A Double-Blind Randomized Placebo-Controlled Single and Multiple Ascending Doses Study of the Safety and Tolerability, Pharmacokinetics (Including Bioavailability Comparison and Food Effect) and Pharmacodynamics of Oral BMS-986251 Administration in Healthy Subjects, with Efficacy Assessment of Multiple Doses in Patients with Moderate-to-Severe Psoriasis

Test Drug: BMS-986251

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1. SCHEDULE OF ACTIVITIES

Schedules of procedures are described in Table 1 for Part A (single ascending dose [SAD] healthy subjects, including a cohort to evaluate relative bioavailability and food effect), Table 2 for Part B (multiple ascending dose [MAD] healthy subjects), Table 3 for Part C - MAD psoriasis patients, intensive pharmacokinetic (PK) sampling sub-cohort, and Table 4 for Part C - MAD psoriasis patients, sparse PK sub-cohort.

For PK, pre-dose samples (in the multiple dose parts this applies to samples before the first dose only) will be obtained between waking up and dosing. For pre-dose (trough) samples during multiple dosing, a 5% time window since the last dose is allowed, but the sample must be taken before the next dose. Post-dose samples will be obtained with time margins of +/- 5% of the time that has passed since (last) dosing. The +/- 5% time window also applies to the start and end times of urine collection intervals and in addition to the total duration of each consecutive collection interval.

For PD, pre-dose samples (in the multiple dose parts this applies to samples before the first dose only) will be obtained between waking up and dosing. Post-dose samples up to 40 min post-dose will be obtained with a time window of +/- 2 minutes. Thereafter, post-dose samples will be obtained with time margins of +/- 5% of the time that has passed since (last) dosing.

For safety assessments, pre-dose assessments will be performed between waking up and dosing. For safety assessments up to 2.5 hours post-dose a time-window of +/- 15 minutes is allowed. Thereafter, assessments will be performed with time margins of +/- 10% of the time that has passed since (last) dosing.

In the event assessments are planned for the same scheme time, the order of the assessments should be arranged in such a way that PK and PD blood sampling will be done after the ECG and vital signs recordings have been conducted, with PK and PD blood sampling as close to the planned time as possible. Clinical laboratory blood samples may be taken thereafter. During the 24-hour periods of Holter monitoring, vital signs may also be recorded after PK blood sampling (when necessary for logistical reasons). When multiple procedures are scheduled at the same time as medication dosing, medication dosing will be done exactly on time and safety assessments and blood sampling for PK and PD will be done before dosing (as close to medication dosing as possible).

Table 1 Study Procedural Outline Part A – SAD Healthy Subjects (IM024 005)

		Period 1 Period 2 (Cohort for Bioavailability and Food Effect Assessment only) Period 3 (Cohort for Bioavailability and Food Effect Assessment only)																				
Visit	**Screening**	**Pre-Treatment**	**Treatment**																			**Follow-up[1]**
Study Days	**-21 to -1**	**-1**	**1**											**2**		**3**	**4**	**5**	**6**	**7**	**9**	**11**
Time Post-Dosing (hrs)			**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**192**	**240**
Confinement		X																				
Discharge[2]																				X		
Ambulant visit	X																				X	X
Informed consent and medical history	X																					
Demographics	X																					
Physical examination	X																					X
Genotyping (CYPs, transporters)[3]				X																		
Vital signs	X		X			X		X		X		X		X		X	X	X	X	X	X	X
Body weight and height (including BMI calculation)[4]	X	X																				X
Eligibility check	X	X	X																			
12-lead ECG	X		X			X		X				X		X		X		X		X		X

[1] For relative bioavailability/food effect cohort follow-up assessments on Day 11 of Period 3 only. At the Day 11 visit in Period 1 and 2 only blood sampling for PK and PD (Period 1 only), vital signs, and drug and alcohol screen will be performed.
[2] Discharge from the clinical research unit.
[3] Mandatory whole blood collection for analysis of DNA variants in ADME-related genes (http://pharmaadme.org/Appendix 6). For relative bioavailability/food effect cohort sample will be collected in Period 1 only. Sample may be taken at any time post-dose during Day 1.
[4] Height will only be measured at screening. BMI will also only be calculated at screening.

