Official Title of Study:

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

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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

Study Director [redacted] **Medical Monitor** [redacted]

24-hr Emergency Telephone Number
North America: [redacted]
Asia-Pacific: [redacted]

Bristol-Myers Squibb Research and Development
3401 Princeton Pike
Lawrenceville, NJ 08648
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium
6-5-1 Nishi-Shinjuku, Shinjuku-ku,
Tokyo, 163-1328, Japan

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. 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: • 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. • 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. • 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: • provided clarifications in the protocol to aid sites and subjects in the conduct of the study. • added and updated relevant protocol deviation criteria for the Per Protocol Set • corrected typographical errors • 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 4.1.6.3 CV Committee 4.1.6.4 Suicidal Ideation and Behavior Adjudication Committee	Updated text to: 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.** 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.** 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: 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: 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 sPGA scores ≥ 3 (See Section 4.1.4): • 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.**	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: 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 comparison 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]	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: **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 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.**	To clarify and document the final list of relevant protocol deviations for Per Protocol Analysis.

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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 • PASI 75
Selected Secondary Endpoints	
• Assess whether BMS-986165 is superior to apremilast at Week 16	• sPGA 0/1 • PASI 75 • PASI 90 • sPGA 0 • PASI 100
• Assess whether BMS-986165 is superior to apremilast at Week 52	• sPGA 0/1 • PASI 75 • PASI 90 • sPGA 0 • PASI 100
• Assess whether BMS-986165 is superior to placebo over the first 16 weeks of treatment	• sPGA 0/1 • PASI 75 • PASI 90 • sPGA 0 • PASI 100
• Assess whether BMS-986165 is superior to apremilast over 52 weeks of treatment	• sPGA 0/1 • PASI 75 • PASI 90 • sPGA 0 • PASI 100
• 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	• Change from baseline in Psoriasis Symptoms and Signs Diary (PSSD) symptom score, sign score, and total score • 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:

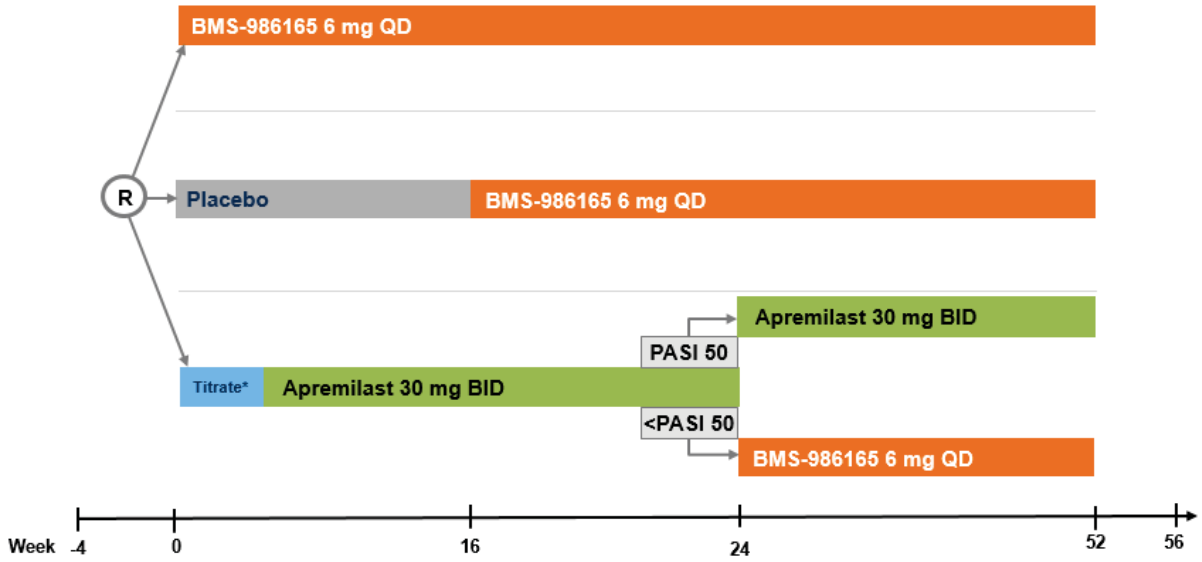
- Primary 1: Proportion of subjects who achieve sPGA 0/1 at Week 16
- Primary 2: Proportion of subjects who achieve PASI 75 at Week 16

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

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.

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; [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; 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 • 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 • PASI 75 response • PASI 90 response • sPGA 0 response • PASI 100 response
• Assess whether BMS-986165 is superior to apremilast at Week 52	• sPGA 0/1 response • PASI 75 response • PASI 90 response • sPGA 0 response • PASI 100 response
• Assess whether BMS-986165 is superior to placebo over the first 16 weeks of treatment	• sPGA 0/1 response • PASI 75 response • PASI 90 response • sPGA 0 response • PASI 100 response [redacted]
• Assess whether BMS-986165 is superior to apremilast over 52 weeks of treatment	• sPGA 0/1 response • PASI 75 response

Table 4: Objectives and Endpoints

Objective	Endpoint
	• PASI 90 response • sPGA 0 response • PASI 100 response [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 [redacted]	• ss-PGA 0/1 response [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]	• PGA-F 0/1 response [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 [redacted]
• 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	• Change from baseline in Psoriasis Symptoms and Signs Diary (PSSD) symptom score, sign score, and total score [redacted] • 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)
	[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. 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. [redacted]

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

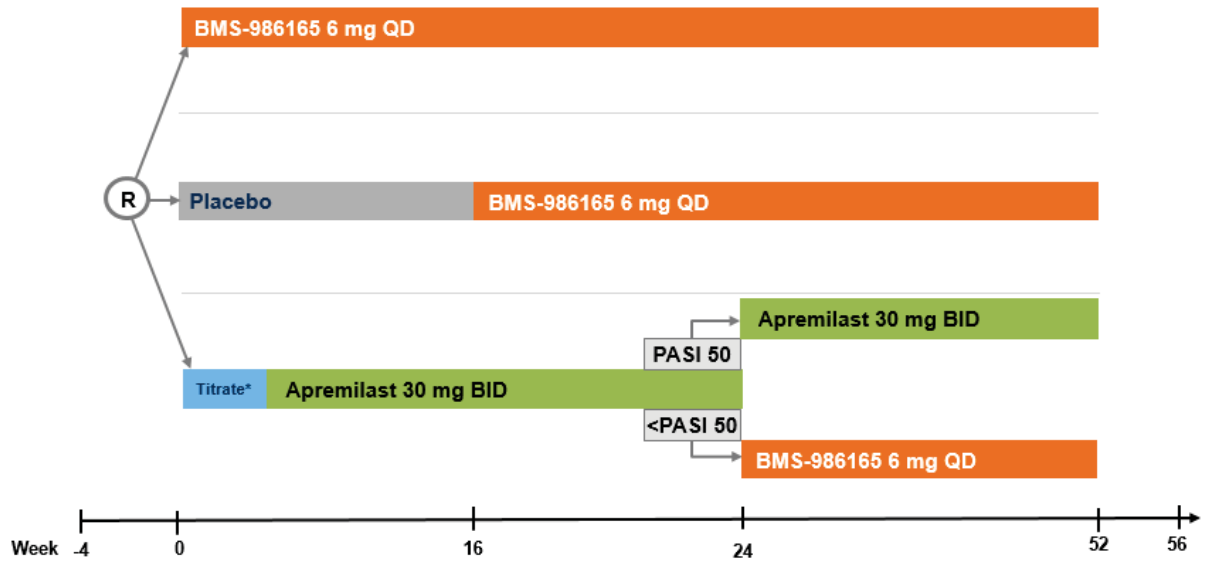
The follow-up period is a 4-week window after the Week 52 visit, unless the subject rolls over into the long-term extension. The subject will be encouraged to report any SAEs or AEs experienced during this time.

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.

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.

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

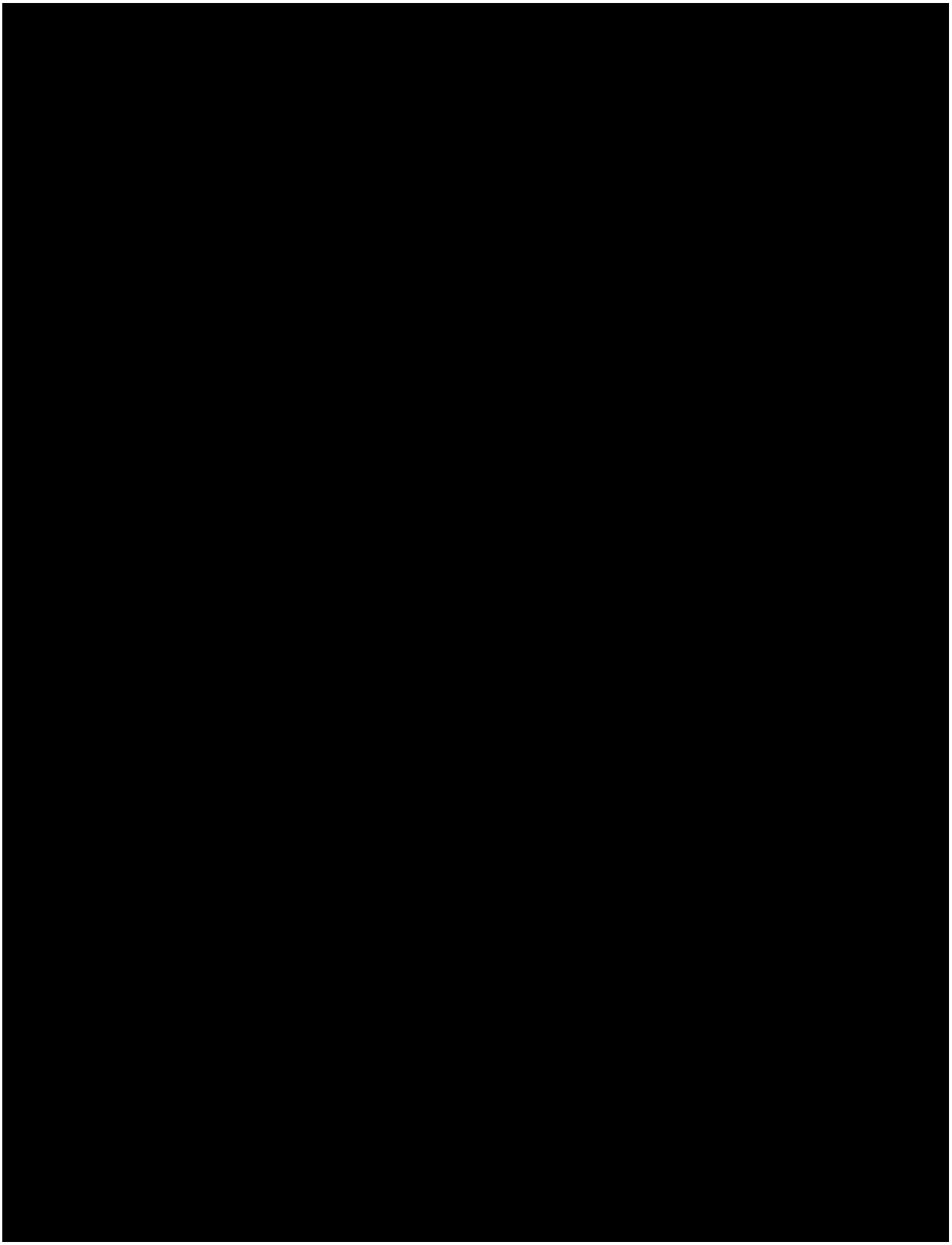
clinical trials.[38] The PSSD assesses severity of 5 symptoms (itch, pain, stinging, burning, skin tightness) and 6 subject-observed signs (skin dryness, cracking, scaling, shedding or flaking, redness, bleeding) using 0–10 numerical ratings. The severity of each item is rated on an 11-point numeric 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]



