully conditional specification (FCS) using PROC MI in SAS with the FCS option. The FCS MI specifies the multivariate imputation model on a variable-by-variable basis by a set of conditional densities. For each missing value at Week *X*, the FCS MI will generate values from a conditional distribution for the missing data given the other data prior to Week *X*. The FCS MI model will include treatment group and stratification factors for randomization. A total of 1000 imputed (complete) datasets will be generated for the MI analysis. The same test procedure used for the main analysis (CMH test), will be used to analyze the responder endpoint from each imputed dataset. SAS PROC MIANALYZE will be used to pool the results from the CMH tests and generate an overall result by Rubin's rules (1987).

#### 6.1.1.3 Supportive Analyses

Per Protocol Population Analysis

The coprimary endpoints will be analyzed using the PPS using the primary analysis methodology and primary imputation method.

### 6.1.2 Key Secondary Endpoints

#### 6.1.2.1 Binary Endpoints

Analysis Model

CMH tests will be used to compare response rates between either BMS-986165 6mg QD and placebo or apremilast using the stratification factors from IRT specified in Section 6.1. The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the odds in the placebo or apremilast group) and the corresponding 2-sided 95% CIs and p-values will be reported. Additionally, treatment differences in proportions and the 95% CI for the treatment difference will be provided.

Imputation Methodology for Week 16 Endpoints

NRI will be used for key secondary efficacy endpoints for subjects who:

- Discontinue treatment or study prior to Week 16
- Have missing Week 16 endpoint data for any reason

Imputation Methodology for Week 24 Endpoints (for comparison of BMS-986165 6 mg QD to apremilast)

NRI will be used for key secondary efficacy endpoints for subjects who:

- Discontinue treatment or study prior to Week 24
- Have missing Week 24 endpoint data for any reason

#### 6.1.2.2 Continuous Endpoints

Analysis Model

Analysis of covariance (ANCOVA) models will be used to compare the change between BMS-986165 6 mg QD and placebo or between BMS-986165 6 mg QD and apremilast at Week 16. Treatment group will be included in the model as well as the stratification factors from IRT specified in Section 6.1 and will be considered as fixed effects. The baseline value will be added into the model as a covariate. The adjusted least-squares (LS) means as well as the treatment differences based on LS means and the corresponding 2-sided 95% CIs will be provided for the difference between BMS-986165 6 mg QD and placebo or apremilast.

Imputation Methodology for Week 16 Endpoints

For continuous key secondary endpoints, a modified baseline observation carried forward (mBOCF) approach will be used for missing data. The baseline observation will be carried forward for subjects who discontinue study treatment prior to Week 16 due to:

- Lack of efficacy
- AEs

Subjects who discontinue study treatment prior to Week 16 for other reasons or who have a missing Week 16 value will have the last valid observation carried forward (including the baseline value as applicable).

#### 6.1.2.3 Time-to-Relapse Endpoint

PASI 75 response will be assessed at each visit between Week 24 and Week 52. Subjects who experience a relapse as defined above at any visit between Week 24 and Week 52 will be considered as having an 'event'. Subjects who discontinue study (or treatment) during this time, have missing data, and subjects that do not have relapse by Week 52 will be censored and the date they experienced the above criteria, will be used as their 'event' date.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to-relapse during the randomized withdrawal period. Treatment comparisons between BMS-986165 6 mg QD and placebo for subjects re-randomized during the randomized withdrawal period will be performed using the log-rank test stratified using the stratification factors from IRT specified in Section 6.1.

[redacted]

[redacted]

### 6.1.4 Subgroup Analyses

Subgroup analyses will be performed on the coprimary endpoints using the FAS. The primary imputation method will be applied for these analyses. The CMH test using the stratification factors from IRT will be the analysis method used. The following subgroups will be considered:

- Geographic region (U.S., Rest of World)
- Country
- Sex (male, female)
- Age group (<65 y, ≥65 y)
- Body weight (<90 kg, ≥90 kg) – from case report form
- Race
- Prior biologic use for psoriasis, psoriatic arthritis and other inflammatory diseases only (yes, no) – from case report form
- Prior systemic treatment use (yes/no)
- Prior phototherapy use (yes/no)
- sPGA (3, 4)
- PASI score (≤20, >20)
- BSA involvement (10-20, >20)
- Duration of disease (< 10 y, ≥ 10 y)
- Age at disease onset (<18, 18-39, ≥40)

[redacted]

[redacted]

[redacted]

## 6.2 Safety

Summaries of safety data will be presented by period and treatment group, as applicable, for the As-treated population.

### 6.2.1 Adverse Events

Adverse events will be presented for the number and percentage of subjects and the number of events. Treatment-emergent will be provided in listings. Summary tables will be reported in decreasing frequency based on the BMS-986165 column. Counting for frequency analysis will be by subject and not by AEs, and subjects are only counted once for recurring AEs within each system organ class (SOC) or preferred term (PT); however, the number of total AEs per subject, including multiple occurrences of individual AEs, will also be presented. For summaries of severity, AEs will be reported only at their maximum severity in each subject. Subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.

AE (including deaths) dates will be imputed according to algorithms detailed in Section 8.0. The imputed date of AE onset will be used to assess whether AEs should be considered as treatment-emergent and included in the safety summaries. The original, partial dates will be included in data listings. No imputation will be performed on missing AE seriousness, severity, or relationship; they will be reported as missing.

AEs will be included in a period if the start date of the AE is after the first dispensation date within a period.

An overall summary for the following categories will be presented:

- Deaths
- SAEs
- Related SAEs
- AEs
- Related AEs
- Discontinued treatment due to AEs

The following summaries will also be provided for the following:

- TEAEs by SOC and PT
- Treatment-related TEAEs by SOC and PT
- TEAEs by PT reported in ≥ 5% of subjects
- TEAEs by PT reported in ≥ 1% of subjects
- Treatment-related TEAEs by PT reported in ≥ 5% of subjects
- TEAEs categorized by severity by SOC and PT
- Exposure-adjusted incidence rate (EAIR) for TEAEs by SOC and PT – EAIR is defined in Section 8.1 of the SAP.

#### 6.2.1.1 Adverse Events of Interest (AEI) and Other Important AEs

Summaries for treatment-emergent AEIs events will be provided by PT for each AEI category:

- Skin-related events
- Infection events
- Malignancy events

Creatine kinase (CK) elevation for CK elevation > 2.5 upper limit of normal will be summarized as CTCAE grade 2 or higher in the clinical laboratory summaries.

Additional information collected for some events as part of the clinical safety program and adjudicated events will also be summarized.

#### 6.2.1.2 Serious Adverse Events

Summaries for treatment-emergent SAEs will be provided for the following:

- Treatment-emergent SAEs by SOC and PT

#### 6.2.1.3 Adverse Events Leading to Discontinuation of Study Treatment or Study Treatment Interruption

Summaries for TEAEs leading to discontinuation of study treatment will be provided for the following:

- TEAEs by SOC and PT

Summaries for TEAEs leading to study treatment interruption will be provided for the following:

- TEAEs by SOC and PT

### 6.2.2 Deaths

All adverse events with an outcome of death will be listed.

### 6.2.3 Clinical Laboratory Data

Laboratory parameters will be summarized using the International System (SI) of Units and US conventional units. Data will be summarized by time point, as applicable. The following summaries will be provided for each parameter:

- Absolute and change from baseline values for continuous parameters
- Number and percentage of subjects for the following:
    - Maximum postbaseline CTCAE grade for each applicable laboratory parameter through Week 16
    - Shifts from baseline based on maximum postbaseline CTCAE grade through Week 16
- Drug-induced Liver Injury (DILI) and Hy's Law summaries

### 6.2.4 Vital Signs and Physical Findings

Vital signs, including weight, will be summarized by time point, as applicable. The following summaries will be provided for each parameter:

- Absolute and change from baseline values
- Number and percentage of subjects for the following:
    - Marked abnormality for each abnormality category as defined in Section 4.2

### 6.2.5 ECGs

ECG parameters will be summarized by time point, as applicable. The following summaries will be provided for each parameter:

- Absolute and change from baseline values
- Number and percentage of subjects for the following:
  - Marked abnormality for each abnormality category as defined in Section 4.2

### 6.2.6 Other Safety Data

#### 6.2.6.1 PHQ-8

PHQ-8 total score will be summarized by time point, as applicable. The following summaries will be provided:

- Absolute and change from baseline values
- Number and percentage of subjects:
  - Shifts from none, mild, moderate, moderately severe and severe scores at baseline and at each time point

#### 6.2.6.2 eC-SSRS

Suicidal ideation and behavior individual item responses will be summarized by time point, as applicable. The following summaries will be provided:

- Number and percentage of subjects with positive responses on suicidal ideation and/or suicidal behavior questions for each question and overall all questions within suicidal ideation and suicidal behavior
- Shifts from baseline based on maximum postbaseline response through Week 16
- Worst postbaseline value for suicidal ideation and behavior through Week 16

## 6.3 General Methodology

The following standards/ methods will be used:

- Statistical package(s) planned to be used
  - All analyses will use SAS version 9.4 or higher.
- Standard summary statistics for continuous and categorical variables:
  - Unless otherwise noted, categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.
  - Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. The median, minimum and maximum values will be displayed to the same level of precision as the raw data, the mean to a further decimal place and the SD to two additional decimal places.
  - Variables will be summarized by period, treatment group, and time point, as applicable.

### 6.3.1 Subject Populations and Disposition

The number of subjects enrolled/screened and the number and percentage of subjects randomized, treated, and in each analysis population will be presented. The number and percentage of subjects randomized in each region, country, and site will be presented.

Additionally, the following summaries will be provided for the FAS by treatment group and overall:

- Number and percentage of subjects who completed 16 weeks of treatment
- Number and percentage of subjects who discontinued treatment prior to Week 16 and reason for treatment discontinuation
- Number and percentage of subject who completed 24 weeks of treatment, who discontinued treatment prior to Week 24 and post Week 16, and those who discontinued at any time prior to week 24 and reason for treatment discontinuation. Denominator will be the number of subjects in the FAS.
- Number and percentages of subjects who completed 52 weeks of treatment, who discontinued treatment prior to Week 52 and post Week 24, and who discontinued treatment at any time and reason for treatment discontinuation. Denominator will be the number of subjects in the FAS.

### 6.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group for the FAS. Demographic characteristics include the following:

- Sex
- Race
- Ethnicity
- Age (in years, at time of signing informed consent) and age category (<65 vs ≥65)
- Weight (in kg, at baseline) and weight category (≥90 kg, <90 kg)
- Body mass index (BMI in kg/$m^2$, at baseline)
- Geographic region (U.S., Rest of World)
- Prior biologic use for psoriasis, psoriatic arthritis and other inflammatory diseases only (yes, no)
- Reason for discontinuation of prior biologic use
- Prior systemic treatment use (yes/no)
- Prior phototherapy use (yes/no)
- Stratification factors obtained from IRT: geographic region by prior biologic use and by body weight
- Stratification factors obtained from database: geographic region by prior biologic use and by body weight
- sPGA (3, 4)
- PASI score (≤20, >20)
- BSA involvement (10-20, >20)
- Duration of disease (< 10 y, ≥ 10 y)
- Age at disease onset (<18, 18-39, ≥40)

Additional demographics or baseline data may be added to summary tables.

General medical history and medical history related to psoriasis will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). General medical history data will be summarized for each SOC and PT by treatment group and overall for the FAS. Separate tables will be provided for psoriasis medical history.

### 6.3.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded according to World Health Organization-Drug Dictionary WHO-DD (version at the time of DBL) and will be summarized by Anatomic Therapeutic Classification (ATC) and preferred term (PT) by treatment group for the As-treated population. The number and percentage of subjects using at least one medication and each medication will be displayed by treatment group. Subjects taking more than one medication within the same ATC or PT will be counted once.