		Period 1 Period 2 (Cohort for Bioavailability and Food Effect Assessment only) Period 3 (Cohort for Bioavailability and Food Effect Assessment only)																				
Visit	**Screening**	**Pre-Treatment**	**Treatment**																			**Follow-up[1]**
Study Days	**-21 to -1**	**-1**	**1**											**2**		**3**	**4**	**5**	**6**	**7**	**9**	**11**
Time Post-Dosing (hrs)			**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**192**	**240**
(triplicate)																						
Holter monitoring[5] [6]			X[7]	X																		
Clinical laboratory, hematology incl. reticulocytes	X	X												X			X			X		X
Drug and alcohol screen	X	X																			X	X
HBsAg, anti-HCV, and anti-HIV 1/2 tests	X																					
Quantiferon Gold test	X																					
FSH (females only)	X																					
Pregnancy test (females only)	X	X																				X
Overnight fast (10 hours)		X																				
Standardized lunch, snacks, dinner[8]				X																		
High-fat breakfast[9]			X																			
Randomization			X																			

[5] For bioavailability/food effect cohort in fasted Period 1 only
[6] Including a 15 minute supine period prior to every PK sample
[7] In triplicate in 3 supine periods
[8] In Period 1 with Holter monitoring only.
[9] In Period 3 of bioavailability/food effect cohort only

		Period 1 Period 2 (Cohort for Bioavailability and Food Effect Assessment only) Period 3 (Cohort for Bioavailability and Food Effect Assessment only)																				
Visit	**Screening**	**Pre-Treatment**	**Treatment**																			**Follow-up[1]**
Study Days	**-21 to -1**	**-1**	**1**											**2**		**3**	**4**	**5**	**6**	**7**	**9**	**11**
Time Post-Dosing (hrs)			**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**192**	**240**
Study drug administration				X																		
Taste questionnaire				X[10]																		
Previous and concomitant medications	X	X																				
PK sampling blood[11]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection for parent drug and metabolites		X		X									X	X		X	X	X	X	X		
Sampling for ex-vivo IL-17 inhibition in whole blood[12]		X	X			X		X		X			X	X		X		X		X		X
Adverse events				X																		
Serious adverse events	X																					

BMI = body mass index; CYP = cytochrome P450; ECG = electrocardiogram; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hrs = hours; IL-17 = interleukin 17; PK = pharmacokinetic

[10] To be completed immediately after drug administration (within first 10 seconds) and after approximately 1 minute (before drinking the provided glass of water)
[11] Including a 15 minute supine period prior to every PK sample during Holter monitoring
[12] Period 1 only

Table 2 Study Procedural Outline Part B – MAD Healthy Subjects (IM024 005)

Visit	Screening	Pre-Treatment	Treatment																		Follow-up
Study Days	**-21 to -1**	**-1**	**1 14[1]**											**2-13**			**15**	**16**	**18**	**20**	**24**
Time Post-Daily Dose (hrs)[2]			**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**Pre-dose**	**0**	**4**	**24**	**48**	**96**	**144**	**240**
Confinement		X																			
Discharge[3]																		X			
Ambulant visit	X																		X	X	X
Informed consent and medical history	X																				
Demographics	X																				
Physical examination	X																				X
Genotyping (CYPs, transporters)[4]				X																	
Vital signs	X		X			X		X		X		X		X		X	X	X	X	X	X
Body weight and height (including BMI calculation)[5]	X	X																			X
Eligibility check	X	X	X[6]																		
12-lead ECG (triplicate)	X		X			X		X				X				X[7]					X

[1] Schedule for Day 1 (first day of dosing) and Day 14 (last day of dosing).
[2] Time is given relative to dosing on the relevant study day. In the CRF, time "0" will be the time of first dosing and all other time points will be relative to time "0".
[3] Discharge from the clinical research unit.
[4] Mandatory whole blood collection for analysis of DNA variants in ADME-related genes (http://pharmaadme.org/Appendix 6). Sample may be taken at any time post-dose during Day 1; no sample to be taken on Day 14.
[5] Height will only be measured at screening. BMI will also only be calculated at screening.
[6] Not on Day 14.
[7] Days 2, 4, 6, 8, 10, and 12 only.