[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) Hematocrit (Hct) White Blood Cell Count, including differential Platelet Count	
Chemistry	
AST ALT Total Bilirubin	Total Protein Albumin Sodium

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

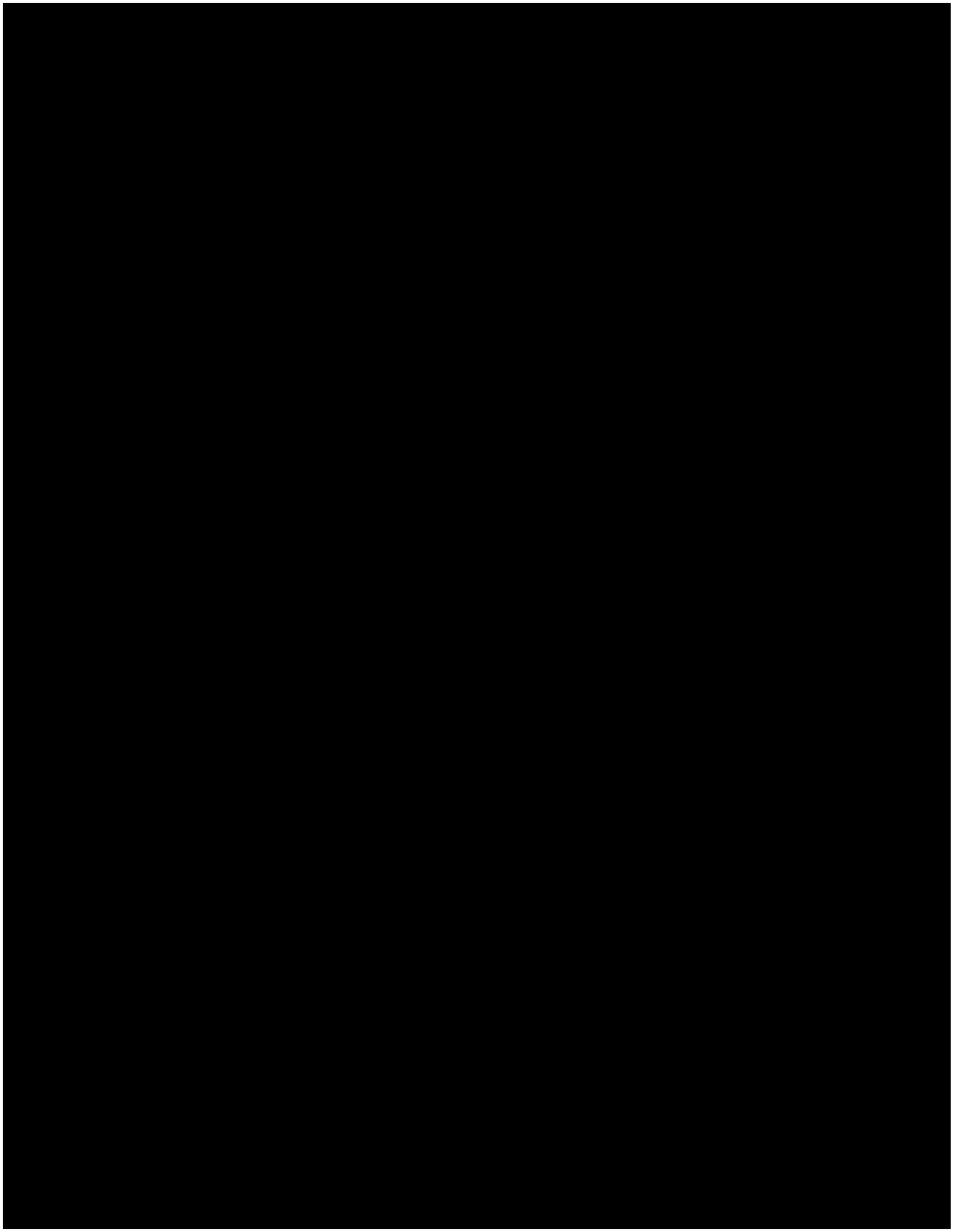
The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) is a computer-automated, patient-reported version of the C-SSRS instrument that defines 11 categories of SIB events.[50,51,52] The categories are as follows:

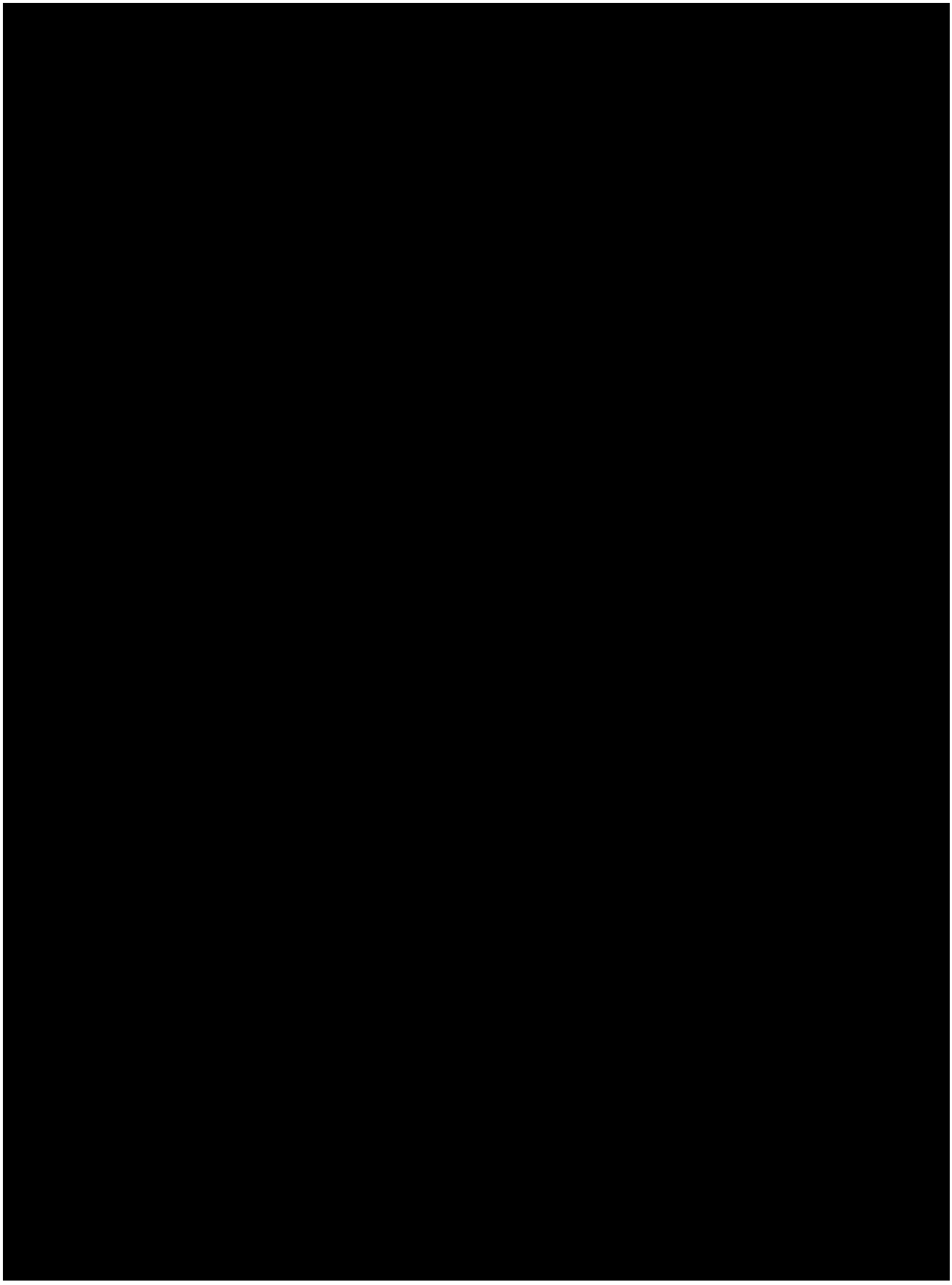
- Suicidal ideation
  1. Passive
  2. Active: Nonspecific (no method, intent, or plan)
  3. Active: Method, but no intent or plan
  4. Active: Method and intent, but no plan
  5. Active: Method, intent, and plan
- Suicidal behavior
  1. Completed suicide
  2. Suicide attempt
  3. Interrupted attempt

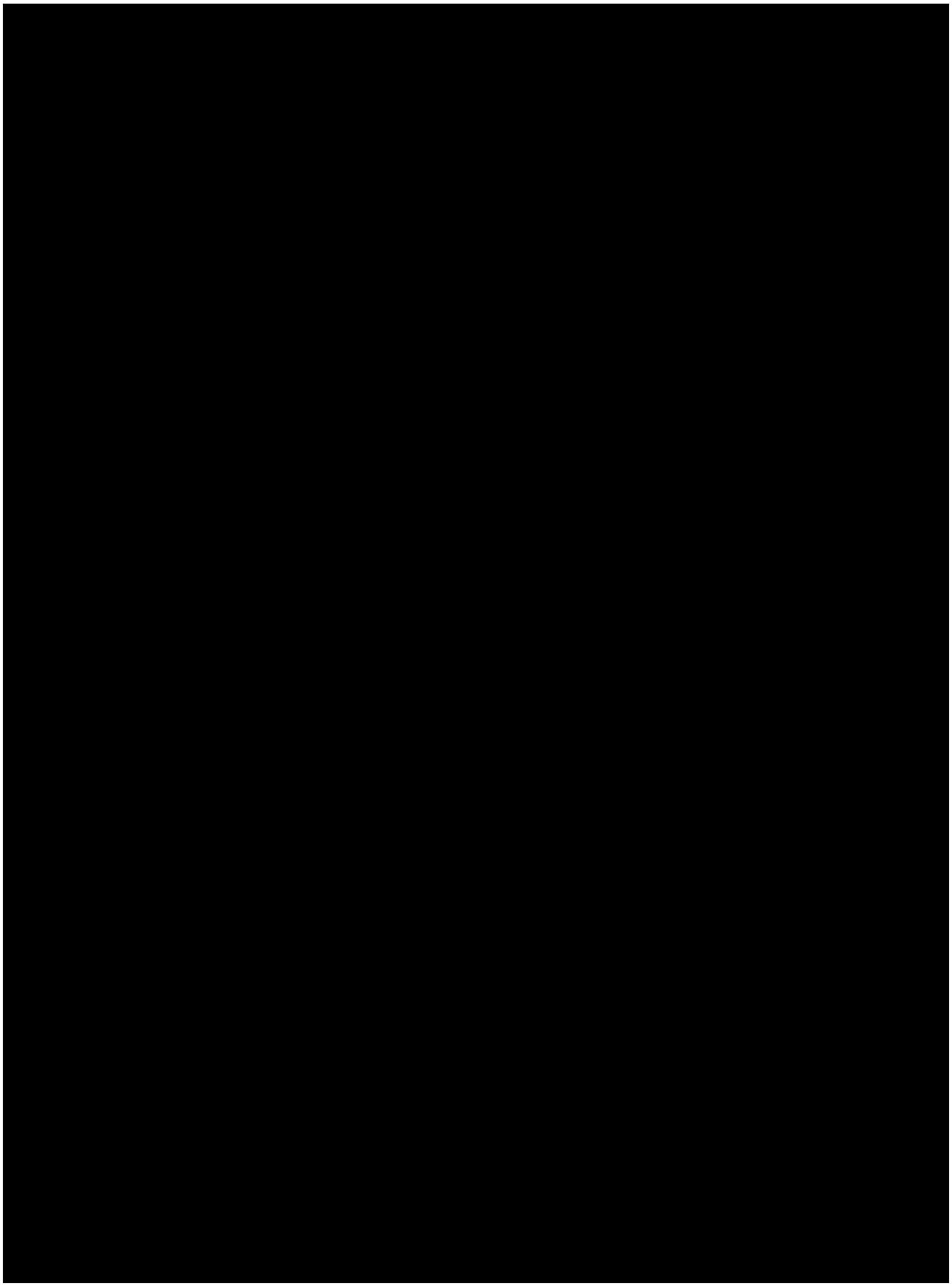
4. Aborted attempt
5. Preparatory actions toward imminent suicidal behaviors