Summaries will be provided for prior medications and medications that started prior to first treatment and were ongoing after first treatment start date as well concomitant medications.

Medication dates will be imputed according to algorithms detailed in Section 8.0. The imputed dates will be used to assess whether medications should be included in the summaries as prior or concomitant, however the original, partial dates will be included in data listings.

#### 6.3.3.1 Psoriasis, Psoriatic Arthritis and Other Inflammatory Disease Related Systemic Medications

Prior medications and medications that started prior to first treatment and were ongoing after first treatment start date for systemic biologic and non-biologic medications will be summarized as described above for the number and percentage of subjects using each reported medication.

#### 6.3.3.2 Concomitant High Potency Corticosteroid Use

The number and percentage of subjects using at least one high potency topical corticosteroid at Week 24 will be summarized by treatment group. Additionally, corticosteroids will be summarized by ATC and PT.

### 6.3.4 Exposure

#### 6.3.4.1 Duration of Treatment

**Duration by Group**

Overall duration of each treatment, in days, will be calculated for each subject in each treatment group. Subjects are dispensed study treatment at each visit, starting with Day 1 (Week 0) and at each subsequent visit. The date of first dose of study treatment is the Week 0 [redacted] dosing date and is recorded on the eCRF. If this date is missing, then the earliest drug dispensation date will be used. The last dose date is recorded on the end of treatment page in the eCRF. If this date is missing, then the latest date from the [redacted] page or drug accountability return date will be used.

Duration of treatment will be summarized descriptively by randomized treatment group.

**BMS-986165:**

Subjects randomized to BMS-986165 continuing on BMS-986165 either if PASI 75 responder at Week 24 or subjects randomized to BMS-986165 and are Week 24 PASI 75 nonresponders will have their duration of treatment derived as:

- Date of last dose – date of first dose +1

Subjects randomized to BMS-986165 and re-randomized to placebo at Week 24 will have their duration of treatment derived as:

- BMS-986165 (Wk 0 through Wk 24) = Date of last dose of BMS-986165 prior to first placebo dose date – date of first dose +1
- Placebo (Wk 24 through final week on placebo) = Date of last dose of placebo - date of first dose of placebo + 1
- BMS-986165 (First dose after relapse on placebo or switched to BMS-986165 due to COVID-19 through Wk 52) = Date of last dose of BMS-986165 – first BMS-986165 dose date after relapse + 1; only calculated for subjects that relapse or are switched to BMS-986165 due to COVID-19
- Total BMS-986165 = Sum BMS-986165 exposure over entire treatment period

**Placebo:**

For subjects randomized to placebo, duration is defined as:

- Placebo = Date of last dose of placebo – date of first dose +1
- BMS-986165 = Date of last dose of BMS-986165 – date of first dose of BMS-986165 +1

**Apremilast:**

For subjects randomized to apremilast, duration is defined as:

- Apremilast (Wk 0 through Wk 24) = Date of last dose of apremilast – date of first dose +1
- Placebo (PASI 75 nonresponders) = Date of last dose of placebo – date of first dose of placebo + 1
- BMS-986165 (switched from apremilast or switched from placebo to BMS-986165 after relapse or due to COVID-19) = Date of last dose of BMS-986165 – date of first dose date of BMS-986165 + 1

**Duration by Period**

Overall duration (in days) of each treatment received within each study period will be calculated. Duration within each period is defined for each treatment group as:

- Duration of the resumed BMS-986165 6 mg QD treatment
- For subjects on BMS-986165 who are treated with placebo following Week 24 re-randomization and resume BMS-986165 treatment prior to Week 52, the duration of the resumed BMS-986165 treatment will be calculated from the first IP dispense date of the resumed BMS-986165 to either Week 52 IP dispense date or the date of the last dose of IP in the study for subjects who discontinue in the period after resuming BMS-986165.
- Duration of the re-randomized placebo treatment

  For all subjects (including those initially on BMS-986165 or apremilast) who are treated with placebo following Week 24 re-randomization, the duration of the re-randomized placebo treatment will be calculated from the IP dispense date at Week 24 to either the first IP dispense date of the BMS-986165 treatment in the period; or Week 52 IP dispense date for subjects who have not resumed BMS-986165 or apremilast in the period or the date of the last dose of IP in the study for subjects who discontinue in the period.

### 6.3.4.2 Summary of Dosing

The number of doses taken for each subject for each period will be determined using the eCRF drug accountability data and is defined as:

$$Doses\ Taken: (number\ of\ tablets\ dispensed - number\ of\ tablets\ returned)$$

The number of doses taken will be summarized descriptively by treatment group within each period and overall.

### 6.3.4.3 Compliance

Treatment compliance will be determined from data captured on the Drug Accountability eCRF.

$$Number\ of\ expected\ doses: (date\ of\ next\ visit - date\ of\ current\ visit)x3$$

Treatment compliance will be derived for each period. Compliance is defined as:

$$\left(\frac{Number\ of\ doses\ taken}{Number\ of\ expected\ doses}\right)x100$$

Period compliance will be calculated by summing over all visits within the period using descriptive statistics by treatment group. The number and percentage of subjects with <75%, 75% to 100%, and >100% compliance will be provided by treatment group for each period. If a subject does not return the container,

then this dispensation event will be excluded in the calculation for the total number of doses taken, total number of expected doses, and total compliance.

[redacted]

## 6.6 Statistical Impacts Due to COVID-19

### 6.6.1 Impact on Efficacy Endpoints

There are no COVID-19-related impacts to the Week 16 efficacy endpoints as all subjects remaining in the trial completed the Week 16 visit prior to COVID-19 site restrictions. Efficacy endpoints involving Week 24 and later visits may be impacted by COVID-19 in the form of missing data and/or a treatment assignment defaulting to BMS-986165.

Censoring rules will be applied to the PASI 75 time-to-relapse endpoint for re-randomized subjects due to the following COVID-19-related issues post Week 24:

- Subject study treatment assignment was defaulted to BMS-986165 because they had a remote safety monitoring visit and efficacy assessments were not performed. The subjects will be censored at the time of the remote visit if relapse had not been observed already;
- Subject has missing visits (ie, efficacy assessments not performed) after Week 24 and assuming relapse was not observed prior to missing visits:
    - If the subject returns at a later visit and is found to have relapsed, midpoint imputation will be used to determine time-to-relapse (ie, midpoint of the censoring interval).
    - If the subject returns at a later visit and has not relapsed, then the subject will continue to be evaluated for relapse.
    - If the subject is discontinued from the study treatment, then the subject will be censored at the time of study treatment discontinuation.

Similar data handling rules will be applied to the following time-to-event endpoints:

- Time to first loss of PASI 75 among subjects that are PASI 75 responders at Week 24
- Time to first loss of sPGA 0/1 among subjects that are sPGA 0/1 responders at Week 24 where loss of sPGA 0/1 is defined as an sPGA score ≥ 2
- Time to rebound as defined above among subjects re-randomized to placebo
- Time-to-relapse for Week 24 PASI 75 apremilast responders switched to placebo

Additional efficacy endpoints involving later visits may be impacted by COVID-19 in the form of missing data and/or a treatment assignment defaulting to BMS-986165. If a subject has missing data or is switched to BMS-986165 from a different treatment due to COVID-19 during the Week 24 through Week 52 period, the subject will be excluded from the analysis.

Additional efficacy endpoints that may be impacted include the following:

- [redacted]
- [redacted]
- Disease relapse assessed as the proportion of subjects who have ≥ 50% loss of Week 24 PASI percent improvement from baseline
- [redacted]

[redacted]

### 6.6.2 Impact on Safety Endpoints

No modifications will be made for the analysis of safety data due to COVID-19-related issues. There will not be any additional safety data handling considerations for missing data or treatment interruptions due to COVID-19.

# 7.0 Sequence of Planned Analyses

## 7.1 Interim Analyses

No interim analysis is planned for this study.

## 7.2 Final Analyses and Reporting

All final, planned analyses identified in this statistical analysis plan will be performed only after the last subject has completed the study and the database has been locked. The randomization codes for all subjects will not be unblinded until after the database has been locked.

Analyses of the palmoplantar pp-PGA 0/1 endpoint are provided for descriptive purposes within the individual CSR due to small sample sizes. A pooled analysis of data from IM011046 and IM011047 will be conducted for the submission.

# 8.0 **Conventions**

## 8.1 General Definitions

The following data definitions and handling conventions will be used for general analysis:

| **Term** | **Definition** |
|---|---|
| Study Day | Study day is calculated as:<br>assessment date – date of first dose + 1 |
| Baseline | Unless otherwise stated, Baseline is defined as the measurement at the randomization visit (Week 0). If the measurement at the randomization visit is missing, then a prior measurement during the screening period may be used as baseline. Baseline assessments must be performed per protocol and standard of care assessments may not be used for baseline.<br>Baseline for each PSSD question will be calculated as the average value over the 7 days prior to the randomization visit. In the event of missing values in the 7 days prior to the randomization visit, daily scores from at least 4 days out of the 7 days can be used to calculate the average score. If > 3 daily scores in the last 7 days are missing for a particular question, then the baseline value for that question will be missing. If any questions are missing baseline after using the described rule, then the baseline value for the subscore using that question and the baseline value for the total score will be missing. |
| Change from Baseline | Change from baseline is defined as (value at post-baseline visit – value at baseline). |
| Change in the maximum post-baseline value or change in the worst post-baseline value | Change from baseline in the maximum post-baseline value or grade is defined as highest observed value post-baseline. The change is calculated using this value as the post-baseline value.<br>Change from baseline in the worst post-baseline value is defined as worst observed value post-baseline. The change is calculated using this value as the post-baseline value. |
| Concomitant and Prior Medication | Prior medications are defined as medications with a stop date prior to the first dose of study treatment. Concomitant medications are defined as any medications ongoing at the start of study treatment or with a start date on or after the first dose date. |
| End of Study (EOS) Date | The EOS date is the date recorded on the eCRF that a randomized subject either discontinued or completed the study. If the subject is |

| | |
|---|---|
| | lost to follow-up, the EOS date will be the date of the last visit assessment obtained. |
| Exposure-adjusted incidence rate (EAIR) | EAIR = 100* 365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment that a subject is exposed. Where total exposure time for each AE within a treatment is calculated as follows:<br>• If a subject has at least 1 event while on a particular treatment, then the exposure time for that subject and AE on that treatment is:<br>o First AE onset date – treatment start date (of that particular treatment) +1<br>• If a subject does not have an event, exposure time for that AE is:<br>o Treatment stop date (of that particular treatment) – Treatment start date (of that particular treatment) + 1 + 30 days (if subject discontinued or subject completed Period 3 and is not rolling into IM011075 study)<br>o Treatment stop date (of that particular treatment) – Treatment start date (of that particular treatment) + 1 (if subject completed Period 3 and is rolling into IM011075 study)<br>• Total exposure time = sum of exposure time for each AE within a treatment |
| First Dose Date – Study | The date a subject received their first dose on Day 1 as recorded in the eCRF Week 0 [redacted] dosing date or the earliest drug dispensation date. |
| Last Dose Date – Study | The date of last recorded dose on the eCRF for a randomized subject. |
| First Dose Date – Period | The date a subject received their first dose as recorded in the eCRF Week 0 [redacted] dosing date or the earliest drug dispensation date for Treatment Period 1 and the earliest drug dispensation date for Treatment Periods 2 and 3. |
| Last Dose Date – Period | The date of the last visit in the periods – 1. If a subject prematurely discontinues study treatment within a period, the date of last recorded dose on the eCRF will be used as the last dose date for the period. |
| Percent Change from Baseline | Percent change from baseline is defined as ([value at post-baseline visit – value at baseline]/value at baseline) x 100.<br>If the baseline value is 0 and the post-baseline value is also 0, then the percent change from baseline is set to 0.<br>If the baseline value is 0 and the post-baseline is >0, then the percent change from baseline value will be missing. |

## 8.2 Calculation of Key Measures

The following efficacy assessments will be used to assess subjects' disease activity and severity during the study. Outcomes are reported via an eCOA tool at various times throughout the study as described in the

protocol Schedule of Activities. At study visits, assessments by the investigator or subjects and results/responses will be reported directly into the eCOA tool at the time of the visit. The tool will open assessments in a sequential manner, meaning that the full assessment is to be completed prior to moving forward to the next assessment. This limits the possibility of partially missing data. Also, as investigators/subjects are prompted to enter data for each assessment for the visit, the possibility of a full assessment being missing is also negated.