Visit	Screening	Pre-Treatment	Treatment																	Follow-up
Study Days	**-21 to -1**	**-1**	**1 14[1]**											**2-13**			**15**	**16**	**18**	**20**	**24**
Time Post-Daily Dose (hrs)[2]			**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**Pre-dose**	**0**	**4**	**24**	**48**	**96**	**144**	**240**
Clinical laboratory, hematology incl. reticulocytes	X	X	X[8]											X[9]				X			X
Holter monitoring [10] [11]			X[12]	X																	
Drug and alcohol screen	X	X																	X		X
HBsAg, anti-HCV, and anti-HIV 1/2 tests	X																				
Quantiferon Gold test	X																				
FSH (females only)	X																				
Pregnancy test (females only)	X	X																			X
Randomization			X[13]																		
Overnight fast (10 hours)		X																			
Standardized lunch, snacks, dinner				X																	
Study drug administration				X											X						
Taste questionnaire				X[14]																	
Previous and concomitant medications	X	X																			

[8] Day 14 only.
[9] Days 3, 7, and 10 only.
[10] Including a 15 minute supine period prior to every PK sample.
[11] If upcoming preclinical safety results indicate the need for a dedicated TQTc study, Holter monitoring for this study will be simplified and not plan for concentration-effect modeling.
[12] In triplicate in 3 supine periods.
[13] On Day 1 only.
[14] On Day 1 only. To be completed immediately after drug administration (within first 10 seconds) and after approximately 1 minute (before drinking the provided glass of water).

Visit	Screening	Pre-Treatment	Treatment																	Follow-up
Study Days	**-21 to -1**	**-1**	**1 14[1]**											**2-13**			**15**	**16**	**18**	**20**	**24**
Time Post-Daily Dose (hrs)[2]			**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**Pre-dose**	**0**	**4**	**24**	**48**	**96**	**144**	**240**
PK sampling blood[15]			X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Urine collection for parent drug and metabolites		X		X[16]																	
Sampling for ex-vivo IL-17 inhibition in whole blood		X	X			X		X		X			X	X[17]				X		X	X
Sampling for IL-17, IL-22, β-defensin, and erythropoietin			X														X				X
Sampling for T, B, and NK cells (TBNK), γδ T cells, T cell subsets.			X														X				X
Adverse events				X																	
Serious adverse events	X																				

BMI = body mass index; CYP = cytochrome P450; ECG = electrocardiogram; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hrs = hours; IL-17 = interleukin-17; IL-22 = interleukin-22; NK = natural killer; PK = pharmacokinetic; TBNK = T, B, and NK cells

[15] Including a 15 minute supine period prior to every PK sample during Holter monitoring.
[16] 24-hours urine collection on Day 14 only
[17] Pre-dose at Days 2, 4 and 7 only.

Table 3 Study Procedural Outline Part C – MAD Psoriasis Patients – Intensive PK Sampling Sub-Cohort (IM024 005)

Visit	Screening	Pre-Treatment	Treatment													Follow-up
Study Days	**-21 to -1**	**-1 13**	**1 14**											**2**	**7**	**15**	**28**
Time post daily dose (hrs)[1]			**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**				
Confinement		X															
Discharge[2]														X		X	
Ambulant visit	X														X		X
Informed consent and medical history	X																
Demographics	X																
Physical examination	X																X
Genotyping (CYPs, transporters)			X														
Vital signs	X		X			X		X		X		X		X	X	X	X
Body weight and height (including BMI calculation)[3]	X	X[4]															X
Eligibility check	X	X[2]	X[5]														
12-lead ECG	X	X				X				X							X
Clinical laboratory, hematology incl. reticulocytes	X	X												X		X	X
Drug and alcohol screen	X	X															X
HBsAg, anti-HCV, and anti-HIV 1/2 tests	X																

[1] Time is given relative to dosing on the relevant study day. In the CRF, time "0" will be the time of first dosing and all other time points will be relative to time "0"
[2] Discharge from the clinical research unit.
[3] Height will only be measured at screening. BMI will also only be calculated at screening.
[4] Only on Day -1
[5] Only on Day 1