- 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

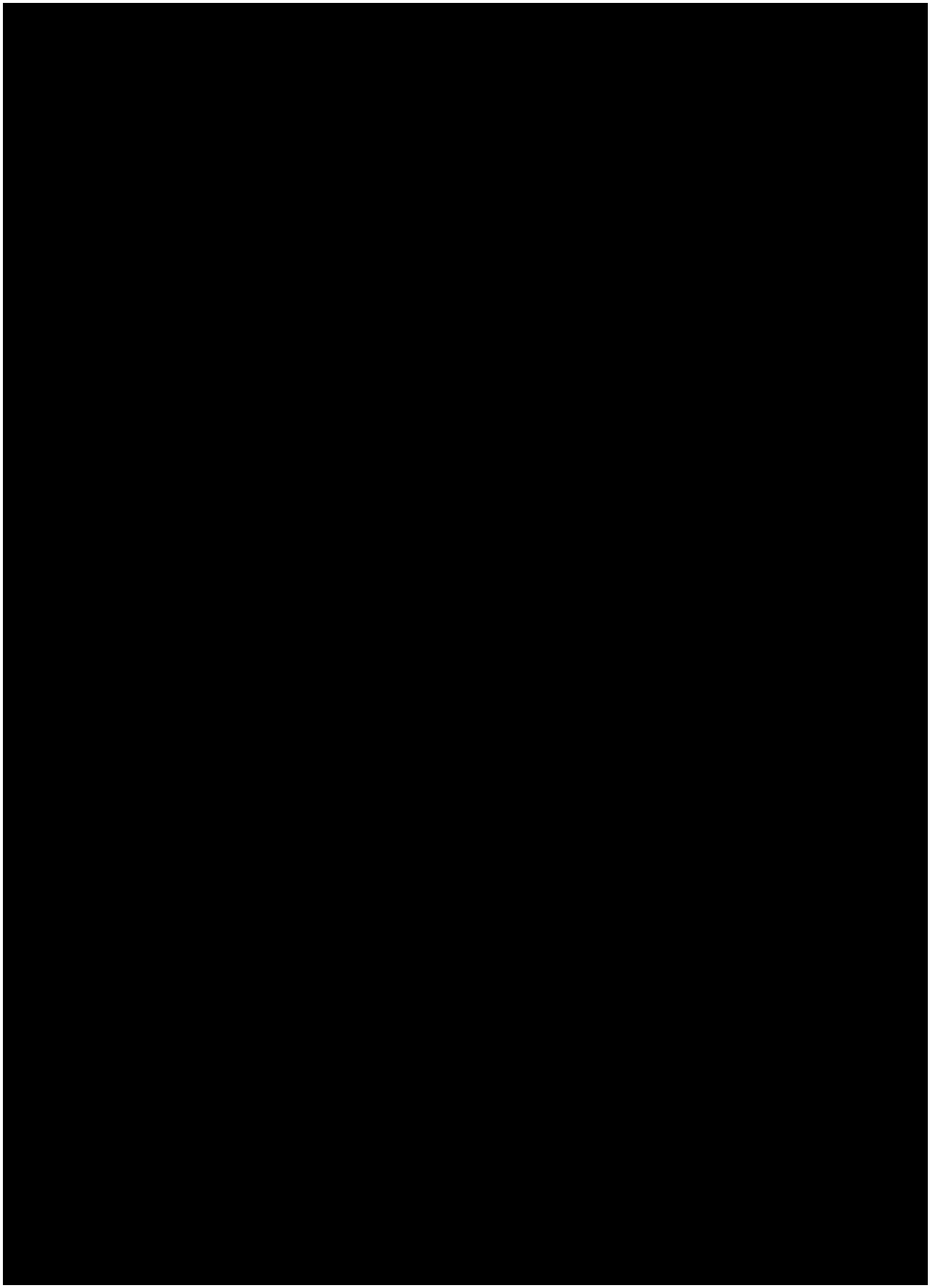
The key secondary endpoints for BMS-986165 compared to apremilast at Week 16 are defined as:

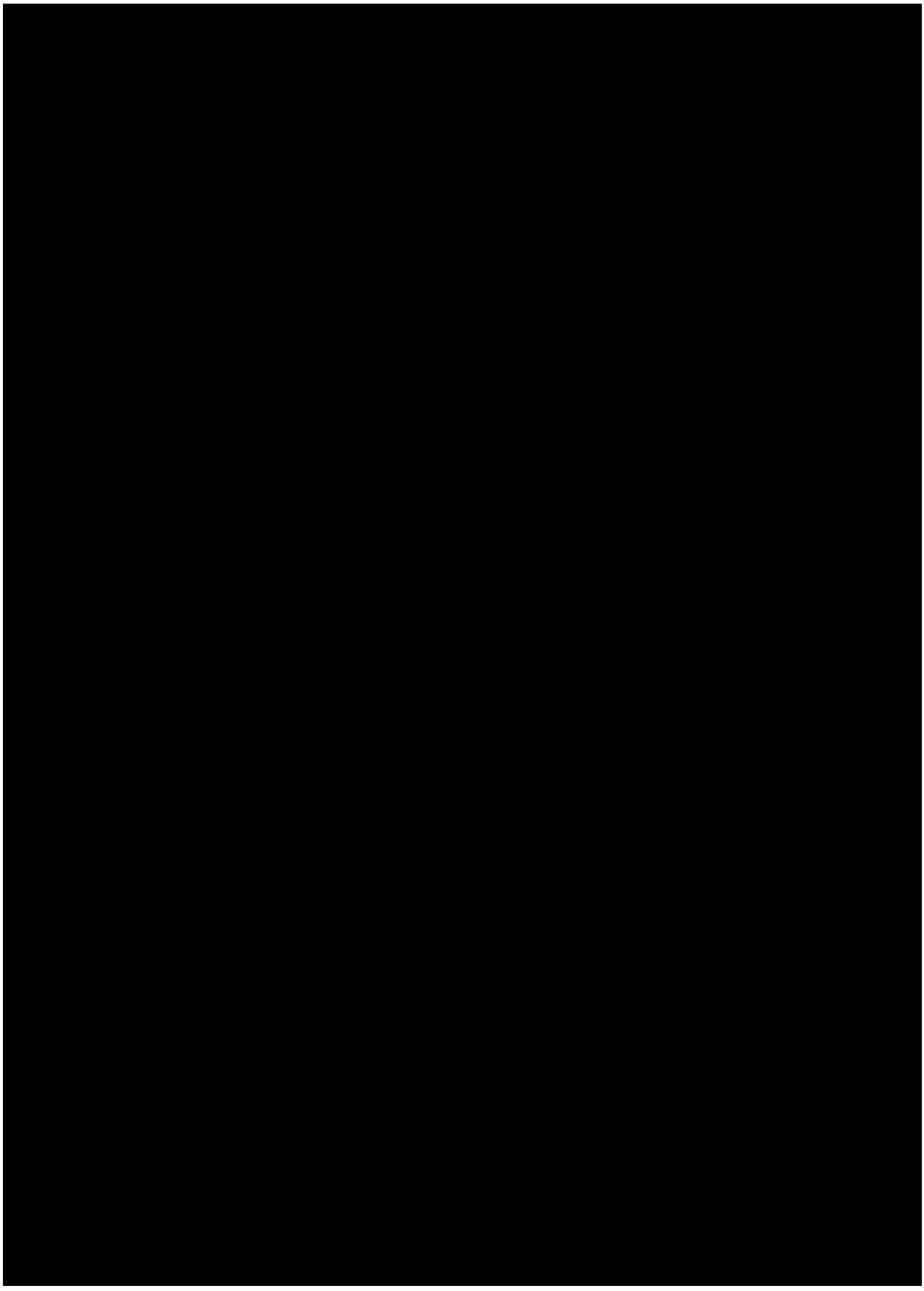
- PASI 75 response assessed as a proportion of subjects who achieve a 75% improvement from baseline in the PASI score
- PASI 90 response assessed as a proportion of subjects who achieve a 90% improvement from baseline in the PASI score
- PASI 100 response assessed as a proportion of subjects who achieve 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

[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 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

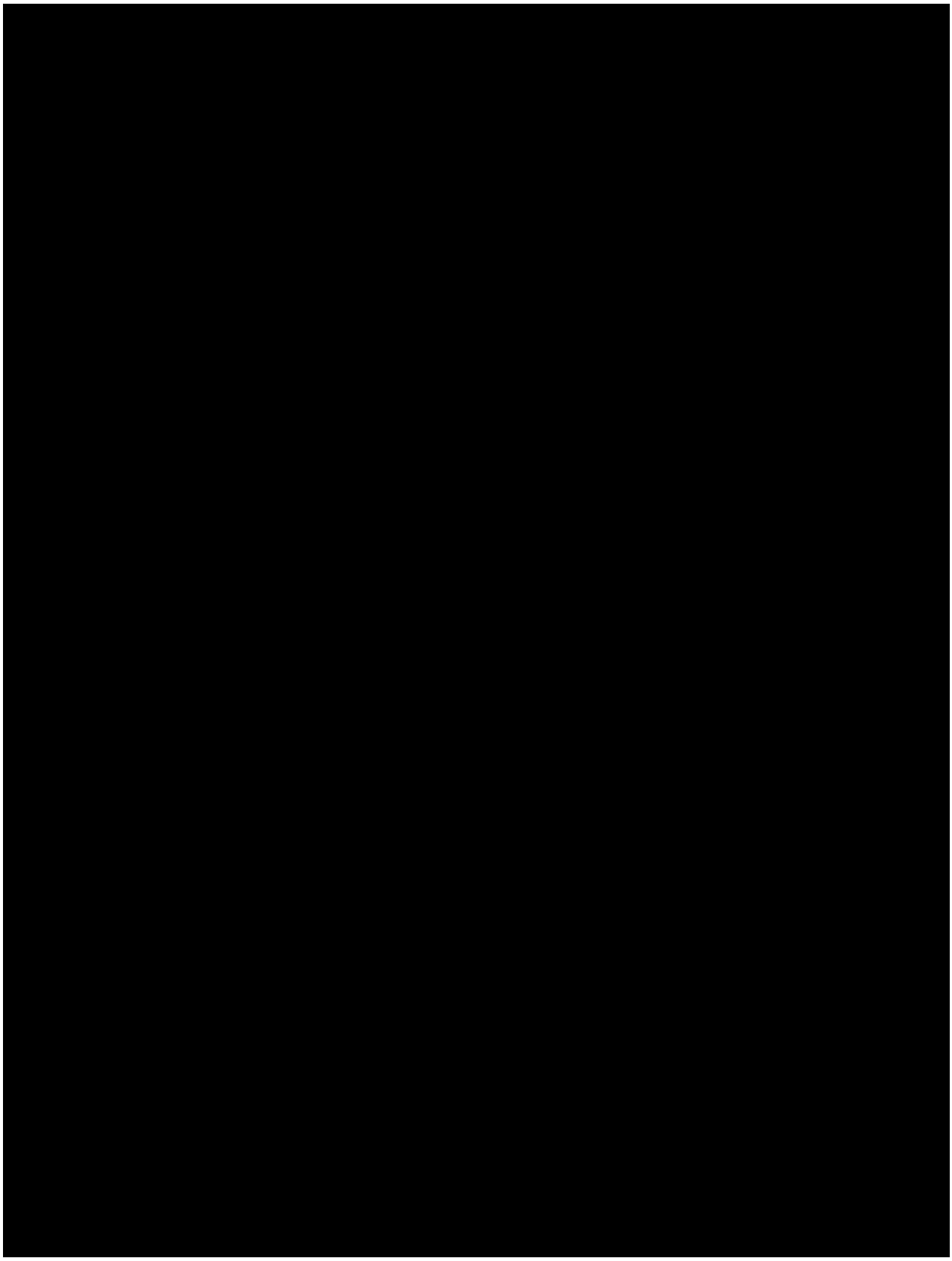
The NRI will be applied to the analyses of binary secondary efficacy endpoints for subjects who discontinue early, start a protocol prohibited medication/therapy that could improve psoriasis, or who have otherwise missing endpoint data prior to the specified timepoint.