Scoring of assessments where validated algorithms are not required will be derived in SAS datasets.

Scoring of assessments where validated scoring tools are required, licenses for these tools will be purchased and used for scoring prior to incorporating into the SAS datasets.

### 8.2.1 Investigator-Administered Assessments

Assessments will be performed by a qualified physician or dermatologist or trained designee who is experienced in the assessment of psoriasis patients. To limit variability, every effort will be made so that the same individual conducts the assessment at all subsequent visits.

#### 8.2.1.1 static Physician's Global assessment (sPGA)

The sPGA is a 5-point scale of an average assessment of all psoriatic lesions based on erythema, scale, and induration. The sPGA measure determines psoriasis severity at a single point in time (without taking into account the baseline disease condition) as clear (0), almost clear (1), mild (2), moderate (3), or severe (4). A higher score equates to higher severity of disease.

The individual scores at each visit for erythema (E), induration (I) and scaling (S) will be captured via the eCOA system. Scores will range from 0 to 4. A total score will also be computed based on the average of the 3 characteristic scores.

$$Total\ average\ score = \frac{E + I + S}{3}$$

The total average score will be calculated in the eCOA system. The average score will be rounded to the nearest whole number. For example, if the total average score is ≤1.49 the score will be rounded to 1. If the score is ≥1.5 the score will be rounded to 2. The primary endpoint is derived from the total average score.

sPGA 0 is derived as the binary indicator for sPGA from the calculation above equal to 0 or not;

sPGA 0/1 is derived as the binary indicator for sPGA from the calculation above equal is less than 2 or not;

[redacted]

All individual scores and total average score assessed at each week throughout the study will be transferred to [redacted] for analysis. The endpoint derivations will be performed in the analysis datasets.

#### 8.2.1.2 Psoriasis Area and Severity Index (PASI)

The PASI is a measure of the average redness, thickness, and scaliness of psoriatic skin lesions (each graded on a 0–4 scale; 0 = none to 4 = very severe), weighted by the area of involvement (head, arms, trunk to groin, and legs to top of buttocks). The PASI produces a numeric score that can range from 0 to 72, with higher PASI scores denoting more severe disease activity. The PASI includes multiple subscores and a final total score that will be provided by the eCOA system. Individual plaque characteristic rating scores are provided for each body region as well as the weighted score. Additionally, the degree of involvement of each body region is assessed and that score is multiplied by the weighted plaque characteristic score for a final score for each body region. The total PASI score is a sum of the 4 body regions: Head, Upper Extremities, Trunk and Lower Extremities.

The PASI Total score will be used to assess response to treatment. The percent change from baseline will be calculated at each visit. The PASI 75 endpoint is the proportion of subjects who experience at least a 75% improvement in PASI score as compared with the baseline value.

1 = $If\ \left(\frac{Baseline\ PASI - Visit\ PASI}{Baseline\ PASI}\right) x100 \geq 75\ then\ subject\ is\ a\ PASI\ 75\ responder$

0 = otherwise

The PASI 50, PASI 90, and PASI 100 are defined similarly. The endpoint derivations will be performed in the analysis datasets.

### 8.2.1.3 Body Surface Area (BSA)

Measurement of psoriasis BSA involvement is estimated using the handprint method with the size of a subject's handprint (including fingers and thumb) representing 1% of BSA involved. 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).

The Total BSA is the sum of each body region and is assessed at each visit and recorded in the eCOA system.

The product of BSA and sPGA will be calculated. At baseline, baseline BSA will be multiplied by baseline sPGA score. The derivation will be performed at each subsequent visit.

### 8.2.1.4 scalp specific Physician's Global Assessment (ss-PGA)

The scalp specific assessment will only be performed in subjects with scalp involvement. If there is evidence of scalp involvement, scalp lesions are evaluated in terms of clinical signs of redness, thickness, and scaliness and scored on the following 5-point ss-PGA scale:

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

The ss-PGA is assessed at each visit throughout the study in subjects that have evidence of scalp psoriasis at baseline. The score will be collected in the eCOA system.

[redacted]

### 8.2.1.6 Physician's Global Assessment-Fingernails (PGA-F)

In this assessment, fingernail psoriasis is evaluated. The PGA-F will be performed at baseline. If a subject shows evidence of psoriatic fingernail involvement, the assessment will be performed at each subsequent visit to assess severity and improvement over time. Only subjects with PGA-F at baseline will be assessed throughout the study. The overall condition of the fingernails is rated on a 5-point scale:

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

The rating score will be collected in the eCOA system.

[redacted]

### 8.2.1.8 Palmoplantar PGA (pp-PGA)

This measure will be used for subjects with palmoplantar (finger and toe surfaces) involvement at baseline. Only subjects with baseline palmoplantar involvement will continue to have these assessments at each subsequent visit throughout the study. The pp-PGA uses a 5-point (0-4) overall severity scale:

0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe.

Scores are collected at each visit and entered in the eCOA system.

[redacted]

## 8.2.2 Subject-Reported Assessments

### 8.2.2.1 Psoriasis Symptoms and Signs Diary (PSSD)

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

The following questions in the instrument are included in the symptom score: Q1, Q4, Q9, Q10, Q11

The following questions in the instrument are included in the sign score: Q2, Q3, Q5, Q6, Q7, Q8

Two versions of the PSSD were developed, one with a 24-hour recall period (PSSD-24h) and one with a 7-day recall period. The PSSD-24h will be administered daily in this trial to avoid recall bias with a longer recall period. Individual scores to each question are collected daily in the PSSD. For visit PSSD scoring, the daily scores (with 24-h recall periods) over the prior 7 day will be used and the average score to each of the 11 questions will be used as the score at that visit. In case missing data arise during the 7 days prior to the visit, daily scores of at least 4 days out of the 7 can be used. If >3 scores are missing, the average score will be missing. Baseline PSSD score is calculated based on the daily diary collected data during the screening period. Baseline for each PSSD question will be calculated as the average value over the 7 days prior to the randomization visit. In the event of missing values in the 7 days prior to the randomization visit, daily scores from at least 4 days out of the 7 days can be used to calculate the average score. If > 3 daily scores in the last 7 days are missing for a particular question, then the baseline value for that question will be missing. If any questions are missing baseline after using the described rule, then the baseline value for the subscore using that question and the baseline value for the total score will be missing.

A symptom score will be derived by averaging the 5 questions included in the symptom score and multiplying by 10. To obtain a symptom score on a given day, responses to at least 2 of the 5 questions must be available. If 3 or more questions are missing, the symptom score is considered missing.

A sign score will be derived by averaging the 6 questions included in the sign score and multiplying by 10. Responses to at least 3 of the 6 questions must be available in order to obtain a sign score for a given day. If more than 3 questions are missing, the sign score is considered missing.

Both scores range from 0-100, where 0 representing the least severe symptom/sign and 100 the most severe. A total PSSD score with range 0-100 will be derived from taking the average of the symptom and sign scores.

### 8.2.2.2 Dermatology Life Quality Index (DLQI)

The DLQI 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 where 0="not at all", 1="a little", 2="a lot", or 3="very much". The scores are summed, giving a range from 0 (no impairment of life quality) to 30 (maximum impairment). Question 7 includes 2 questions, if the subject answers ‘Yes’ to Q7, the score given is a 3. If the subject answers ‘No’ to Q7, they are asked the second question where a score of 0=’not at all’, 1=’a little’, or 2=’a lot’ is given. Certain questions include an option for not relevant. When scoring, any questions deemed ‘not relevant’ will take on a value of 0.

. Interpretation of DLQI scores is as follows:

- 0-1 = no effect at all on patient’s life
- 2-5 = small effect on patient’s life

- 6-10 = moderate effect on patient's life
- 11-20 = very large effect on patient's life
- 21-30 = extremely large effect on patient's life

Individual scores for each question will be provided by the eCOA system. The DLQI score will be derived in the analysis datasets.

[redacted]

[redacted]

### 8.2.2.8 Psoriatic Arthritis Screening and Evaluation (PASE) Questionnaire

The PASE questionnaire will be administered at Screening in subjects with peripheral joint complaints. The PASE questionnaire is a self-administered tool that is used to screen for psoriatic arthritis among subjects who have psoriasis. The PASE questionnaire consists of 15 questions subdivided into 7 questions focusing on symptoms of psoriatic arthritis, and 8 questions focusing on the impact of psoriatic arthritis on function. Each question is scored on a 1 to 5 scale, with a maximum symptom sub-scale score of 35, a maximum function sub-scale score of 40 giving a total maximum score of 75. A score of 47 or above has been shown to distinguish between psoriatic arthritis and non-psoriatic arthritis. This questionnaire is only intended to be a screening tool for psoriatic arthritis and does not replace a comprehensive musculoskeletal exam performed by a rheumatologist. This information will not be summarized.

### 8.2.2.9 Eight-Item Patient Health Questionnaire (PHQ-8)

The PHQ-8 is established as a valid diagnostic and severity measure for depressive disorders in large clinical studies. Each of the 8 questions is based on a 2-week recall and scored on a scale of 0 to 3 by a tick box as: 0=Not at All, 1=Several Days, 2=More than Half the Days, and 3=Nearly Every Day. A PHQ-8 score is derived by summing the scores for the 8 questions. The total PHQ-8 score ranges from 0-24. Scoring interpretation is as follows:

- 0-4 = no significant depressive symptoms
- 5-9 = mild depressive symptoms
- 10-14 = moderate depressive symptoms
- 15-19 = moderately severe depressive symptoms
- 20-24 = severe depressive symptoms

Response to each individual question is collected in the eCOA system. The total score will be derived in the analysis datasets.

### 8.2.2.10 electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) is a computer-automated, patient-reported version of the C-SSRS instrument that defines 11 categories of suicidal ideation and behavior (SIB) events. Categories and definitions are provided in Appendix 23 of the protocol. The categories are as follows:

- Suicidal ideation
    1. Wish to be dead
    2. Non-specific active suicidal thoughts

3. Active suicidal ideation with any methods without intent to act
4. Active suicidal ideation with some intent to act, without specific plan
5. Active suicidal ideation with specific plan and intent

- Suicidal behavior
  1. Preparatory acts or behavior
  2. Aborted attempt
  3. Interrupted attempt
  4. Actual attempt (Non-fatal)
  5. Completed suicide
- Self-injurious behavior, no suicidal intent

## 8.3 Missing, Unknown, or Partial Dates

| Start Date | | Stop Date: Complete: *yyyymmdd* <1st dose | Complete: *yyyymmdd* ≥1st dose | Partial: *yyyymm* <1st dose *yyyymm* | Partial: *yyyymm* ≥1st dose *yyyymm* | Partial: *yyyy* <1st dose *yyyy* | Partial: *yyyy* ≥1st dose *yyyy* | Missing/ Ongoing |
|---|---|---|---|---|---|---|---|---|
| Partial: *yyyymm* | = 1st dose *yyyymm* | 2 | 1 | n/a | 1 | n/a | 1 | 1 |
| | ≠ 1st dose *yyyymm* | | 2 | 2 | 2 | 2 | 2 | 2 |
| Partial: *yyyy* | = 1st dose *yyyy* | 3 | 1 | 3 | 1 | n/a | 1 | 1 |
| | ≠ 1st dose *yyyy* | | 3 | | 3 | 3 | 3 | 3 |
| Missing | | 4 | 1 | 4 | 1 | 4 | 1 | 1 |

**1** = Impute as the date of first dose
**2** = Impute as the first of the month
**3** = Impute as January 1 of the year
**4** = Impute as January 1 of the stop year
Note: If the start date imputation leads to a start date that is after the stop date, then there is a data error and do not impute the start date.