Visit	Screening	Pre-Treatment	Treatment														Follow-up
Study Days	**-21 to -1**	**-1 13**	**1 14**											**2**	**7**	**15**	**28**
Time post daily dose (hrs)[1]			**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**				
Quantiferon Gold test	X																
FSH (females only)	X																
Pregnancy test (females only)	X	X															X
Randomization			X														
Overnight fast (10 hours)		X															
Study drug administration[6]		X[7]		X										X			
Previous and concomitant medications	X	X															
PK sampling blood			X		X	X	X	X	X	X	X	X	X	X[8]	X[8]	X	X
Sampling for ex-vivo IL-17 inhibition in whole blood		X	X			X		X		X			X	X		X	X
Sampling for IL-17, IL-22,β-defensin, and erythropoietin			X												X		X
Sampling for T, B, and NK cells (TBNK), γδ T cells, T cell subsets.			X												X		X
Plaque biopsy for immunochemistry and RNA analysis		X[9]								X[10]							
Psoriasis affected body area	X	X															
Psoriasis Area and Severity Index (PASI) score			X												X		X

[6] Study drug will be administered in the clinical research unit on Days 1, 2, 7, and 14. On Days 3-6 and 8-13, subjects will take the study drug at home.
[7] Day 13 only
[8] Pre-dose
[9] Day -1 only
[10] Day 14 only

Visit	Screening	Pre-Treatment	Treatment													Follow-up
Study Days	**-21 to -1**	**-1 13**	**1 14**										**2**	**7**	**15**	**28**
Time post daily dose (hrs)[1]			**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**				
Physician Global Assessment (PGA) score			X												X		X
Dermatology Life Quality Index (DLQI)			X												X		X
Adverse events	X			X													
Serious adverse events	X																

BMI = body mass index; CYP = cytochrome P450; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hrs = hours; IL-17 = interleukin-17; IL-22 = interleukin-22; NK = natural killer; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; PK = pharmacokinetic; TBNK = T, B, and NK cells

Table 4 Study Procedural Outline Part C – MAD Psoriasis Patients – Sparse PK Sampling Sub-Cohort (IM024 005)

Visit	Screening	Pre-Treatment	Treatment			Follow-up
Study Days	**-21 to -1**	**1**	**1**	**7**	**14**	**28**
Ambulant visit	X	X	X	X	X	X
Informed consent and medical history	X					
Demographics	X					
Physical examination	X					X
Genotyping (CYPs, transporters)		X				
Vital signs	X	X		X	X	X
Body weight and height (including BMI calculation)[1]	X	X				X
Eligibility check	X	X				
12-lead ECG	X	X			X	X
Clinical laboratory, hematology incl. reticulocytes	X	X			X	X
Drug and alcohol screen	X	X			X	X
HBsAg, anti-HCV, and anti-HIV 1/2 tests	X					
Quantiferon Gold test	X					
FSH (females only)	X					
Pregnancy test (females only)	X	X				X
Randomization		X				
Study drug administration[2]			X			
Previous and concomitant medications	X	X				
PK sampling blood[3]		X		X	X	
Sampling for ex-vivo IL-17 inhibition in whole blood		X		X	X	X
Sampling for IL-17, IL-22, β-defensin, and erythropoietin		X		X	X	X
Sampling for T, B, and NK cell (TBNK), γδ T cells, T cell subsets.		X		X	X	X
Plaque biopsy for immunochemistry and RNA analysis		X			X	
Psoriasis affected body area	X	X				
Psoriasis Area and Severity Index (PASI) score		X		X	X	X

[1] Height will only be measured at screening. BMI will also only be calculated at screening.
[2] Study drug will be administered in the clinical research unit on Days 1, 7, and 14. On Days 2-6 and 8-13, subjects will take the study drug at home.
[3] Pre-dose PK blood sampling on Days 1, 7 and 14

Visit	Screening	Pre-Treatment	Treatment			Follow-up
Study Days	**-21 to -1**	**1**	**1**	**7**	**14**	**28**
Physician Global Assessment (PGA) score		X		X	X	X
Dermatology Life Quality Index (DLQI)		X		X	X	X
Adverse events			X			
Serious adverse events	X					

BMI = body mass index; CYP = cytochrome P450; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hrs = hours; IL-17 = interleukin-17; IL-22 = interleukin-22; NK = natural killer; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; PK = pharmacokinetic; TBNK = T, B, and NK cells