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.



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.

10 REFERENCES

1 Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013;133(2):377-85.

2 Kupetsky EA, Keller M. Psoriasis vulgaris: an evidence-based guide for primary care. J Am Board Fam Med 2013;26(6):787-801.

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

4 Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis 2005;64(Suppl II):ii18-ii23.

5 Queiro R, Tejón P, Alonso S, Coto P. Age at disease onset: a key factor for understanding psoriatic disease. Rheumatology (Oxford) 2014;53(7):1178-85.

6 Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011 Jan;303(1):1-10.

7 Rapp SR, Feldman SR, Exum ML, Fleischer AB, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol. 1999;41:401-7.

8 Nestle FO, Kaplan DH, Barker J. Mechanisms of Disease: Psoriasis. N Engl J Med 2009;361:496-509.

9 Mehta NN, Afzar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. European Heart J 2010;31:1000–1006.

10 Novartis. Rheumatrex® (methotrexate). United States Prescribing Information. 2016.

11 Novartis. Neoral® (cyclosporine). United States Prescribing Information. 2009.

12 Celgene. Otezla® (apremilast). United States Prescribing Information. 2017.

13 Abbvie. Humira® (adalimumab). United States Prescribing Information. 2017.

14 Janssen Biotech. Remicade® (infliximab). United States Prescribing Information. 2013.

15 Janssen Biotech. Stelara® (ustekinumab). United States Prescribing Information. 2016.

16 Novartis. Cosentyx® (sekukinumab). United States Prescribing Information. 2015.

17 Eli Lilly. Taltz® (ixekizumab). United States Prescribing Information. 2017.

18 Valeant. Siliq® (brodalumab). United States Prescribing Information. 2017.

19 Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, Treatment Trends, and Treatment Dissatisfaction Among Subjects with Psoriasis and Psoriatic Arthritis in the United States. Findings from the National Psoriasis Foundation Surveys, 2003-2011. JAMA Dermatol 2013;149(10):1180–1185.

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

[21] Tokarski JS, Zupa-Fernandez A, Tredup JA, et al.. Tyrosine Kinase 2-Mediated Signal Transduction in T Lymphocytes Is Blocked by Pharmacological Stabilization of its Pseudokinase Domain. J Biol Chem 2015;290:11061-11074.

[22] Shaw MH, Boyartchuk V, Wong S, et al. A natural mutation in the Tyk2 pseudokinase domain underlies altered susceptibility of B10.Q/J mice to infection and autoimmunity. Proc Natl Acad Sci U S A. 2003;100:11594-11599.

[redacted]

[24] Carlin CS, Feldman SR, Krueger JG, Menter A, Krueger GG. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol 2004;50:859-66.

[25] Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis 2005;64:ii65-ii68.

[26] Fredriksson T, Pettersson U. Severe psoriasis-oral therapy with a new retinoid. Dermatologica 1978;157(4):238-44.

[27] Rossiter ND, Chapman P, Haywood IA. How big is a hand? Burns. 1996;22:230-1.

[28] Thomas CL, Finlay AY. The 'handprint' approximates to 1% of the total body surface area whereas the 'palm minus the fingers' does not. Br J Dermatol. 2007;157(5):1080-1.

[29] Long CC, Finlay AY, Averill RW. The rule of hand: 4 hand areas = 2 FTU = 1 g. Arch Dermatol. 1992;128:1129–30.

[30] Kragballe K, Menter A, Lebwohl M, et al. Long-term management of scalp psoriasis: perspectives from the international psoriasis council. J Dermatol Treat. 2013;24:188-192.

[redacted]

[32] Tan EST, Chong W-S, Liang Tey H. Nail psoriasis: a review. Am J Clin Dermatol. 2012;13:375-388.

[redacted]

[34] Bissonnette R, Pariser DM, Wasel NR, et al. Apremilast, an oral phosphodiesterase-4 inhibitor, in the treatment of palmoplantar psoriasis: Results of a pooled analysis from phase II PSOR-005 and phase III Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis

(ESTEEM) clinical trials in patients with moderate to severe psoriasis. J Am Acad Dermatol. 2016;75:99-105.

[redacted]

36 Feldman SR. Development of a patient-reported outcome questionnaire for use in adults with moderate-to-severe plaque psoriasis: The Psoriasis Symptoms and Signs Diary. Journal of Dermatology & Dermatologic Surgery. 2016;20:19–26.

37 Mathias SD. Measurement properties of a patient-reported outcome measure assessing psoriasis severity: The psoriasis symptoms and signs diary. Journal of Dermatological Treatment. 2016;27(4):322-327.

38 Armstrong A, Puig L, Langley R, et al. Validation of psychometric properties and development of response criteria for the Psoriasis Symptoms and Signs Diary (PSSD): results from a phase III clinical trial. Journal of Dermatological Treatment. 2017: 1-31. DOI: 10.1080/09546634.2017.1364694.

39 Finlay, AY, Khan, GK: Dermatology Life Quality Index (DLQI): A simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19:210–216.

[redacted]

47 Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247–54.

48 Kroenke K, Strine TW, Spitzer RL, et al. The PHQ-8 as a measure of current depression in the general population. J Affect Disord. 2009;114(1-3):163-173.

[49] Dhingra SS, Kroenke K, Zack MM, Strine TW, Balluz LS. PHQ-8 Days: a measurement option for DSM-5 Major Depressive Disorder (MDD) severity. Population Health Metrics. 2011;9:11. doi:10.1186/1478-7954-9-11.

[50] The Federal Register. Guidance for Industry- Suicidal ideation and behavior: prospective assessment of occurrence in clinical trials. (06-Aug-2012). https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf. Accessed 22-Mar-2018.

[51] Greist JH, Mundt JC, Gwaltney CJ, Jefferson JW, Posner K. Predictive value of baseline electronic Columbia–Suicide Severity Rating Scale (eC–SSRS) assessments for identifying risk of prospective reports of suicidal behavior during research participation. Innov Clin Neurosci. 2014;11(9–10):23–31.

[52] Mundt JC, Greist JH, Jefferson JW, Federico M, Mann JJ, Posner K. Prediction of suicidal behavior in clinical research by lifetime suicidal ideation and behavior ascertained by the electronic Columbia-Suicide Severity Rating Scale. J Clin Psychiatry. 2013;74(9):887-893.

[53] Posner, K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. Am J Psychiatry. 2007;164:1035-1043.

[54] Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain. 1997;72(1-2):95-7.

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: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product

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

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

Case Report Forms

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

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

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

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

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

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

Monitoring

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

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

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

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

Records Retention

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

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

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

Return of Study Treatment

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

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

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

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

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

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

Clinical Study Report and Publications

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

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

Evaluating AEs and SAEs

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

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

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

All SAEs must be followed to resolution or stabilization.

Reporting of SAEs to Sponsor or Designee

SAEs, whether related or not related to study drug, and pregnancies must be reported to [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 *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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) • Withdrawal (coitus interruptus). • Spermicide only • 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) (averaged over the whole body)		0 = No evidence of erythema, but post inflammatory hyper/hypopigmentation changes may be present 1 = Faint erythema 2 = Light red coloration 3 = Moderate red coloration 4 = Bright red coloration
Induration (I) (averaged over the whole body)		0 = No evidence of plaque elevation 1 = Minimal plaque elevation, barely palpable, = 0.25 mm 2 = Mild plaque elevation, slight but definite elevation, indistinct edge, = 0.5 mm 3 = Moderate plaque elevation, elevated with distinct edges, = 0.75 mm 4 = Severe plaque elevation, hard/sharp borders, ≥1 mm
Scaling (S) (averaged over the whole body)		0 = No evidence of scaling 1 = Minimal; occasional fine scaling 2 = Mild; fine scale dominates 3 = Moderate; coarse scale predominates 4 = Severe; thick scale predominates

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

Physician's Static Global Assessment based upon above Total Average

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

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

APPENDIX 6 PSORIASIS AREA AND SEVERITY INDEX (PASI)

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

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

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

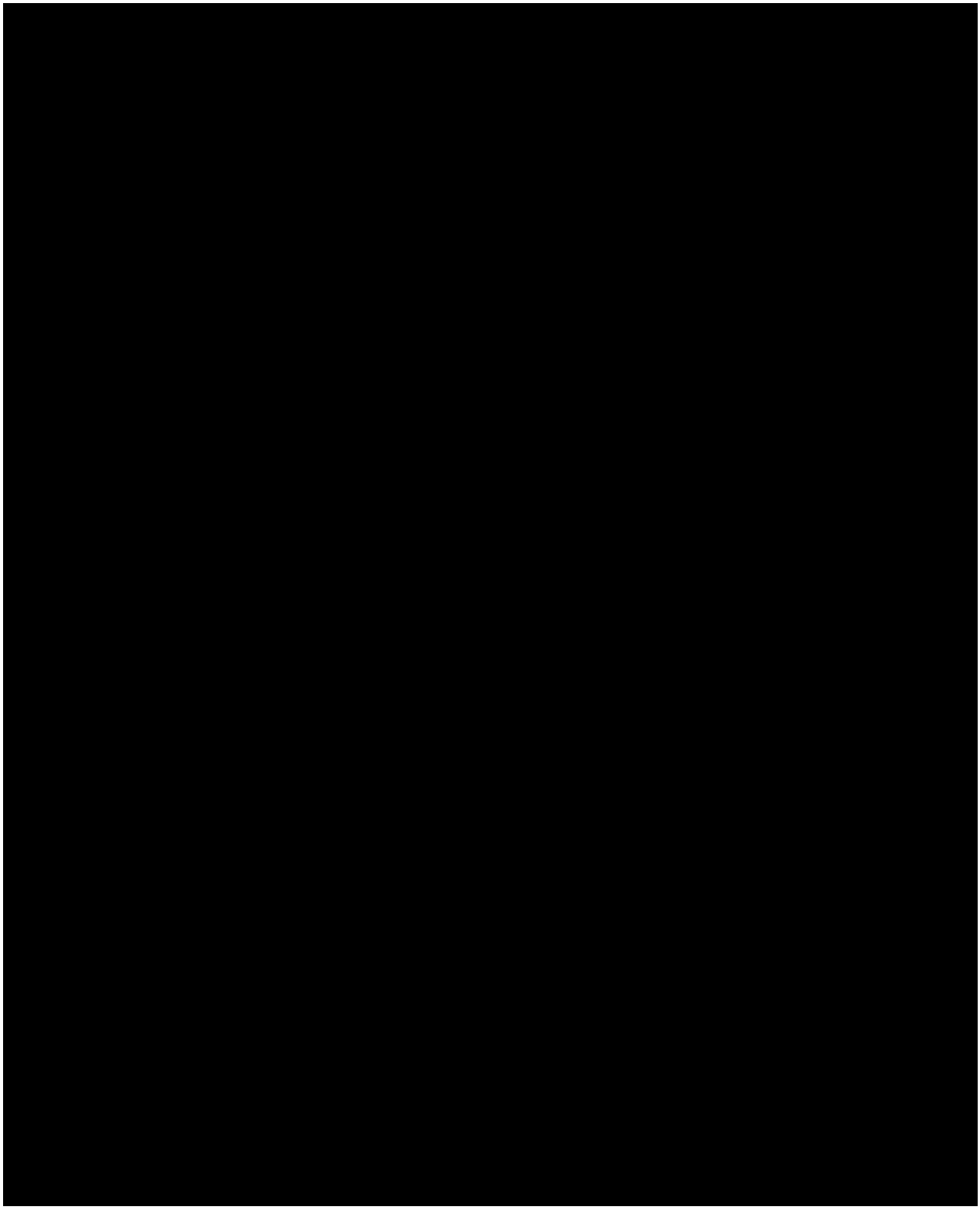
Please rate overall scalp psoriasis severity by selecting the overall score based on the following rating scale:

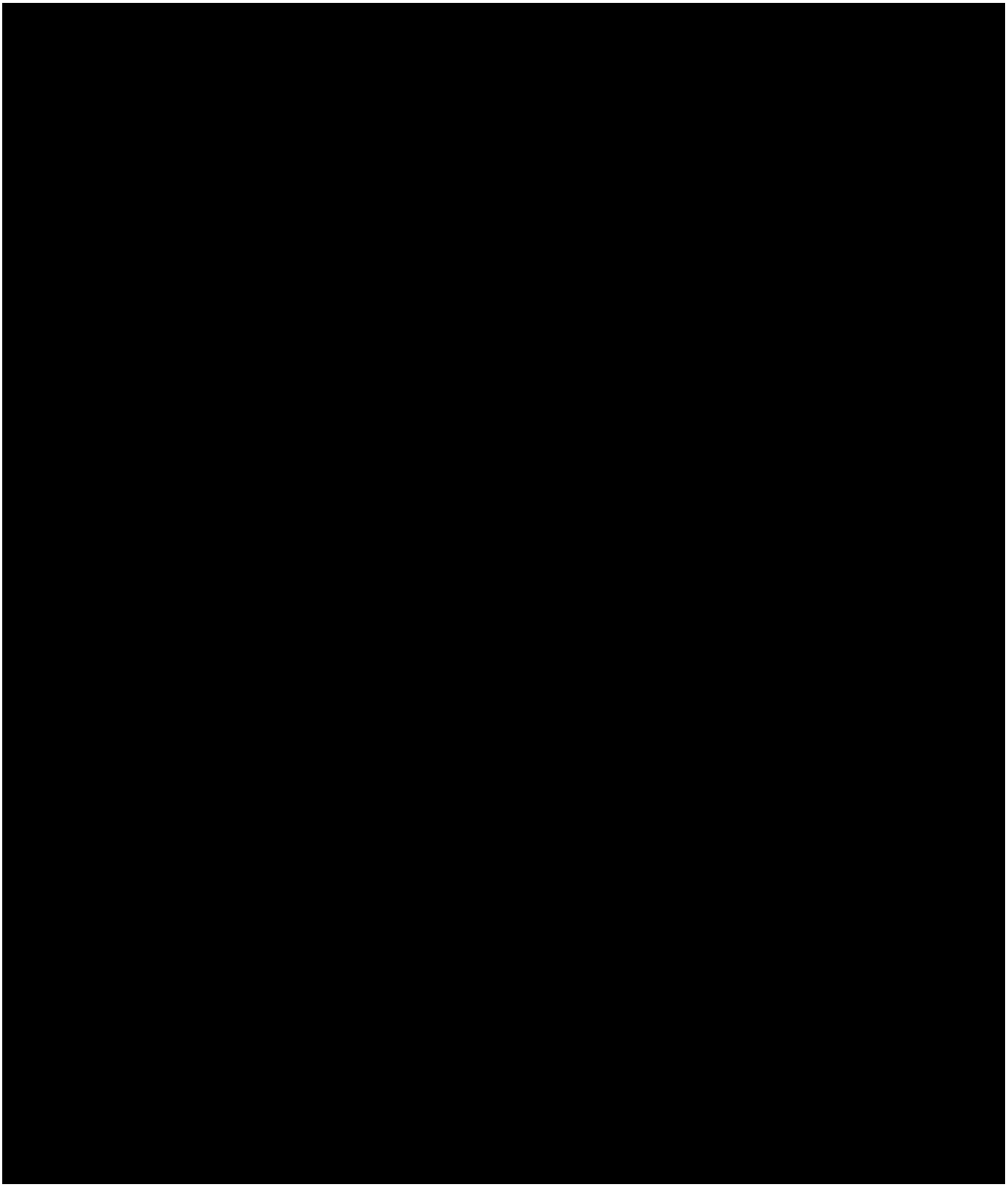
Score	Category	Description
0	Absence of Disease	No evidence of redness, no evidence of thickness, and no evidence of scaliness on the scalp
1	Very Mild Disease	The overall clinical picture consists of flat lesions with barely perceptible erythema, with or without a trace of overlying fine scale
2	Mild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

APPENDIX 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 **AND** Hyperkeratosis- none **AND** Splinter Hemorrhages-consistent with non-psoriatic splinter hemorrhages **AND** 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 **OR** Hyperkeratosis- present, but barely detectable elevation of nail plate **OR** Nail Bed Erythema- faint **AND** Splinter Hemorrhages- consistent with non-psoriatic splinter hemorrhages	No more than 5 pits or psoriatic leukonychia on any nail **AND** No crumbling
Mild	2	Onycholysis- >10% on five or more nails **OR** Hyperkeratosis- present with mild elevation of nail plate **OR** Splinter Hemorrhages- present on four or fewer nails **OR** Nail Bed Erythema- mild	Five or more nails with mild pitting (eg, >10 pits/nail) or psoriatic leukonychia **AND** No crumbling
Moderate	3	Onycholysis- >30% on at least one nail **OR** Hyperkeratosis- present with moderate elevation of nail plate **OR** Splinter Hemorrhages- scattered and present on five or more nails **OR** Nail Bed Erythema- moderate	Five or more nails with moderate pitting (eg, >25 pits/nail) **AND** ≤25% crumbling on any nails
Severe	4	Onycholysis- >50% on at least one nail **OR** Hyperkeratosis- present with severe elevation of nail plate **OR** Splinter Hemorrhages- numerous and present on five or more nails **OR** Nail Bed Erythema- severe	Five or more nails with severe pitting (>50 pits/nail) **OR** >25% crumbling on any nail

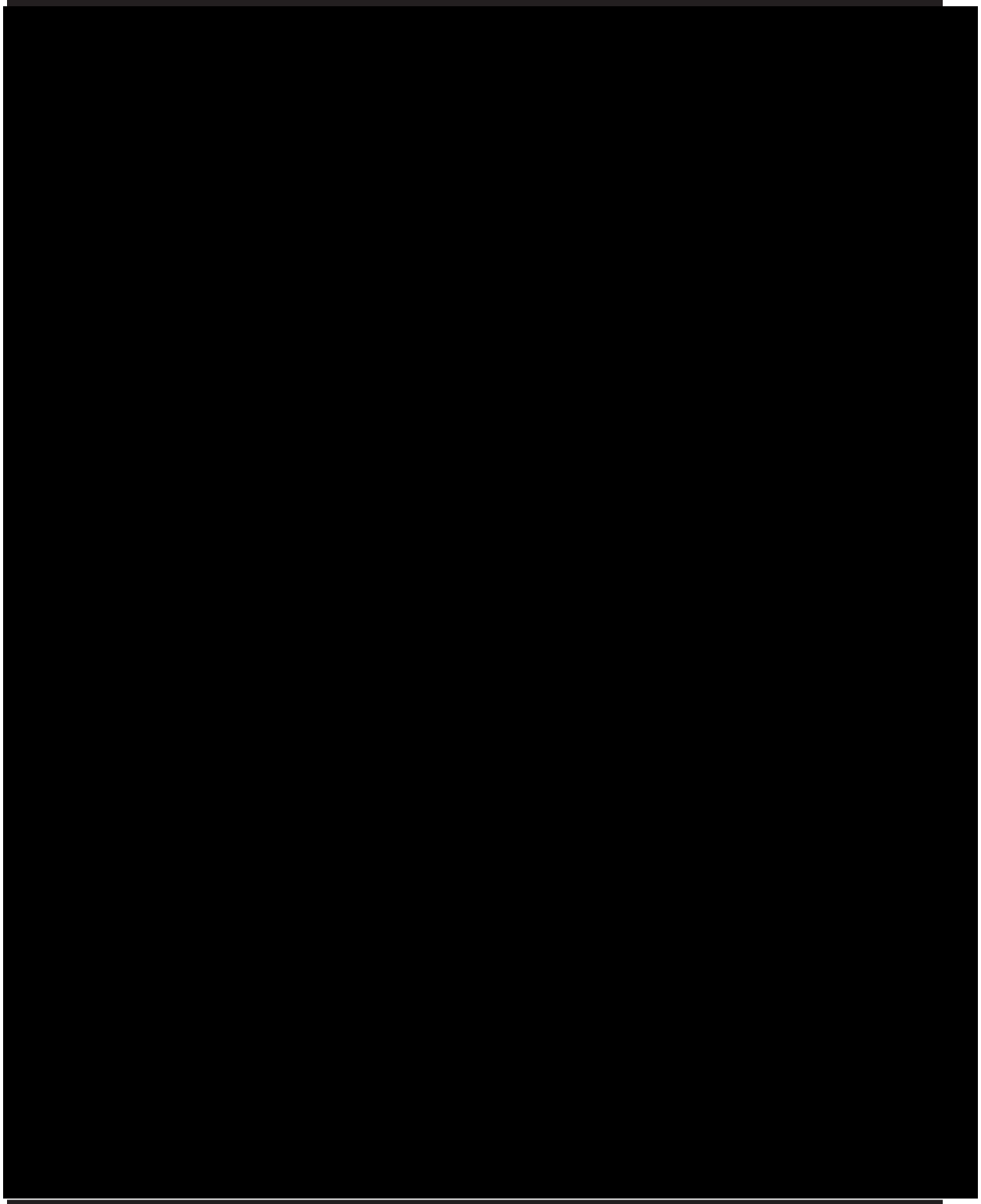




APPENDIX 11 PALMOPLANTAR PSORIASIS PHYSICIAN'S GLOBAL ASSESSMENT (pp-PGA)

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:

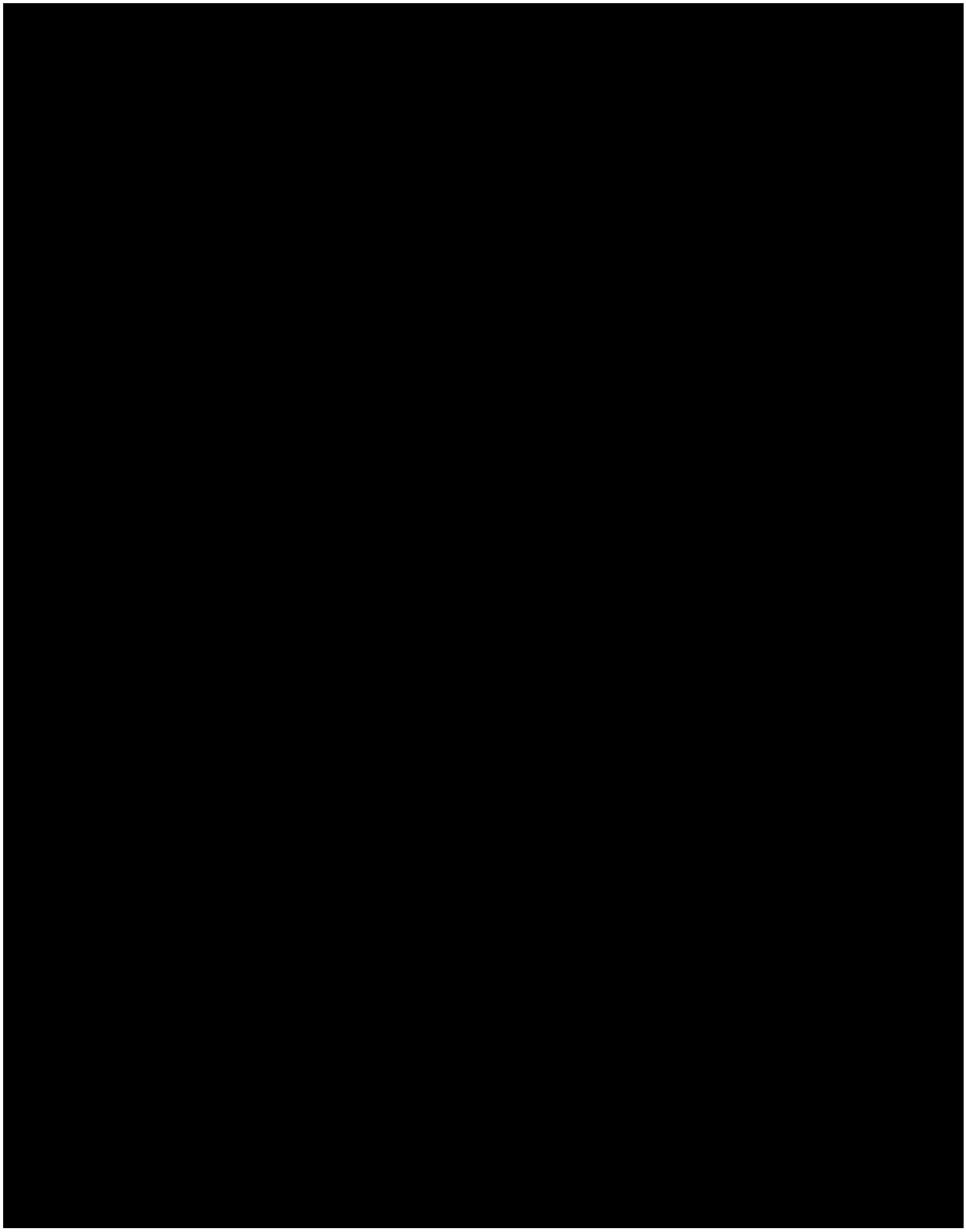
Name: Diagnosis:

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

Please check you have answered EVERY question. Thank you



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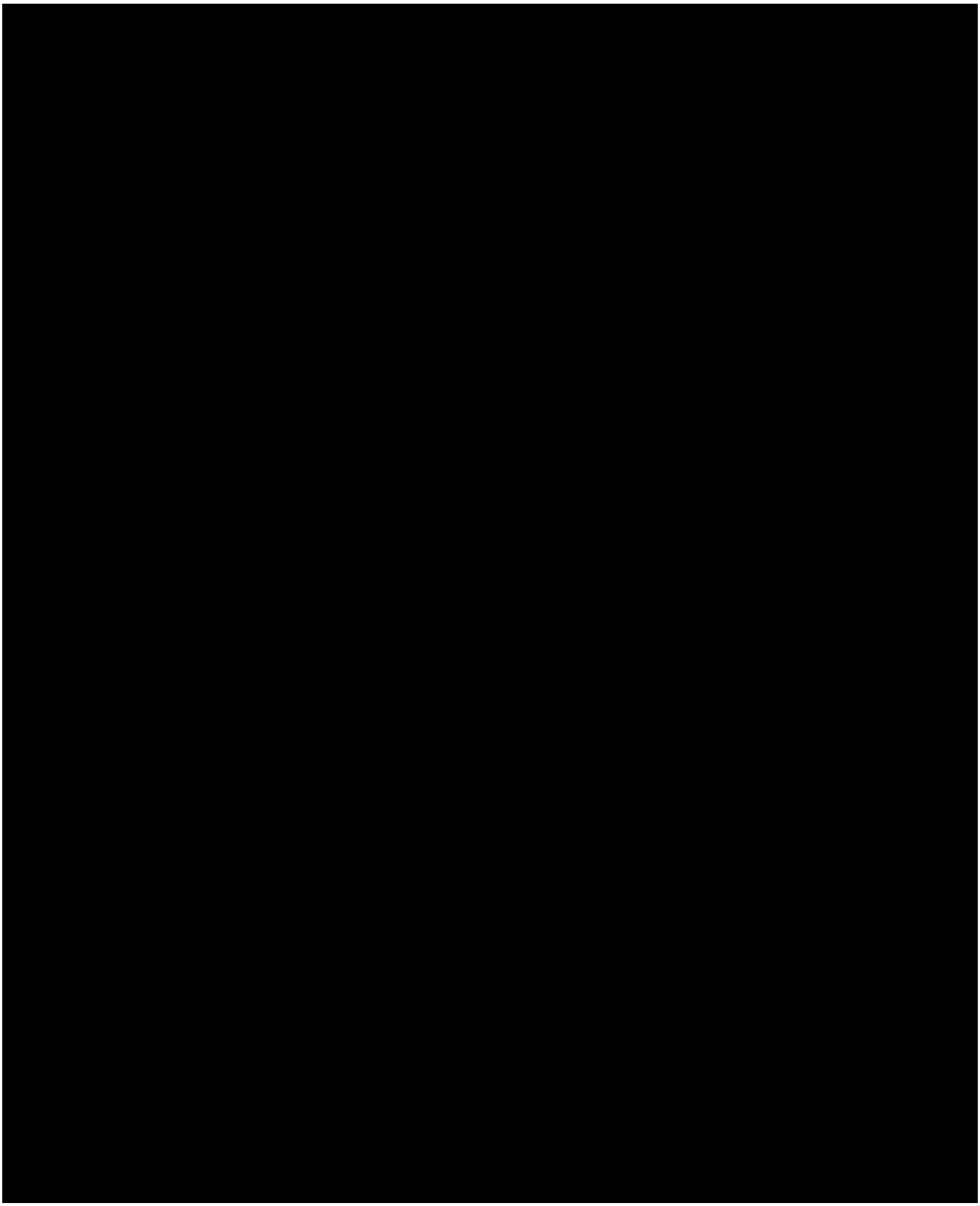

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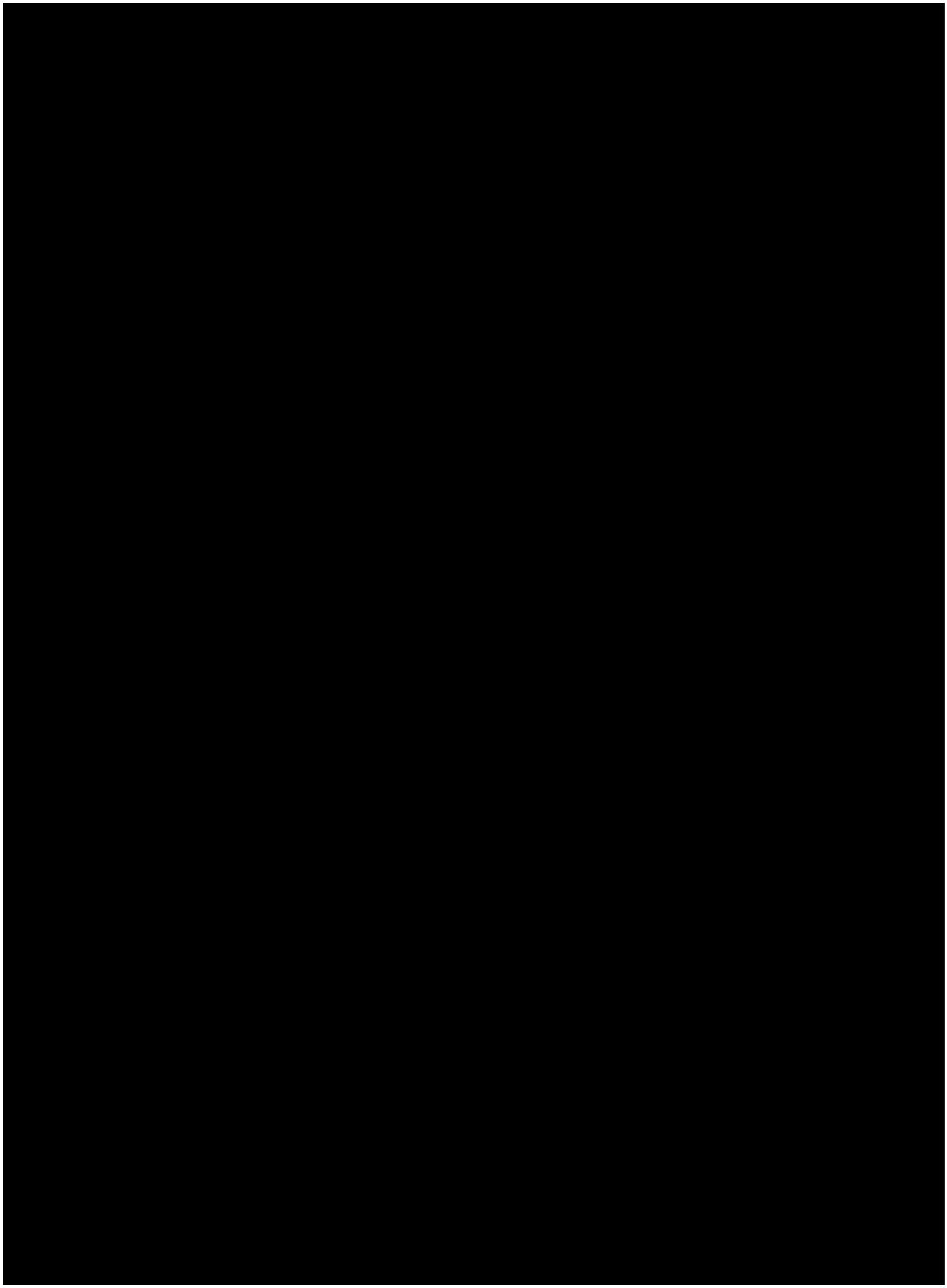