Imputation rules for partial or missing stop dates:

1. Initial imputation
   a. For partial stop date “mmyyyy”, impute the last of the month.
   b. For partial stop date “yyyy”, impute December 31 of the year.
   c. For completely missing stop date, do not impute.
2. If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
3. If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date.

Imputation rules for partial or missing death dates:

1. If death year and month are available but day is missing:
   a. If “mmyyyy” for last contact date = “mmyyyy” for death date, set death date to the day after the last contact date.
   b. If “mmyyyy” for last contact date < “mmyyyy” for death date, set death date to the first day of the death month.
   c. If “mmyyyy” for last contact date > “mmyyyy” for death date, data error and do not impute.

If both month and day are missing for death date or a death date is totally missing, set death date to the day after the last contact date.

## 8.4 Study Periods

Period 1 = Week 0 to Week 16 visit date

Period 2 = Week 16 visit date +1 to Week 24 visit date

Period 3 = Week 24 visit date +1 to Week 52 visit date

Follow-up = 4-week follow-up period

## 8.5 Day Ranges for Analysis Visits

Below are the day ranges for the analysis visit definitions. If more than one visit occurs within an analysis visit, then the visit that is closest to the target date should be used for analysis.

| Period<br>Week | Target Day | Day Range |
|---|---|---|
| **Baseline** | | Screening, 1 |
| **Period 1** | | |
| Week 1 | 8 | 2, 11 |
| Week 2 | 15 | 12, 18 |
| Week 4 | 29 | 19, 43 |
| Week 8 | 57 | 44, 71 |
| Week 12 | 85 | 72, 99 |
| Week 16 | 113 | 100, 127 (or Week 16 drug dispense date) |
| **Period 2** | | |
| Week 20 | 141 | 1st day after Week 16 drug dispense date, 155 |
| Week 24 | 169 | 156, 183 (or Week 24 drug dispense date) |
| **Period 3** | | |
| Week 28 | 197 | 1st day after Week 24 drug dispense date, 211 |
| Week 32 | 225 | 212, 239 |
| Week 36 | 253 | 240, 267 |
| Week 40 | 281 | 268, 295 |
| Week 44 | 309 | 296, 323 |
| Week 48 | 337 | 324, 351 |
| Week 52 | 365 | 352, last visit date prior to Safety Follow-up |
| Safety Follow-up | 393 | Safety Follow-up visit |

# 9.0 References


- Campbell G, Pennello G, Yue L. Missing data in the regulation of medical devices. Journal of Biopharmaceutical Statistics 2011;21:180-195.
- Yan X, Lee S, Li N. Missing data handling methods in medical device clinical trials. Journal of Biopharmaceutical Statistics 2009;19:1085-1098.
- Kenward MG, Roger J. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997;53(3):983-997.
- Rubin, DB (1987). Multiple Imputation for Nonresponse in Surveys. New York, J. Wiley & Sons.

# 10.0 Document History

| Version Number | Version Date | Summary of Changes |
|---|---|---|
| 1.0 - Original Document | 09-Jun-2019 | Not applicable |
| 2.0 – Amendment 01 | 30-Sep-2020 | Revisions provided below. |

**Revisions for Amendment 01:** In addition to the revisions specified below, there were some minor typographical and formatting changes made. Additions are noted by bold text. Removals are noted by strikethrough.

| SAP Section | Revised Text | Rationale for Change |
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| 2.0 Study Description<br>2.1 Study Design | Following a screening period of up to 4 weeks, qualified subjects who have completed the screening procedures and have met the inclusion/exclusion criteria will be randomized in a **blinded manner in a** 2:1:1 ratio via interactive response technology (IRT) to one of the following 3 treatment groups:<br>Dummy tablets (placebo for the BMS-986165 6 mg tablet, placebo for apremilast 30 mg tablet BID, and placebo for apremilast 10 mg, 20 mg, 30 mg during titration) will be administered to the subjects to maintain blinding in a double-dummy fashion. ~~Note that apremilast will not be used as a treatment arm in China.~~<br>**Week 16 activities**<br>The coprimary endpoints, static Physician Global Assessment (sPGA) 0/1 and Psoriasis Area and Severity Index (PASI) 75 will be assessed at Week 16. Subjects receiving placebo will be switched in a blinded manner to BMS-986165 6 mg QD at Week 16. Subjects who are randomized to BMS-986165 6 mg QD or apremilast will continue on their assigned treatment regimen **in a blinded manner**. | Clarified randomization is done is a blinded fashion.<br>Removed reference to apremilast in China as this is only applicable to IM011046, |
| [redacted] | | |
| 2.5 Changes in Statistical Considerations from the Protocol | ~~**There are no changes in statistical considerations from the protocol at this time.**~~ **The following is a list of the important changes in the SAP from the Statistical Considerations section in the protocol:**<br>• **The hierarchical testing order for the key secondary endpoints has been updated and two separate hierarchies have been provided, one for US** | The definition for the Full Analysis Set was modified to include all randomized subjects. |

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| | **submission and one for ex-US submission (see Tables 1 and 2 in Sec. 6.1.3). The hierarchies presented here supersede the one that is in the protocol.**<br>• **Key secondary endpoints were added for the comparison of BMS-986165 to apremilast for sPGA 0/1, PASI 75, and PASI 90 at Week 24.**<br>• **Imputation methods were updated to remove the prohibited medication/therapy criteria for binary and continuous endpoints.**<br>• **The Full Analysis Set was changed from "all subjects who were randomized to receive assigned study treatment" in the protocol to "all subjects who are randomized".**<br>• **The list of relevant protocol deviations provided in the protocol was updated for determination of the Per Protocol population.**<br>• **Logistic regression analyses for binary endpoints were removed as these are similar to the CMH analyses.** | Noted that the relevant deviation list was updated from the list in the protocol.<br>Additional Week 24 endpoints were added.<br>Imputation methods were updated to remove prohibited medication/ therapy criteria.<br>Hierarchical testing order of key secondary endpoints were updated and accounting of regional regulatory needs.<br>Removed logistic regression analyses. |
| 3.2 Secondary [redacted] Objectives | • **Assess whether BMS-986165 is superior to apremilast in scalp psoriasis through Week 16 in those subjects who have baseline ss-PGA score ≥3**<br>• Assess whether BMS-986165 is superior to ~~placebo~~**apremilast** in nail psoriasis through Week 16 in those subjects who have baseline PGA-F psoriasis score ≥3 | Aligned objectives with the most recent protocol amendment. |
| 4.1.2 Secondary Endpoints<br>4.1.2.1 Key Secondary Endpoints for Comparisons to Placebo | The key secondary efficacy endpoints for BMS-986165 compared to placebo at Week 16 are defined as:<br>• PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in PASI score<br>• sPGA 0 response assessed as a proportion of subjects with an sPGA score of 0<br>• Scalp specific Physician's Global Assessment (ss-PGA) 0/1 assessed as a proportion of subjects with a ss-PGA score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA score ≥3<br>• PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥1 | Updated key secondary endpoints compared to placebo and re-ordered. |

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| | • PASI 100 response assessed as a proportion of subjects who achieve a 100% improvement from baseline in PASI score<br>• Physician Global Assessment-Fingernails (PGA-F) 0/1 assessed as a proportion of subjects with a PGA-F score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline PGA-F score ≥3<br>• ~~Change from baseline in Psoriasis Symptoms and Signs Diary (PSSD) symptom score~~<br>• DLQI 0/1 assessed as a proportion of subjects with a DLQI score of 0 or 1 among subjects with a baseline DLQI score ≥2 **(Ex-US submission only)**<br>• ~~Palmoplantar Physician's Global Assessment (pp-PGA) 0/1 assessed as a proportion of subjects with a pp-PGA score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline pp-PGA score ≥3~~<br>An additional key secondary endpoint to assess the maintenance and durability of efficacy of BMS-986165 during the randomized withdrawal period through Week 52 among Week 24 PASI 75 responders compared with re-randomized placebo is defined as:<br>• ~~Mediant~~**T**ime-to-relapse (where relapse is defined as ≥ 50% loss of Week 24 PASI percent improvement from baseline) until Week 52 for Week 24 BMS-986165 PASI 75 responders **(Ex-US submission only)** | |
| 4.1.2.2 Key Secondary Endpoints for Comparisons to Apremilast | The key secondary endpoints for BMS-986165 compared to apremilast at Week 16 are defined as:<br>• sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least a 2-point improvement from baseline<br>• PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score<br>• PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score<br>• Change from baseline in PSSD symptom score<br>• ss-PGA 0/1 assessed as a proportion of subjects with a ss-PGA score of 0 or 1 with at least a 2-point improvement from baseline among subjects with a baseline ss-PGA score ≥3<br>• ~~PASI 100 response assessed as a proportion of subjects who achieve a 100% improvement from baseline in the PASI score~~ | Updated key secondary endpoints compared to apremilast and re-ordered.<br>Added some clarifying language. |

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| | • sPGA 0 response assessed as a proportion of subjects with an sPGA score of 0<br>• PSSD symptom score of 0 assessed as a proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score ≥1<br>**The key secondary endpoints for BMS-986165 compared to apremilast at Week 24 are defined as:**<br>• **sPGA 0/1 response assessed as a proportion of subjects with an sPGA score of 0 or 1 with at least a 2-point improvement from baseline at Week 24**<br>• **PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score at Week 24**<br>• **PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score at Week 24** | |

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| 4.2 Safety | • Treatment-emergent adverse events (TEAEs) – defined as:<br>o ~~New nonserious~~ AEs which ~~first~~ occur after the first dose of study treatment through **30 days** 4 ~~weeks~~ after the final dose of the study treatment or subject's participation in the study if the last scheduled visit occurs at a later time.~~;~~<br>~~New serious adverse events (SAEs) which first occur after the first dose of study treatment through 4 weeks after the final dose of the study treatment or subject's participation in the study if the last scheduled visit occurs at a later time;~~ | Removed redundant language for treatment-emergent adverse events.<br>Clarified final list for adverse events of interest. |

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| | ~~o SAEs reported prior to first dose of study treatment that increase in severity or frequency after first dose of study treatment through 4 weeks after the final dose of the study treatment or subject's participation in the study if the last scheduled visit occurs at a later time.~~<br>o Treatment-emergent adverse events of interest (AEIs) ~~as determined through the Clinical Safety Program (CSP)~~ for the following events:<br>▪ Skin-related AEs<br>▪ Infection AEs, **including influenza**<br>▪ Creatine kinase (CK) elevation **(evaluated as lab toxicity grade 2 or higher)**<br>▪ Malignancy<br>▪ **Deaths**<br>o Laboratory abnormalities (as determined by Common Terminology Criteria for Adverse Events [CTCAE **v5.0**] grading) **presented as the worst postbaseline toxicity group**<br>o Shifts from baseline **to maximum postbaseline value**<br>o **ALT or AST elevation >5 times ULN**<br>≥ 500 **msec**<br>**Males: < 450 msec, ≥ 450 msec**<br>**Females: < 470 msec, ≥ 470 msec**<br>**In cases where the QT interval is corrected using Bazett's (QTcB) formula is captured instead of QTcF, then QTcB will be converted to QTcF for analyses.**<br>• Eight-Item Patient Health Questionnaire (PHQ-8) total score<br>o Absolute and change from baseline values<br>o Shifts from baseline scores<br>o ~~PHQ-8 total scores ≥ 15~~<br>o Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)<br>o ~~eC-SSRS items~~**Suicidal ideation and suicidal behavior responses by visit**<br>o **Shifts from baseline to postbaseline value for suicidal ideation and suicidal behavior** | Specified that deaths would be evaluated.<br>Version number added for CTCAE.<br>Added missing msec for ECG category, new categories for ECG by males and females, and clarification that QTcB will be converted to QTcF for analysis.Removed PHQ-8 total scores >=15 as this is provided in the shift table.<br>Clarified the variables for eC-SSRS to be summarized. |