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
A	active
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BA	bioavailability
BCRP	Breast Cancer Resistance Protein
BMI	body mass index
BMS	Bristol-Myers Squibb
BSEP	bile salt export pump
CFR	Code of Federal Regulations
CL_{CR}	creatinine clearance
CLT_p	total plasma clearance
CONSORT	Consolidated Standards of Reporting Trials
CRO	contract research organization
CRU	clinical research unit
CTD	Clinical Trial Directive
CV	coefficient of variation
CYP	cytochrome P450
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
EC_{50}	concentration at which 50% effect is observed
ECG	electrocardiogram
eCRF	electronic case report form
EDS	Early Development Services
EU	European Union
FDA	Food and Drug Administration
FE	food effect
FIH	first in human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
hPBMCs	human peripheral blood mononuclear cells
hsCRP	high sensitivity C-reactive protein

HRT	hormone replacement therapy
HV	healthy volunteers
IB	Investigator's Brochure
IC_{50}	concentration at which 50% inhibition is observed
IC_{90}	concentration at which 90% inhibition is observed
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
IMP	investigational medicinal product
IP	investigational product
LC-MS/MS	liquid chromatography tandem mass spectometry
LDL	low-density lipoprotein
LDH	lactate dehydrogenase
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MRP	multi drug-resistance protein
MRSD	maximum recommended starting dose
N	number
NK	natural killer cells
NOAEL	no observed adverse effect level
NTCP	sodium-taurocholate cotransporting polypeptide
OATP	organic-anion transporting polypeptide
OCT	organic cation transporter
OTC	over-the-counter
P	placebo
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
P-gp	P-glycoprotein
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
PO	per os (oral)
QD	once daily
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard of deviation
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis

TBNK	T, B, and NK cells
TNF	tumor necrosis factor
UGT	uridine diphosphate-glucuronyltransferase
ULN	upper limit of normal
US(A)	United States (of America)
Vss	volume of distribution at steady state
WOCBP	women of childbearing potential

Definitions of PK parameters to be calculated in this study are provided in Section 8.5.3.
Definitions of PD parameters to be calculated in this study are provided in Section 8.5.4.

4. ETHICS

4.1 Ethics Committee

This study will be conducted in compliance with Independent Ethics Committee (IEC) and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and in accordance with applicable regulations regarding clinical safety data management (E2A, E2B[R3]) and scientific integrity (E4, E8, E9, and E10). In addition, this study will adhere to all local regulatory requirements, and requirements for data protection.

Before initiating a study, the Investigator must obtain written and dated approval from the IEC for the study protocol, written informed consent form (ICF), participant recruitment procedures (eg, advertisements), written information to be provided to participants, and a statement from the IEC that these comply with GCP requirements. The approval must identify the protocol version as well as the documents reviewed.

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with the European Union (EU) Clinical Trial Directive (CTD) (Directive 2001/20/EC), the Note for Guidance on GCP (ICH Harmonised Tripartite Guideline E6 [R1]; United States (US) Food and Drug Administration [FDA] Code of Federal Regulations [CFR] [21 CFR Parts 50, 56, and 312]), Declaration of Helsinki (Seoul 2008), and all applicable regulatory requirements.

4.3 Subject Information and Consent

The Investigator will explain the benefits and risks of participation in the study to each subject in language readily understood by the subject. Written informed consent must be obtained before the subject enters the study and before any study-specific procedures are performed. If important new information becomes available requiring revisions to the ICF, the IEC-approved revised form will be used for re-consent of all subjects.

7. STUDY OBJECTIVES

7.1 Study Objectives

7.1.1 Primary Study Objective

- To evaluate the safety, tolerability and PK of escalating single and multiple ascending doses of BMS-986251 in healthy subjects, and of multiple doses of BMS-986251 in patients with moderate-to-severe psoriasis.

7.1.2 Secondary Study Objectives

- To evaluate the PD of escalating single and multiple ascending doses of BMS-986251 in healthy subjects, and of multiple doses of BMS-986251 in patients with moderate-to-severe psoriasis.
- To evaluate the oral BA of an oral suspension of BMS-986251 relative to a liquid dosage form at a single dose level in healthy subjects.
- To evaluate the effect of a high-fat meal on the PK of an oral suspension of BMS-986251 at a single dose level in healthy subjects.
- To explore clinical effects of multiple doses of BMS-986251 in patients with moderate-to-severe psoriasis.