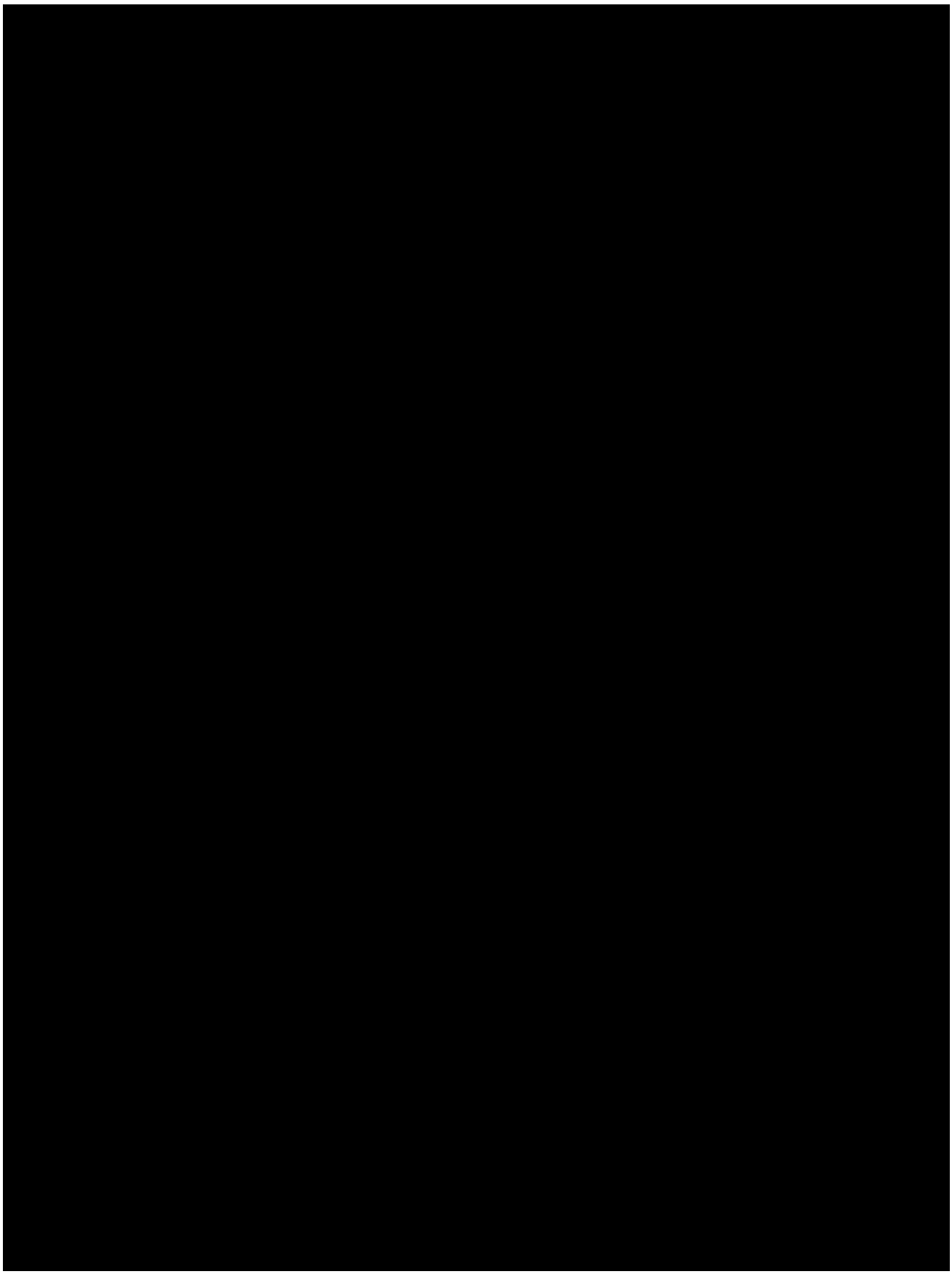

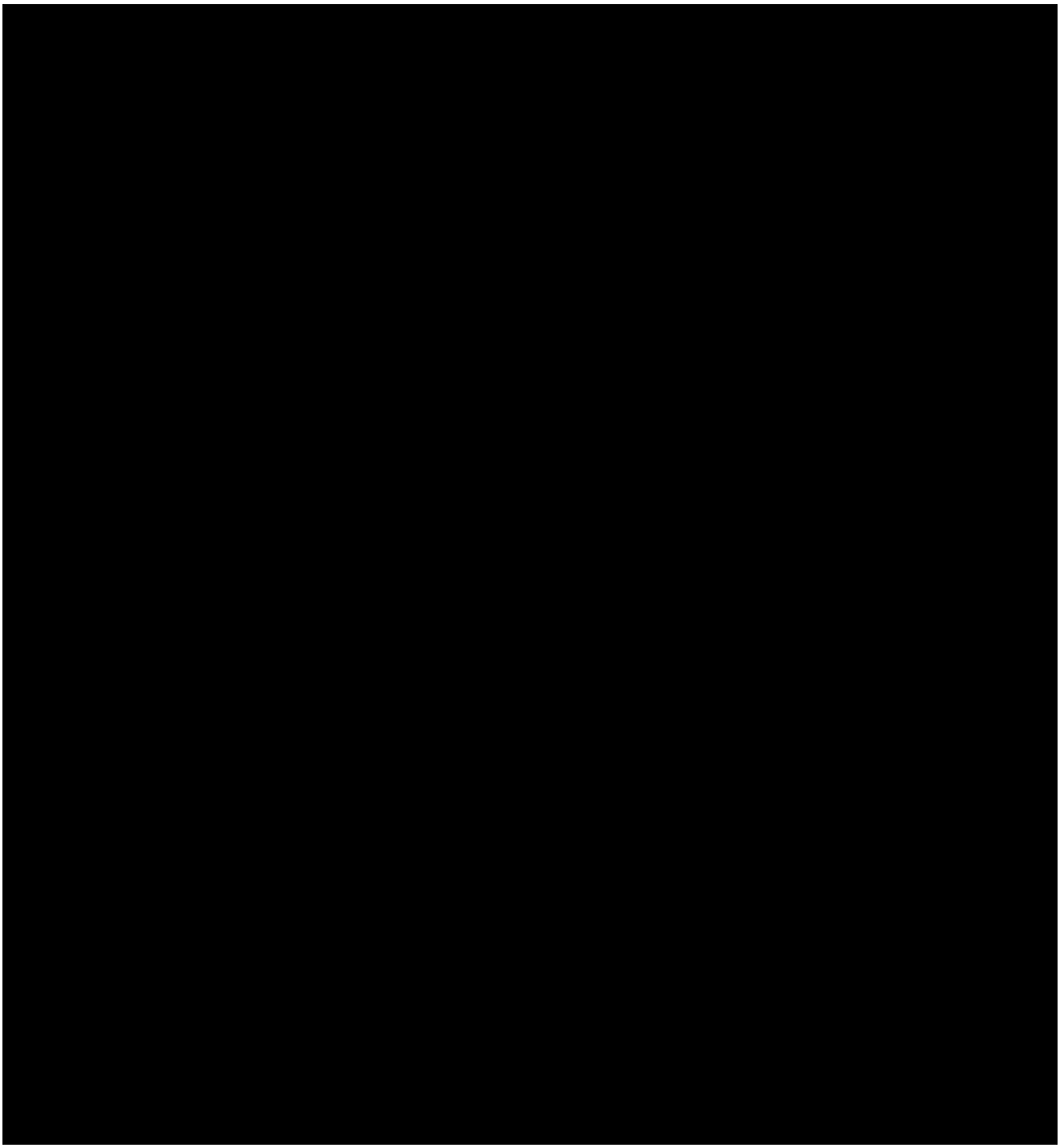

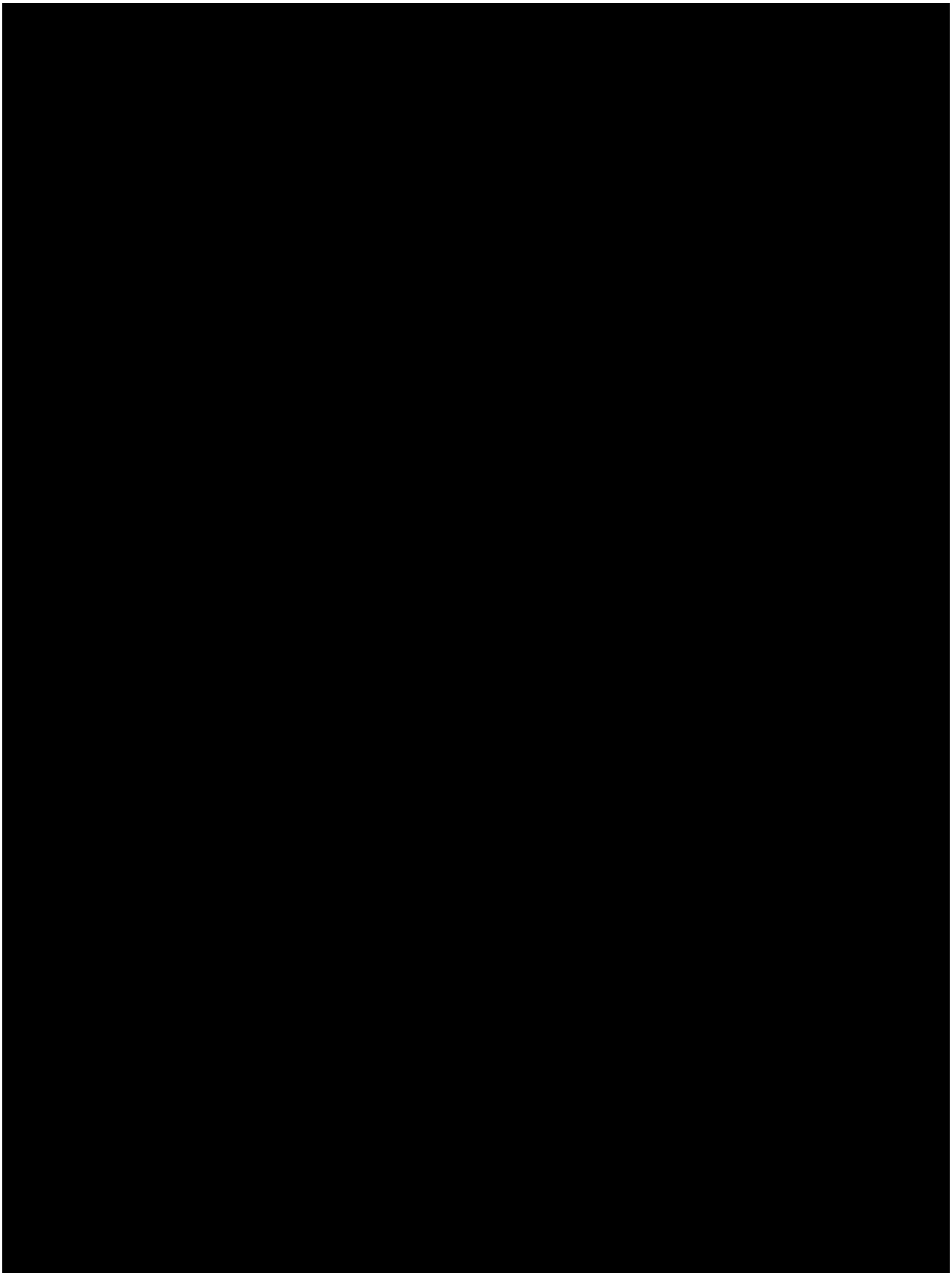

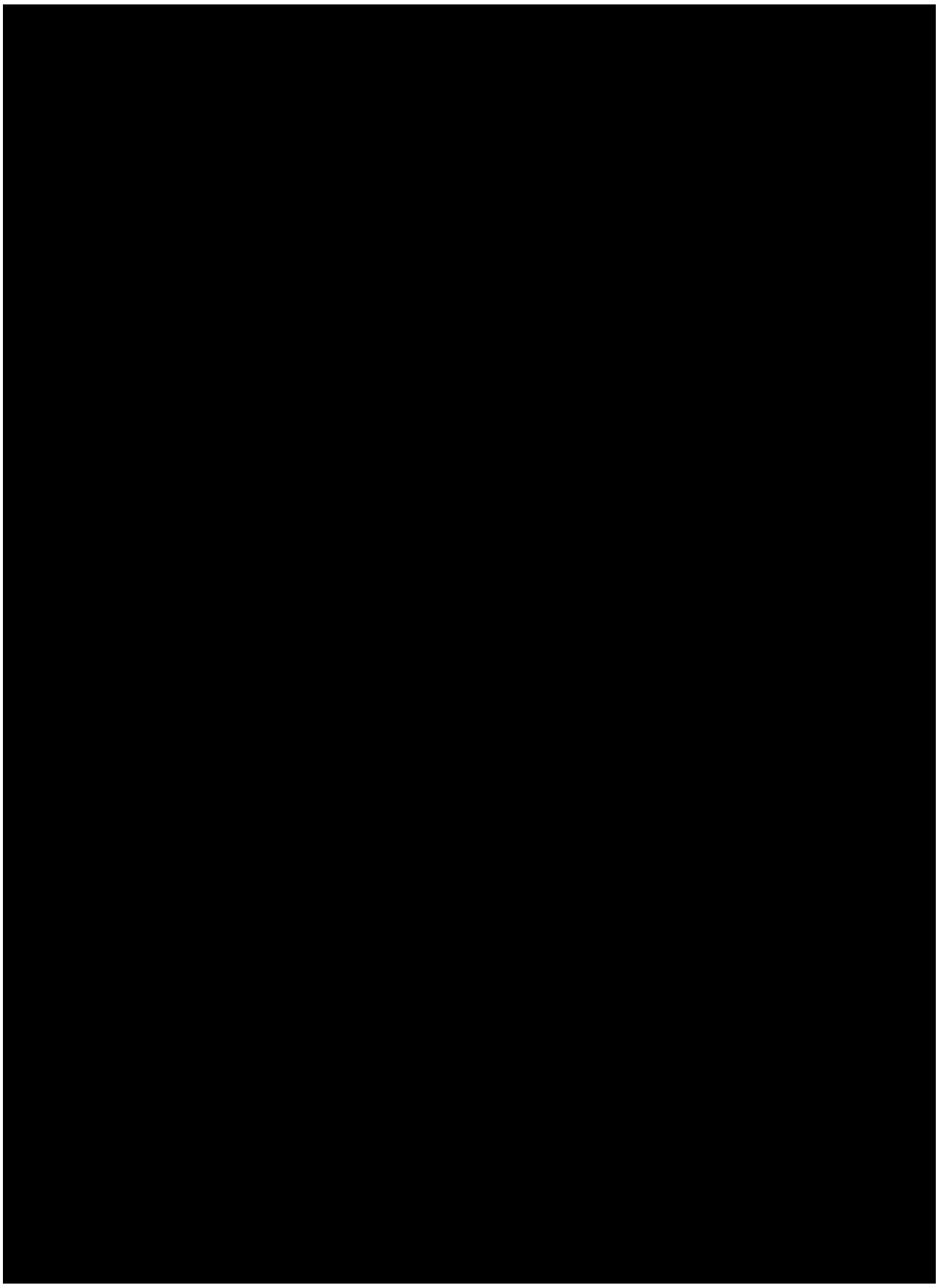

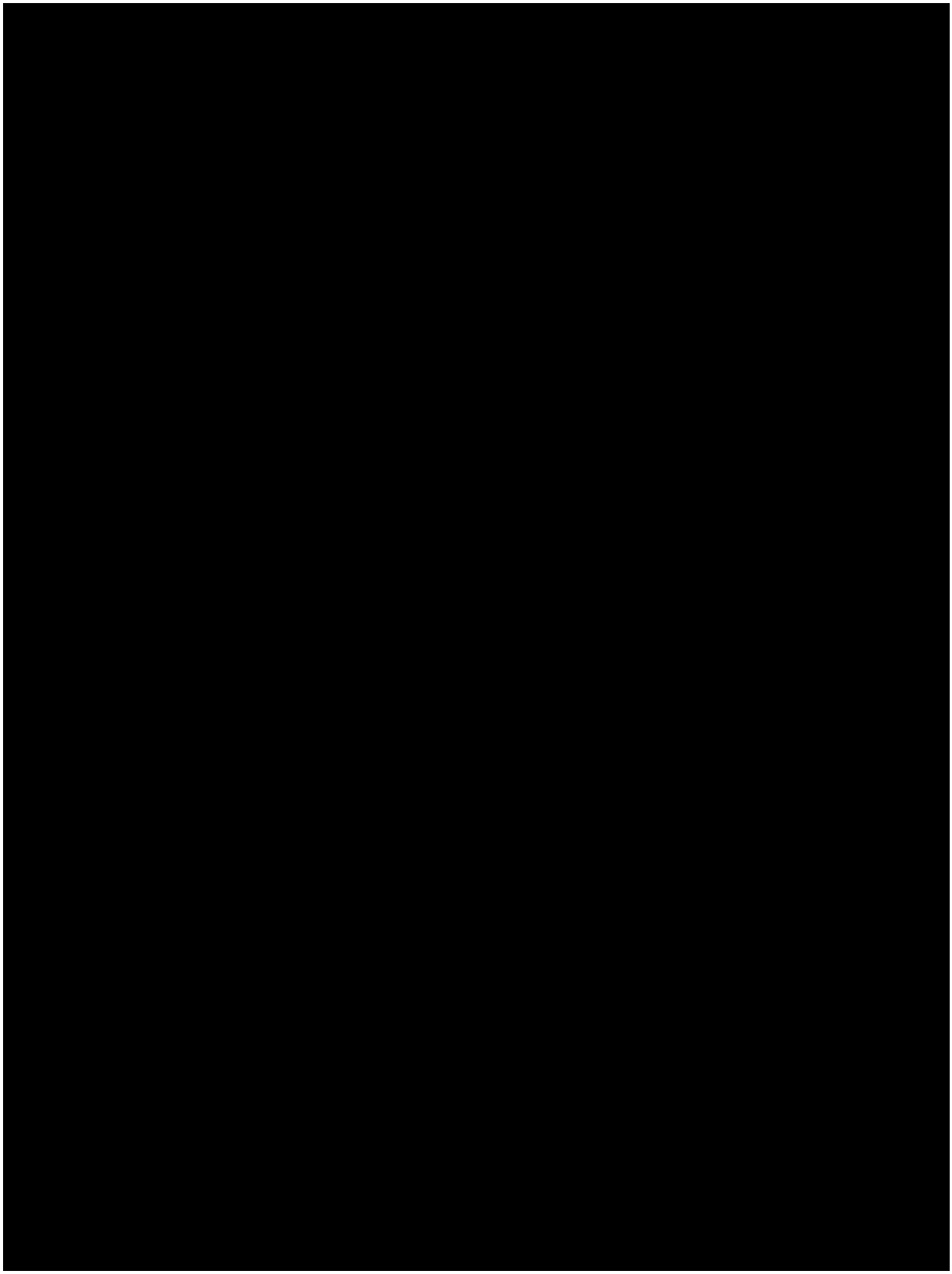