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| | ○ **Worst postbaseline value for suicidal ideation and behavior through Week 16** | |
| 5.0 Populations for Analysis | Full Analysis Set (FAS): All **subjects who are** randomized ~~subjects who are assigned study treatment~~.<br><br>Per Protocol Set (PPS): A subset of the FAS who are compliant with study treatment and who do not have any ~~statistically~~ relevant protocol deviations that may impact the coprimary efficacy endpoint assessments. | The definition for the Full Analysis Set was modified to clarify that the population includes all randomized subjects. Removed "statistically" from relevant deviations in the PPS description to align with standard naming. |
| 5.1 Relevant Protocol Deviations | Relevant protocol deviations are deviations that can have an impact on the primary efficacy endpoints. The impact of relevant protocol deviations on the primary efficacy results will be assessed by excluding subjects from the FAS to define the PPS in supportive analyses of the primary efficacy endpoints. Relevant protocol deviations to be considered regarding exclusion of subjects from the FAS will include the following:<br><br>• Randomized but did not take any study treatment<br><br>• **No postbaseline PASI or sPGA**<br>• **Baseline BSA involvement < 10%**<br>• **Baseline PASI score < 12**<br>• **Baseline sPGA < 3**<br>• **Did not have non-plaque psoriasis at baseline**<br><br>• Poor compliance to study medication within the first 16 weeks of treatment defined as <~~80~~**75**% compliant with study<br><br>• Failure to adhere to prohibited concomitant medication restrictions **as described below**:<br>○ **Investigational drug or placebo taken outside of the study any time between Day 1 and the Week 16 assessment**<br>○ **Phototherapy within 4 weeks prior to the Week 16 assessment**<br>○ **Biologic medications (eg, adalimumab, etanercept, infliximab, ustekinumab) any time between Day 1 and the Week 16 assessment**<br>○ **Oral psoriasis medications any time between Day 1 and the Week 16 assessment**<br>○ **Oral corticosteroids (unless for the treatment of an adverse event) within 4 weeks prior to the Week 16 assessment** | Deviations were updated with final categories. |

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| | ○ **Topical medications/treatments that could affect psoriasis evaluations within 2 weeks prior to the Week 16 assessment**<br>○ **Medicated shampoos within 2 weeks prior to the Week 16 assessment**<br>• ~~Subject overdosed, misused or abused study treatment prior to Week 16~~<br>• ~~Actual treatment received is different than randomized treatment~~**Subject received treatment that was different than intended treatment at any visit prior to Week 16.**<br><br>All subjects with relevant protocol deviations will be identified prior to database lock and unblinding of treatment assignment **with the exception of subjects where actual treatment received is different than randomized treatment which will be determined after treatment unblinding**. Relevant protocol deviations will be summarized by treatment group and deviation category for the FAS population.<br><br>~~Additionally, all important protocol deviations, which are deviations that may impact the efficacy and safety of subjects, will be identified prior to database lock and unblinding of treatment assignment. Important protocol deviations will be summarized by treatment group and deviation category for the FAS population.~~ | |
| 6.1 Efficacy Analyses | Tests of significance of BMS-986165 6 mg QD vs. placebo for the coprimary endpoints will be two-sided with a significance level of 0.05. Both **coprimary** endpoints need to demonstrate statistical significance to result in a successful study.<br><br>The key secondary endpoints will be **tested with a** two-sided ~~with a~~ significance level of 0.025 to compare BMS-986165 6mg QD vs. placebo and vs. apremilast ~~(equivalent to 0.05 level of significance)~~. A hierarchical **testing** approach will be used ~~in~~ **for** testing of key secondary endpoints **(see Section 6.1.3)**~~within each comparison branch~~. Two-sided 95% confidence intervals (CIs) will be provided for all efficacy estimates. [redacted]<br><br>Coprimary and key secondary efficacy endpoints will be displayed graphically by treatment group and visit, as applicable. ~~Binary endpoints will be displayed using bar charts and continuous endpoints will be displayed using line plots.~~ All efficacy endpoints will be summarized descriptively.<br><br>**The stratified levels are provided below:**<br>▪ **US/PRIOR USE/< 90 KG**<br>▪ **US/PRIOR USE/>=90 KG**<br>▪ **US/NAÏVE/<90 KG**<br>▪ **US/NAÏVE/>=90 KG**<br>▪ **ROW/PRIOR USE/< 90 KG**<br>▪ **ROW/PRIOR USE/>=90 KG** | Removed plot description to allow flexibility in data presentation plan.<br><br>Clarified the language for testing of secondary endpoints.<br><br>Updated the stratification levels to a combination stratification factor to align with IM011046. |

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| | ▪ **ROW/NAÏVE/<90 KG**<br>▪ **ROW/NAÏVE/>=90 KG** | |
| 6.1.1 Primary Endpoints<br>6.1.1.1 Primary Analysis | Analysis Model<br>A stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare the sPGA 0/1 response rates at Week 16 between BMS-986165 6 mg QD and placebo **using the stratification factors from IRT specified in Section 6.1**. ~~The following prognostic factors are included in the model: geographic region (U.S. and Rest of World), body weight (<90 kg, ≥90 kg) and prior biologic use (yes/no).~~ The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the odds in the placebo group) and the corresponding 2-sided 95% CIs and p-values will be reported. Additionally, treatment differences in proportions and the 95% CI for the treatment difference will be provided. The common treatment difference in proportion with the confidence interval, common odds ratio with the confidence interval and p-value will be estimated by the Mantel-Haenszel method consistently. ~~A similar analysis will be performed to compare the PASI 75 response rates at Week 16 between BMS-986165 6mg QD and placebo.~~<br>A similar analysis will be performed to compare the PASI 75 response rates at Week 16 between BMS-986165 6mg QD and placebo.<br>Imputation Methodology<br>Non-responder imputation (NRI) will be used for coprimary efficacy endpoints for subjects who:<br>• Discontinue treatment or study prior to Week 16<br>• ~~Start a protocol prohibited medication/therapy that could improve psoriasis during the first 16 weeks of treatment, or~~<br>• Have missing Week 16 endpoint data for any reason<br>~~Subjects taking protocol prohibited medications during the first 16 weeks of treatment will be identified prior to database lock and treatment unblinding.~~ NRI will be used as the primary method of imputation for the coprimary efficacy endpoints. | Clarified stratification to be used and removed prohibited medication criteria. |
| 6.1.1.2 Sensitivity Analyses | As a method to assess the sensitivity of the primary imputation method for the coprimary endpoints, further imputation methods will be used to impute Week 16 data in subjects who:<br>• Discontinue treatment or study prior to Week 16<br>• ~~Start a protocol prohibited medication/therapy that could improve psoriasis during the first 16 weeks of treatment, or~~<br>• Have missing Week 16 endpoint data for any reason<br>Tipping Point Analysis<br>Tipping point analysis will further be used to assess the robustness of the primary study results. Different number of | Removed prohibited medication criteria.<br>Added some clarification for the tipping point analysis.<br>Added a sensitivity analysis for |

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| | events between treatment groups will be assessed until the study conclusion is changed. Each imputed value is initially imputed as a responder. The imputed values in the placebo group will remain as responders while the BMS-986165 imputed values are replaced as a nonresponders one at a time, therefore changing the number of events between groups. Once all imputed values in the BMS-986165 group have been replaced with nonresponders values, the data will reset to where the BMS-986165 group imputed values are all responders and one by one the imputed values in the placebo group are replaced with a nonresponder until all placebo are nonresponders and all BMS-986165 are responders. Furthermore, every pair of imputations between the placebo and BMS-986165 groups will be assessed similarly, creating a matrix of possible patterns.<br><br>At each iteration, the statistical analysis is assessed, and the direction of the analysis is recorded. A graph will be provided to identify at what point to which the difference in events cause a direction shift in study results. **The tipping point analyses will be based on a two-sample chi-square test approach rather than a stratified CMH test approach for simplicity of the analysis.**<br><br>**<u>Multiple Imputation</u>**<br><br>**Multiple imputation (MI) will be used for sensitivity analyses for each of the coprimary efficacy endpoints, PASI 75 response at Week 16 and sPGA 0/1 response at Week 16. Multiple imputation of missing data for PASI 75 response and sPGA 0/1 response will be performed by fully conditional specification (FCS) using PROC MI in SAS with the FCS option. The FCS MI specifies the multivariate imputation model on a variable-by-variable basis by a set of conditional densities. For each missing value at Week *X*, the FCS MI will generate values from a conditional distribution for the missing data given the other data prior to Week *X*. The FCS MI model will include treatment group and stratification factors for randomization. A total of 1000 imputed (complete) datasets will be generated for the MI analysis. The same test procedure used for the main analysis (CMH test), will be used to analyze the responder endpoint from each imputed dataset. SAS PROC MIANALYZE will be used to pool the results from the CMH tests and generate an overall result by Rubin's rules (1987).** | multiple imputation. |
| 6.1.1.3 Supportive Analyses | ~~<u>Additional Analysis</u>~~<br><br>~~Additionally, a logistic regression model will be used to compare the sPGA 0/1 response rates at Week 16 between BMS-986165 6mg QD and placebo. The prognostic factors will be included in the model as covariates. The estimated odds of response with corresponding 2-sided 95% CIs and p-values will be reported. A similar analysis will be performed on the PASI 75 response rates at Week 16. These analyses will be performed on the FAS.~~ | Removed this analysis since it similar to CMH analysis. |

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| 6.1.2 Key Secondary Endpoints<br><br>6.1.2.1 Binary Endpoints | Analysis Model<br><br>CMH tests will be used to compare response rates between either BMS-986165 6mg QD and placebo or apremilast **using the stratification factors from IRT specified in Section 6.1**. ~~The following prognostic factors are included in the model: geographic region (U.S. and Rest of World), body weight (<90 kg, ≥90 kg) and prior biologic use (yes/no).~~ The odds ratio (ratio of odds in BMS-986165 6 mg QD group to the odds in the placebo **or apremilast** group) and the corresponding 2-sided 95% CIs and p-values will be reported. Additionally, treatment differences in proportions and the 95% CI for the treatment difference will be provided ~~from Chi-square tests~~.<br><br>Imputation Methodology for Week 16 Endpoints<br><br>NRI will be used for ~~coprimary~~**key secondary** efficacy endpoints for subjects who:<br><br>• Discontinue treatment or study prior to Week 16<br>• ~~Start a protocol prohibited medication/therapy that could improve psoriasis during the first 16 weeks of treatment, or~~<br>• Have missing Week 16 endpoint data for any reason<br><br>~~Subjects taking protocol prohibited medications during the first 16 weeks of treatment will be identified prior to database lock and treatment unblinding. NRI will be used as the primary method of imputation for the coprimaryefficacy endpoints.~~<br><br>**Imputation Methodology for Week 24 Endpoints (for comparison of BMS-986165 6 mg QD to apremilast)**<br><br>**NRI will be used for key secondary efficacy endpoints for subjects who:**<br><br>• **Discontinue treatment or study prior to Week 24**<br>• **Have missing Week 24 endpoint data for any reason**<br><br>~~Subjects taking protocol prohibited medications will be identified prior to database lock and treatment unblinding.~~ | Clarified stratification to be used and removed prohibited medication criteria.<br><br>Corrected coprimary to key secondary.<br><br>Added imputation for Week 24 endpoints. |
| 6.1.2.2 Continuous Endpoints | Analysis Model<br><br>Analysis of covariance (ANCOVA) models will be used to compare the change between BMS-986165 6 mg QD and placebo or between BMS-986165 6 mg QD and apremilast **at Week 16**. Treatment group will be included in the model as well as the **stratification factors from IRT specified in Section 6.1**~~following baseline prognostic factors: geographic region (U.S. and Rest of World), body weight (<90 kg, ≥90 kg) and prior biologic use (yes/no)~~ and will be considered as fixed effects. The baseline value will be added into the model as a covariate. The adjusted least-squares (LS) means as well as the treatment differences based on LS means and the corresponding 2-sided 95% CIs will be provided for the difference between BMS-986165 6 mg QD and placebo or apremilast. | Clarified stratification to be used and removed prohibited medication criteria.<br><br>Added a clarification that subjects with missing baseline values will be excluded from the analysis for change from |