8. INVESTIGATIONAL PLAN

8.1 Overall Study Design

This is a double-blind, placebo-controlled, randomized SAD and MAD study in 3 parts in approximately 103 participants: 88 healthy subjects and 15 patients with psoriasis. The present study is designed to evaluate the safety and tolerability, PK, PD and efficacy of BMS-986251. Part A and B will enroll healthy subjects and will be conducted at a single site. Part C will enroll patients with psoriasis and will be conducted as a multi-center study in multiple countries.

Part A will be an SAD study in a planned number of 6 sequential cohorts of 8 healthy subjects (6 active + 2 placebo) each, receiving single escalating oral doses of BMS-986251. In the 1st cohort, sentinel dosing will be employed (1 active + 1 placebo, followed after 72 hours by the remaining subjects of the 1st cohort [5 active + 1 placebo]). In addition to the 6 ascending dose cohorts, a cohort of 8 healthy subjects (8 active) will be included to assess the relative BA of an oral suspension (under development; representative for the solid dosage form to be used in Part C) compared to the solution formulation, and to evaluate the effect of food on the BA of the oral suspension in a 3-period sequential design (BA/FE cohort).

Part B will be a MAD study in a planned number of 4 sequential cohorts of 8 healthy subjects (6 active + 2 placebo) each, receiving daily oral doses of escalating BMS-986251 for 2 weeks.

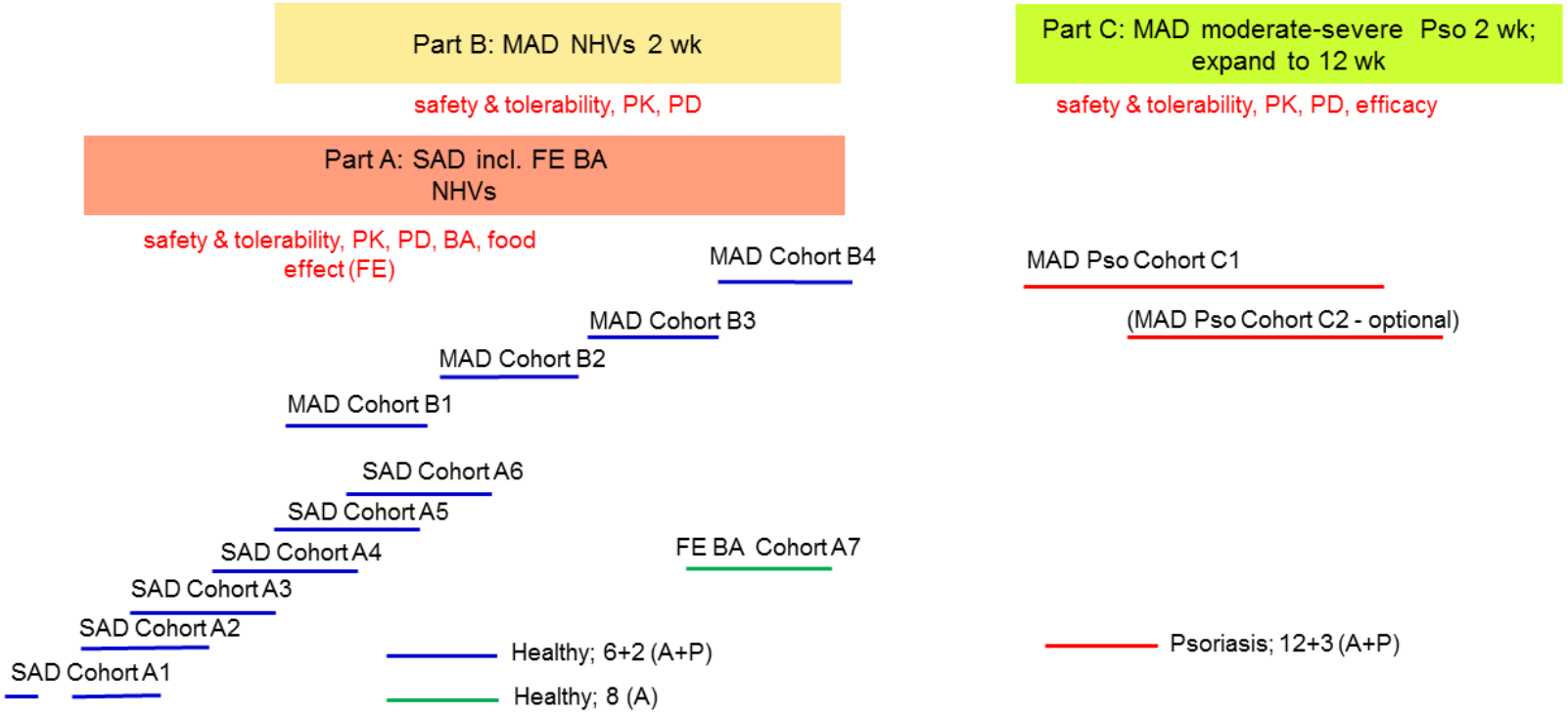
Part C will be a multiple dose part in one cohort of 15 patients with moderate-to-severe psoriasis (12 active + 3 placebo), treated for 2 weeks, with a potential extension to 12 weeks by protocol amendment. Per protocol amendment, this study part may be extended with further cohorts, receiving lower repeated BMS-986251 doses than Cohort C1. A decision to extend the study with (a) lower-dosed cohort(s) will be based on the efficacy/safety balance of the 1st patient cohort. A high therapeutic response or, alternatively, poor safety or tolerability observed in the 1st patient cohort may be the basis to amend the study protocol for extension to a lower dosed cohort.