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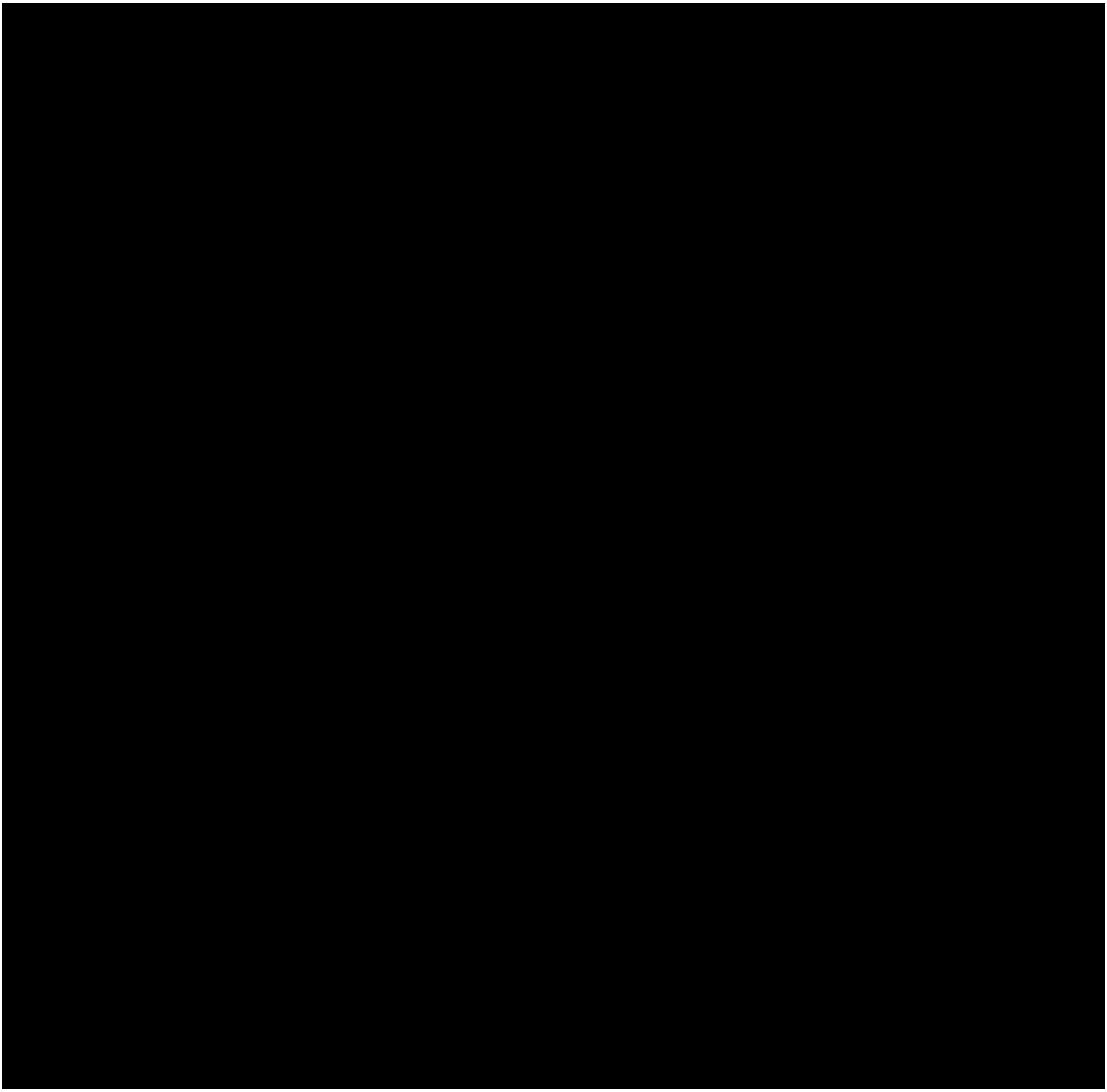

APPENDIX 21 PSORIATIC ARTHRITIS SCREENING AND EVALUATION (PASE) QUESTIONNAIRE

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.