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| | Imputation Methodology **for Week 16 Endpoints**<br><br>For continuous **key** secondary endpoints, a modified baseline observation carried forward (mBOCF) approach will be used for missing data. The baseline observation will be carried forward for subjects who discontinue study treatment **prior to Week 16** due to:<br>• Lack of efficacy<br>• AEs<br><br>Subjects who discontinue study treatment **prior to Week 16** for other reasons **or who have a missing Week 16 value** will have the last valid observation carried forward (including the baseline value as applicable).<br><br>~~For subjects who start a protocol prohibited medication/therapy that could improve psoriasis prior to the endpoint will also have their endpoint value imputed as the baseline value. The last valid observation will be carried forward for all other subjects with missing data.~~ **Subjects with a missing baseline value will be excluded from the analysis for the change from baseline endpoint.** | baseline endpoint. |
| 6.1.2.3 Time-to-Relapse Endpoint | PASI 75 response will be assessed at each visit between Week 24 and Week 52. Subjects who experience a relapse as defined above at any visit between Week 24 and Week 52 will be considered as having an 'event'. Subjects who discontinue study (or treatment) during this time, ~~start a protocol prohibited medication/therapy that could improve their response or otherwise~~ have missing data, and subjects that do not have relapse by Week 52 will be censored and the date they experienced the above criteria, will be used as their 'event' date.<br><br>The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to-relapse during the randomized withdrawal period. Treatment comparisons between BMS-986165 6 mg QD and placebo for subjects re-randomized during the randomized withdrawal period will be performed using the log-rank test stratified **using the stratification factors from IRT specified in Section 6.1**~~by geographic region (U.S. and Rest of World), body weight (<90 kg, ≥90 kg) and prior biologic use (yes/no)~~. | Removed prohibited medications criteria.<br><br>Clarified stratification factors. |
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| 6.1.4 Subgroup Analyses | Subgroup analyses will be performed on the coprimary endpoints using the FAS. The primary imputation method will be applied for these analyses. The CMH test The CMH test **using the stratification factors from IRT** will be the analysis method used where the stratification factor is the specified subgroup will be the analysis method used ~~where the stratification factor is the specified subgroup~~. The following subgroups will be considered:<br>• Geographic region (U.S., ~~Japan, China,~~ Rest of World)<br>• Country<br>• Sex (male, female)<br>• Age group (<65 ~~years~~y, ≥65 ~~years~~y)<br>• Body weight (<90 kg, ≥90 kg) **– from case report form**<br>• Race<br>• Prior biologic use for psoriasis, psoriatic arthritis and other inflammatory diseases only (yes, no) **– from case report form**<br>• **Prior systemic treatment use (yes/no)**<br>• **Prior phototherapy use (yes/no)**<br>• sPGA (3, 4)<br>• PASI score (≤20, >20)<br>• BSA involvement (10-20, >20)<br>• ~~DLQI (0-5, 6-10, 11-30)~~<br>• Duration of disease (< 10 y, ≥ 10 y)<br>• Age at disease onset (<18, 18-39, ≥40)<br>• ~~Smoking status:~~<br>~~Currently non-smoker – never smoked or quit smoking ≥6 months from the 1st treatment~~<br>~~Currently non-daily smoker or light smoker - smoked on no more than 25 days in the previous 30 days to < 5 cigarettes per day~~<br>• ~~Currently moderate to heavy smoker – ≥10 cigarettes per day~~ | Removed some subgroups that will not be analyzed.<br>Clarified weight and prior biologic use to be taken from CRF and stratification factors for the CMH statement will use IRT stratification factors. |

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| 6.2.1 Adverse Events | Adverse events ~~(AE)~~ will be presented for the number and percentage of subjects and the number of events. ~~All adverse events (t~~**T**reatment-emergent ~~[TEAE] and non-treatment emergent)~~ will be provided in listings. Summary tables will be reported in decreasing frequency based on the ~~total~~ **BMS-986165** column. Counting for frequency analysis will be by subject and not by AEs, and subjects are only counted once for recurring AEs within each system organ class (SOC) or preferred term (PT); however, the number of total AEs per subject, including multiple occurrences of individual AEs, will also be presented. For summaries of severity, AEs will be reported only at their maximum severity in each subject. Subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.<br><br>An overall summary for the following categories will be presented:<br><br>~~• Subjects with at least one TEAE~~<br>~~• Subjects with at least one related TEAE~~<br>~~• Subjects with at least one treatment-emergent SAE~~<br>~~• Subjects with at least one related treatment-emergent SAE~~<br>~~• Subjects discontinuing study treatment due to a TEAE~~<br>~~• Subjects discontinuing from study due to a TEAE~~<br>~~• Subjects who died due to an AE~~<br>~~• Subjects who died due to a TEAE~~<br>• **Deaths**<br>• **SAEs**<br>• **Related SAEs**<br>• **AEs**<br>• **Related AEs**<br>• **Discontinued treatment due to AEs**<br><br>~~A summary of TEAEs leading to discontinuation of study treatment or study will be provided, grouped by SOC and PT for all TEAEs and treatment-related TEAEs.~~ | Modified text for overall summary to align with the data presentation plan.<br><br>TEAEs leading to discontinuation was removed from this section as this is described in a separate section. |
| 6.2.1.1 Adverse Events of Interest (AEI) **and Other Important AEs** | Summaries for treatment-emergent AEIs events will be provided **by PT** for each AEI category~~for the following~~:<br><br>~~• TEAEs by SOC and PT~~<br><br>~~Skin Events~~ | Modified the text for the final list of adverse events of interest and the adjudicated |

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| | ~~The number and percentage of subjects reporting each type of skin event and the corresponding location will be summarized.~~<br><br>~~Infections~~<br><br>~~The number and percentage of subjects reporting infections will be summarized.~~<br><br>~~Creatine kinase (CK) elevation~~<br><br>~~The number and percentage of subjects reporting CK elevations will be summarized.~~<br><br>~~Malignancies~~<br><br>~~The number and percentage of subjects reporting malignancies will be summarized.~~<br><br>~~Cardiovascular~~<br><br>~~The number and percentage of subjects reporting cardiovascular event will be summarized.~~<br><br>• **Skin-related events**<br>• **Infection events**<br>• **Malignancy events**<br><br>**Creatine kinase (CK) elevation for CK elevation >2.5 upper limit of normal will be summarized as CTCAE grade 2 or higher in the clinical laboratory summaries.**<br><br>**Additional information collected for some events as part of the clinical safety program and adjudicated events will also be summarized.** | cardiovascular events. |
| 6.2.1.2 Serious Adverse Events | Summaries for treatment-emergent SAEs will be provided for the following:<br><br>• Treatment-emergent SAEs by SOC and PT<br><br>~~Treatment-related treatment-emergent SAEs by SOC and PT~~ | Aligned with the Data Presentation Plan |
| 6.2.1.3 Adverse Events Leading to Discontinuation of Study Treatment **or Study Treatment Interruption** | Summaries for TEAEs leading to discontinuation of study treatment will be provided for the following:<br><br>• TEAEs by SOC and PT<br>• ~~Treatment-related TEAEs by SOC and PT~~<br><br>**Summaries for TEAEs leading to study treatment interruption will be provided for the following:**<br><br>• **TEAEs by SOC and PT** | Added summary for TEAEs leading to study treatment interruption and aligned with the Data Presentation Plan. |
| 6.2.3 Clinical Laboratory Data | Laboratory parameters will be summarized using the International System (SI) of Units~~, unless otherwise specified~~ **and US conventional units**. Data will be summarized by time point, as applicable. The following summaries will be provided for each parameter:<br><br>• Absolute and change from baseline values for continuous parameters | Added summaries for US conventional units.<br><br>Removed urinalysis categorical summaries to |

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| | • Number and percentage of subjects for the following:<br>~~o Categorical urinalysis parameter results~~<br>o Maximum postbaseline CTCAE grade for each applicable laboratory parameter **through Week 16**<br>o Shifts from baseline based on maximum postbaseline CTCAE grade **through Week 16**<br>• Drug-induced Liver Injury (DILI) and Hy's Law summaries<br>All laboratory data specified in the summary tables will be present in listings. | align with data presentation plan.<br>Added additional clarifications to align with data presentation plan. |
| 6.2.4 Vital Signs and Physical Findings | Vital signs**, including weight,** will be summarized by time point, as applicable. The following summaries will be provided for each parameter: | Clarified that weight will be summarized. |
| 6.2.6 Other Safety Data<br>6.2.6.1 PHQ-8 | PHQ-8 total score will be summarized by time point, as applicable. The following summaries will be provided:<br>• Absolute and change from baseline values<br>• Number and percentage of subjects:<br>o Shifts from none, mild, moderate, moderately severe and severe scores at baseline and at each time point<br>o ~~PHQ-8 total scores ≥ 15~~ | Removed PHQ-8 total score >=15 summaries as this is provided in the shift summary. |
| 6.2.6.2 eC-SSRS | Suicidal ideation and behavior individual item responses will be summarized by time point, as applicable. The following summaries will be provided:<br>• Number and percentage of subjects with positive responses on suicidal ideation and/or suicidal behavior **questions**~~responses~~ **for each question and overall all questions within suicidal ideation and suicidal behavior**<br>• **Shifts from baseline based on maximum postbaseline response through Week 16**<br>• **Worst postbaseline value for suicidal ideation and behavior through Week 16** | Additional analyses have been added for eC-SSRS. |
| 6.3.2 Demographic and Baseline Characteristics | Demographic **and baseline** characteristics will be summarized by treatment group for **the FAS** ~~all of the analysis populations~~**.** Demographic and baseline characteristics include the following:<br>• **Prior systemic treatment use (yes/no)**<br>• **Prior phototherapy use (yes/no)**<br>• Geographic ~~Region~~**region** (U.S., ~~Japan, China,~~ Rest of World)<br>• ~~DLQI (0-5, 6-10, 11-30)~~<br>• ~~Smoking status (Current daily smoker and whether heavy vs. light, Current occasional smoker, former~~ | Updated populations to be used for summaries and removed baseline characteristic that will not be summarized. |

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| | ~~smoker, never smoker, smoker current status unknown, unknown if ever smoked)~~<br><br>Additional demographics or baseline data may be added to summary tables.<br><br>General medical history and medical history related to PsA will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) ~~(version 21.0 or an updated version at the time of database lock)~~. General medical history data will be summarized for each SOC and PT by treatment group and overall for the FAS ~~and Safety Set populations~~. Separate tables will be provided for ~~general~~ **psoriasis** medical history. | |
| 6.3.3 Prior and Concomitant Medications | Prior and concomitant medications will be coded according to World Health Organization-Drug Dictionary WHO-DD (version at the time of DBL) and will be summarized by Anatomic Therapeutic Classification (ATC) and preferred term (PT) by treatment group for the **As-treated population**~~FAS~~. The number and percentage of subjects using at least one medication and each medication will be displayed by treatment group. Subjects taking more than one medication within the same ATC or PT will be counted once.<br><br>**Summaries will be provided for prior medications and medications that started prior to first treatment and were ongoing after first treatment start date as well as concomitant medications.** | Clarified summaries to be provided and the population to be used for the summaries. |
| 6.3.3.1 Psoriasis, Psoriatic Arthritis and Other Inflammatory Disease Related Systemic Medications | Prior **medications and medications that started prior to first treatment and were ongoing after first treatment start date for** systemic biologic and non-biologic medications will be summarized as described above for the number and percentage of subjects using each reported medication. Concomitant use of DMARDs like methotrexate will be summarized. | Added clarification for prior and ongoing medications to be summarized. |
| 6.3.3.2 Concomitant Corticosteroid Use | Additionally, corticosteroids will be summarized by ATC and PT ~~for the FAS~~. | Removed reference to analysis population as this is redundant information with Section 6.3.3. |
| 6.3.4 Exposure<br><br>6.3.4.1 Duration of Treatment | <u>Duration by Group</u><br><br>Overall duration of each treatment, in days, will be calculated for each subject in each treatment group. Subjects are dispensed study treatment at each visit, starting with Day 1 (Week 0) and at each subsequent visit~~. Subjects are also to record daily dosing in an eDiary.~~ The ~~Day 1 dispensed date will be considered as the~~ date of first dose of study treatment **is the Week 0 [redacted] dosing date** and is recorded on the eCRF. **If this date is missing, then the earliest drug dispensation date will be used.** The last **dose** date ~~of dose~~ is ~~defined as the last~~ | Updates to duration of exposure formula's were made to align with the manner in which data will be summarized. |

~~day a subject received drug and is~~ recorded on the end of treatment page in the eCRF. **If this date is missing, then the latest date from the [redacted] page or drug accountability return date will be used.**

~~If the date of last dose of study treatment is missing, i.e.: subject lost to follow-up, the end of study date or last contact date (whichever comes first) will be used to calculate duration of treatment.~~ Duration of treatment will be summarized descriptively by **randomized** treatment group.

Subjects randomized to BMS-986165 and re-randomized to placebo at Week 24 will have their duration of treatment derived as:

- BMS-986165 (Wk 0 through Wk 24) = ~~Week 24 date~~**Date of last dose of BMS-986165 prior to first placebo dose date** – date of first dose +1
- Placebo (Wk 24 through final week on placebo) = Date of last dose of placebo - ~~Week 24 date~~**date of first dose of placebo + 1**
- BMS-986165 (First dose after relapse on placebo **or switched to BMS-986165 due to COVID-19** through Wk 52) = ~~Wk 52~~ **Date of last dose of BMS-986165** – first **BMS-986165** dose **date** after **relapse + 1; only calculated for subjects that relapse or are switched to BMS-986165 due to COVID-19** ~~placebo~~
- Total BMS-986165 = **Sum BMS-986165 exposure over entire treatment period** ~~Wk 0-Wk 24 + BMS-986165 first dose after switch from placebo-Wk 52~~

**Placebo** ~~and placebo switches~~:For subjects randomized to placebo, ~~the Week 16 date will be used as the date of last dose of placebo. Formula for~~ duration is defined as:

- Placebo = **date of last dose of placebo** ~~Week 16 date~~ – date of first dose +1
- BMS-986165 = Date of last dose of BMS-986165 – ~~Week 16 date~~**date of first dose of BMS-986165 +1**

~~If a placebo subject discontinues study treatment on or before the Week 16 visit, the date of last dose will be used to calculate the duration of placebo.~~

**Apremilast:**

For subjects randomized to apremilast, ~~the Week 24 date will be used as the date of last dose of apremilast and the date of first dose of either apremilast or BMS-986165 (for PASI 75 non-responders on apremilast). Subjects who continue on apremilast from Week 24 through to Week 52 will be counted as a sum of the first 24 weeks of treatment and the next treatment period from Week 24 to Week 52.~~**duration is defined as:**

- Apremilast (Wk 0 through Wk 24) = ~~Week 24 date~~**Date of last dose of apremilast** – date of first dose +1

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| | ~~• Apremilast (Wk 24 through Wk 52) = Date of last dose – Week 24 date~~<br>~~• Total Apremilast = Apremilast Wk 0-24 + apremilast Wk 24-52~~<br>• **Placebo (PASI 75 nonresponders) = Date of last dose of placebo – date of first dose of placebo + 1**<br>• BMS-986165 (switched from apremilast **or switched from placebo to BMS-986165 after relapse or due to COVID-19**) = Date of last dose of BMS-986165 – ~~Week 24 date~~**date of first dose date of BMS-986165 + 1**<br>~~• Placebo = Date of last placebo dose – Week 24 date~~<br>~~Total apremilast duration of treatment will be displayed as well as BMS-986165 and placebo treatment duration. If subject discontinues their study treatment during the initial 24 weeks of apremilast treatment, the date of last dose will be used as the duration of apremilast.~~<br><u>Duration by Period</u><br>Overall duration (in days) of each treatment received within each study period will be calculated. Duration within each period is defined for each treatment group as:<br>$Last\ dose\ date\ \boldsymbol{in\ period} - first\ dose\ date\ \boldsymbol{in\ period} + 1$<br>~~Subjects are dispensed study treatment at each visit, starting with Day 1 (Week 0) and at each subsequent visit. Subjects are also to record daily dosing in an eDiary. The dispensed drug date of Day 1 of the study period will be considered as the date of first dose of study treatment for that period and is recorded on the eCRF. The last date of dose within the period will be considered as the day prior to the next period start date.~~<br>~~If the date of last dose of study treatment is missing, i.e.: subject lost to follow-up, the end of study date or last contact date (whichever comes first) will be used to calculate duration of treatment.~~ | |
| 6.3.4.2 Summary of Dosing | The number of doses taken for each subject for each period will be determined using the eCRF drug accountability data and is defined as:<br>$Doses\ Taken = \frac{(number\ of\ tablets\ dispensed - number\ of\ tablets\ returned)}{3}$<br>The number of doses taken will be summarized descriptively by treatment group **within each study period and overall**. | Clarified how data will be summarized. |
| 6.3.4.3 Compliance | Treatment compliance will be determined from data captured on the Drug Accountability eCRF.<br>~~The number and percentage of subjects who have missed at least one dose will be provided.~~<br>~~Additionally, descriptive statistics for the number of missed doses within each treatment period and overall will be provided~~ | Clairfied how data will be summarized. |

~~by treatment group. The number of missed doses for each subject will be calculated for each period.~~

$$Number\ of\ expected\ doses: (date\ of\ next\ visit - date\ of\ current\ visit) x3$$

~~$$Number\ of\ missed\ doses: Number\ of\ expected\ doses - number\ of\ doses\ taken$$~~

Treatment compliance will be derived for each period ~~and overall~~. Compliance is defined as:

$$\left(\frac{Number\ of\ doses\ taken}{Number\ of\ expected\ doses}\right) x100$$

Period compliance will be calculated by summing over all visits within the period ~~and overall compliance will be calculated by summing each visit in the study~~ and summarized using descriptive statistics by treatment group. The number and percentage of subjects with <~~80~~**75**%, ~~80~~**75**% to 1~~2~~**0**0%, and >1~~2~~**0**0% compliance will be provided by treatment group for each ~~visit,~~ period ~~and overall~~. **If a subject does not return the container, then this dispensation event will be excluded in the calculation for the total number of doses taken, total number of expected doses, and total compliance.**

[redacted]

[redacted]

[redacted]

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| **6.6 Statistical Impacts Due to COVID-19** | **Statistical Impacts Due to COVID-19**<br>**Impact on Efficacy Endpoints**<br>**There are no COVID-19-related impacts to the Week 16 efficacy endpoints as all subjects remaining in the trial completed the Week 16 visit prior to COVID-19 site** | New section added to address COVID-19. |

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| **6.61 Impact on Efficacy Endpoints** | **restrictions. Efficacy endpoints involving Week 24 and later visits may be impacted by COVID-19 in the form of missing data and/or a treatment assignment defaulting to BMS-986165.**<br><br>**Censoring rules will be applied to the PASI 75 time-to-relapse endpoint for re-randomized subjects due to the following COVID-19-related issues post Week 24:**<br><br>• **Subject study treatment assignment was defaulted to BMS-986165 because they had a remote safety monitoring visit and efficacy assessments were not performed. The subjects will be censored at the time of the remote visit if relapse had not been observed already;**<br><br>• **Subject has missing visits (ie, efficacy assessments not performed) after Week 24 and assuming relapse was not observed prior to missing visits:**<br><br>o **If the subject returns at a later visit and is found to have relapsed, midpoint imputation will be used to determine time-to-relapse (ie, midpoint of the censoring interval).**<br><br>o **If the subject returns at a later visit and has not relapsed, then the subject will continue to be evaluated for relapse.**<br><br>o **If the subject is discontinued from the study treatment, then the subject will be censored at the time of study treatment discontinuation.**<br><br>**Similar data handling rules will be applied to the following time-to-event endpoints:**<br><br>• **Time to first loss of PASI 75 among subjects that are PASI 75 responders at Week 24**<br><br>• **Time to first loss of sPGA 0/1 among subjects that are sPGA 0/1 responders at Week 24 where loss of sPGA 0/1 is defined as an sPGA score ≥ 2**<br><br>• **Time to rebound as defined above among subjects re-randomized to placebo**<br><br>• **Time-to-relapse for Week 24 PASI 75 apremilast responders switched to placebo**<br><br>**Additional efficacy endpoints involving later visits may be impacted by COVID-19 in the form of missing data and/or a treatment assignment defaulting to BMS-986165. If a subject has missing data or is switched to BMS-986165 from a different treatment due to Covid-19 during the Week 24 through Week 52 period, the subject will be excluded from the analysis.** | |

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| | **Additional efficacy endpoints that may be impacted include the following:**<br>• [redacted]<br>• [redacted]<br>• **Disease relapse assessed as the proportion of subjects who have ≥ 50% loss of Week 24 PASI percent improvement from baseline**<br>• [redacted]<br>[redacted] | |
| **6.6.2 Impact on Safety Endpoints** | **Impact on Safety Endpoints**<br>**No modifications will be made for the analysis of safety data due to COVID-19-related issues. There will not be any additional safety data handling considerations for missing data or treatment interruptions due to COVID-19.** | New section added to address COVID-19. |
| 7.2 Sequence of Planned Analyses | ~~Any exploratory analyses completed to support study analyses in the Clinical Study Report (CSR), which were not identified in the statistical analysis plan, will be documented as such in the CSR.~~ | Removed text for exploratory analyses.<br>Added clarification for |

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| 7.2.2 Final Analyses and Reporting | **Analyses of the palmoplantar pp-PGA 0/1 endpoint are provided for descriptive purposes within the individual CSR due to small sample sizes. A pooled analysis of data from IM011046 and IM011047 will be conducted for the submission.** | the analyses of palmoplantar (pp-PGA 0/1 endpoint). |
| 8.1 General Definitions | Study day is calculated as:<br><br>assessment date – date **of first dose** ~~the subject is randomized~~ + 1<br><br>Baseline - Unless otherwise stated, Baseline is defined as the ~~last~~ measurement ~~prior to dosing on Day 1~~ **at the randomization visit** (Week 0). If the measurement **at the randomization visit**~~on Day 1~~ is missing~~ or not available~~, then a prior measurement during the screening period may be used as baseline. Baseline assessments must be performed per protocol and standard of care assessments may not be used for baseline.<br><br>**Baseline for each PSSD question will be calculated as the average value over the 7 days prior to the randomization visit. In the event of missing values in the 7 days prior to the randomization visit, daily scores from at least 4 days out of the 7 days can be used to calculate the average score. If > 3 daily scores in the last 7 days are missing for a particular question, then the baseline value for that question will be missing. If any questions are missing baseline after using the described rule, then the baseline value for the subscore using that question and the baseline value for the total score will be missing.**<br><br>First Dose Date – Study: The date a subject received their first dose on Day 1 as recorded in the eCRF ~~as date study treatment was dispensed~~**Week 0 [redacted] dosing date or the earliest drug dispensation date**.<br><br>First Dose Date – Period: The date a subject received their first dose ~~in the defined study period~~ as recorded in the eCRF ~~as date study treatment was dispensed~~**Week 0 [redacted] dosing date or the earliest drug dispensation date for Treatment Period 1 and earliest drug dispensation date for Treatment Periods 2 and 3**.<br><br>Change from baseline in the maximum post-baseline value is defined as highest observed value **or grade** post-baseline. The change is calculated using this value as the post-baseline value.<br><br>Change in the maximum post-baseline value **or change in the worst post-baseline value: Change from baseline in the worst post-baseline value is defined as worst observed value post-baseline. The change is calculated using this value as the post-baseline value.**<br><br>**If the baseline value is 0 and the post-baseline is >0, then the percent change from baseline value will be missing.**<br><br>EAIR: | Updated first and last dose date definitions and other definitions.<br><br>Added an additional rule for percent change from baseline. |

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| | EAIR = 100*~~The number of subjects with a specific event divided by the total exposure time (in years) among the subjects in the treatment group, where the total exposure time in years is calculated by dividing the sum of exposure time in days over all subjects included in the treatment group*~~365.25***(total number of subjects with the AE)/total exposure time for the selected AE under each treatment that a subject is exposed. Where total exposure time for each AE within a treatment is calculated as follows:**<br>• **If a subject has at least 1 event while on a particular treatment, then the exposure time for that subject and AE on that treatment is:**<br>  o **First AE onset date – treatment start date (of that particular treatment) +1**<br>• **If a subject does not have an event, exposure time for that AE is:**<br>  o **Treatment stop date (of that particular treatment) – Treatment start date (of that particular treatment) + 1 + 30 days (if subject discontinued or subject completed Period 3 and is not rolling into IM011075 study)**<br>  o **Treatment stop date (of that particular treatment) – Treatment start date (of that particular treatment) + 1 (if subject completed Period 3 and is rolling into IM011075 study)**<br>• **Total exposure time = sum of exposure time for each AE within a treatment** | |
| 8.2.1.3 Body Surface Area (BSA) | The product of BSA and sPGA will be **calculated**~~derived as a potential proxy measure to PASI scores~~. | Updated the product score language. |
| 8.2.2.1 Psoriasis Symptoms and Signs Diary (PSSD) | **Baseline for each PSSD question will be calculated as the average value over the 7 days prior to the randomization visit. In the event of missing values in the 7 days prior to the randomization visit, daily scores from at least 4 days out of the 7 days can be used to calculate the average score. If > 3 daily scores in the last 7 days are missing for a particular question, then the baseline value for that question will be missing. If any questions are missing baseline after using the described rule, then the baseline value for the subscore using that question and the baseline value for the total score will be missing.** | Clarified baseline definition for PSSD. |
| [redacted] | | |

[redacted]

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| 8.2.2.8 Psoriatic Arthritis Screening and Evaluation (PASE) Questionnaire | The PASE questionnaire will be administered at Screening in subjects with peripheral joint complaints. The PASE questionnaire is a self-administered tool that is used to screen for psoriatic arthritis among subjects who have psoriasis. The PASE questionnaire consists of 15 questions subdivided into 7 questions focusing on symptoms of psoriatic arthritis, and 8 questions focusing on the impact of psoriatic arthritis on function. Each question is scored on a 1 to 5 scale, with a maximum symptom sub-scale score of 35, a maximum function sub-scale score of 40 giving a total maximum score of 75. A score of 47 or above has been shown to distinguish between psoriatic arthritis and non-psoriatic arthritis. This questionnaire is only intended to be a screening tool for psoriatic arthritis and does not replace a comprehensive musculoskeletal exam performed by a rheumatologist. **This information will not be summarized.**<br><br>~~Individual score to each of the 15 questions will be collected in the eCOA system. The sub-scale scores and total score will be derived in the analysis datasets.~~ | Clarified that PASE information will not be summarized. |
| 8.2.2.10 electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) | The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) is a computer-automated, patient-reported version of the C-SSRS instrument that defines 11 categories of suicidal ideation and behavior (SIB) events. Categories and definitions are provided in Appendix 23 of the protocol. The categories are as follows:<br>• Suicidal ideation<br>6. **Wish to be dead**~~Passive~~ | Updated descriptions of categories to align with data presentation plan and put behavior categories in proper ascending order. |

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|---|---|---|
| | 7. **Non-specific active suicidal thoughts**~~Active: Nonspecific (no method, intent, or plan)~~<br>8. **Active suicidal ideation with any methods without intent to act**~~Active: Method, but no intent or plan~~<br>9. **Active suicidal ideation with some intent to act, without specific plan**~~Active: Method and intent, but no plan~~<br>10. **Active suicidal ideation with specific plan and intent**~~Active: Method, intent, and plan~~<br>• Suicidal behavior<br>6. **Preparatory acts or behavior**~~Completed suicide~~<br>7. **Aborted attempt**~~Suicide attempt~~<br>8. Interrupted attempt<br>9. **Actual attempt (Non-fatal)**~~Aborted attempt~~<br>10. **Completed suicide**~~Preparatory actions toward imminent suicidal behaviors~~<br><br>Self-injurious behavior, no suicidal intent | |
| 8.4 Study Periods | Period 1 = ~~the first 16 weeks of treatment~~**Week 0 to Week 16 visit date**<br><br>Period 2 = **Week 16 visit date +1 to Week 24 visit date** ~~after Week 16 to Week 24~~<br><br>Period 3 = **Week 24 visit date +1 to Week 52 visit date**~~after Week 24~~<br><br>**Follow-up = 4-week follow-up period** | Clarified study periods. |
| 8.5 Day Ranges for Analysis Visits | Week 16 100, 127 (or Week 16 drug dispense date ~~if earlier~~)<br><br>Week 24 156, 183 (or Week 24 drug dispense date ~~if earlier~~) | Clarified Week 16 and Week 24 analysis range criteria |

# Appendix 1 Planned Analyses

| List of Planned Analyses: Comparisons of BMS-986165 6 mg QD vs. Placebo | | | |
|---|---|---|---|
| **Measure of Interest** | **Population** | **Analysis at Week 16** | [redacted] |
| sPGA 0/1 – coprimary<br>PASI 75 - coprimary | FAS | NRI+CMH - primary | |
| sPGA 0/1 – coprimary<br>PASI 75 – coprimary | FAS | LOCF+CMH – sensitivity<br>LOCF/NRI+CMH – sensitivity<br>Tipping Point+CMH – sensitivity<br>Multiple Imputation + CMH - sensitivity | |
| sPGA 0/1 – coprimary<br>PASI 75 – coprimary | PPS | NRI+CMH - supportive | |
| sPGA 0/1 – coprimary<br>PASI 75 - coprimary | FAS | NRI+CMH – subgroups | |
| PASI 90 – key secondary | FAS | NRI+CMH | |
| sPGA 0 – key secondary | FAS | NRI+CMH | |
| ss-PGA 0/1 among subjects with a baseline ss-PGA ≥ 3 – key secondary | FAS | NRI+CMH | |
| PSSD symptom score of 0 – key secondary | FAS | NRI+CMH | |
| DLQI 0/1 – key secondary (EX-US submission only) | FAS | NRI+CMH | |
| PGA-F 0/1 among subjects with a baseline PGA-F ≥ 3 | FAS | NRI+CMH | |

| List of Planned Analyses: Comparisons of BMS-986165 6 mg QD vs. Apremilast | | | |
|---|---|---|---|
| **Measure of Interest** | **Population** | **Primary Analysis at Week 16/24** | [redacted] |
| sPGA 0/1 at Week 16 – key secondary<br>PASI 75 at Week 16 – key secondary | FAS | NRI+CMH | |
| PASI 90 at Week 16 – key secondary | FAS | NRI+CMH | |
| Change from baseline in PSSD symptom score at Week 16 – key secondary | FAS | mBOCF+ANCOVA | |
| ss-PGA 0/1 among subjects with a baseline ss-PGA ≥ at Week 16 – key secondary | FAS | NRI+CMH | |
| sPGA 0 at Week 16 – key secondary | FAS | NRI+CMH | |
| PSSD symptom score of 0 at Week 16 – key secondary | FAS | NRI+CMH | |
| sPGA 0/1 at Week 24 – key secondary<br>PASI 75 at Week 24 – key secondary | FAS | NRI+CMH | |
| PASI 90 at Week 24 – key secondary | FAS | NRI+CMH | |
| | | | |

## Appendix 2 Summary of Efficacy Assessments

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| sPGA (Sec 8.2.1.1) | sPGA 0/1 with at least 2 point improvement from baseline | W16 | BMS vs. PBO | CMH, sensitivity analyses including tipping point analysis, multiple imputation (Sec 6.1.1.1-3) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | W24 | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | [redacted] | | |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | Baseline->W24 over time | BMS vs. apremilast | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | sPGA 0 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | [redacted] | | | |
| PASI (Sec 8.2.1.2) | PASI 75 | W16 | BMS vs. PBO | CMH, sensitivity analyses including tipping point analysis, multiple imputation (Sec 6.1.1.1-3) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | W24 | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| [redacted] | | | | |

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| | | Time-to-first loss of PASI 75 response between W24 and W52 | BMS only | Kaplan-Meier (Sec 6.1.5.3) |
| | | Baseline->Week 16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | Baseline->Week 24 over time | BMS vs. apremilast | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | PASI 90 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| [redacted] | | | | |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | Baseline->W24 over time | BMS vs. apremilast | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | PASI 100 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | [redacted] | | |

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| [redacted] | | | | |
| ss-PGA (Sec 8.2.1.4) | ss-PGA 0/1 among subjects with a baseline ss-PGA ≥3 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| [redacted] | | | | |
| PGA-F (Sec 8.2.1.6) | PGA-F 0/1 among subjects with a baseline PGA-F score ≥3 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| [redacted] | | | | |

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| [redacted] | | | | |
| pp-PGA (Sec 8.2.1.8) | pp-PGA 0/1 among subjects with a baseline pp-PGA ≥3 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | CMH by Week (Sec 6.1.5.1) |
| [redacted] | | | | |
| PSSD / Symptom Score (Sec 8.2.2.1) | PSSD/Symptom 0 among subjects with baseline PSSD/symptom score ≥1 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | | BMS vs. apremilast | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| [redacted] | | | | |

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| [redacted] | | | | |
| DLQI (Sec 8.2.2.4) | DLQI 0/1 among subjects with a baseline DLQI score ≥2 | W16 | BMS vs. PBO | CMH (Sec 6.1.2.1) |
| | | Baseline->W16 over time | BMS vs. PBO | Binary GEE & CMH by Week (Sec 6.1.5.1) |
| | | [redacted] | | |
| [redacted] | | | | |

| Assessment | Outcome Measure | Endpoint | Comparison | Analyses |
|---|---|---|---|---|
| [redacted] | | | | |
| PASE (Sec 8.2.2.11) | PASE | Screening only | | No Analysis |