An overview of the study is provided in Figure 1.

Any study part may be extended with further cohorts of healthy subjects or patients by protocol amendment, when justified by data generated in the study.

This study may be extended by protocol amendment with a study part bridging safety, tolerability and PK of BMS-986251 from the current study population to Japanese subjects.

Figure 1 Study Design Schematic



A = active; BA = bioavailability; FE = food effect; MAD = multiple ascending dose; NHV = healthy volunteers; P = placebo; PD = pharmacodynamics; PK = pharmacokinetics; Pso = psoriasis; SAD = single ascending dose; wk = week

Note: SAD Cohort A1 will have a sentinel dosing design with 2 subjects (1 active and 1 placebo) dosed 72 hours prior to the remaining subjects in the cohort.

Subjects will undergo screening evaluations to determine eligibility within 21 days prior to (first) administration of study drug.

In all study parts, physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations will be performed at selected times throughout the study (see Section 1). In addition, Holter monitoring will be performed for the first 24 hours post-dose in Parts A (Day 1) and B (Day 1 and Day 14). Subjects will be closely monitored for AEs throughout the study. In all study parts, blood and urine samples (urine in Part A and B only) will be collected for PK analysis and blood samples will be collected for PD analyses. In Part C, plaque biopsies will be taken at selected times for exploratory PD analysis. Preliminary efficacy assessments will be performed in Part C as well.

8.1.1 Part A SAD, Healthy Volunteers

Subjects will be admitted to the clinical research unit (CRU) on the day prior to (first) drug administration (Day -1). Following drug administration of a single dose of BMS-986251 on Day 1, they will remain in the CRU for close observation until discharge from the CRU on Day 7 (144 hours post-dose). Subjects will return for ambulatory assessments on Days 9 and 11, including follow-up assessments on Day 11.

Subjects enrolled in the BA/FE cohort will return to the CRU for a 2nd and 3rd study period. Washout between single dose administrations will be at least 2 weeks, based on an anticipated terminal half-life of BMS-986251 of approximately 40 hours. The design of the 2nd and 3rd study period is the same as the first period, with a mandatory in-clinic stay from Day -1 to Day 7 and ambulatory visits on Days 9 and 11. Subjects will be dosed on Day 1 of each period. Follow-up assessments will be performed on Day 11 of Period 3 only; on Day 11 of Period 1 and 2 limited assessments including blood sampling for PK and PD (PD only in Period 1) will be performed. Please refer to the procedural outline in Table 1 to see which assessments are to be performed at each visit.

The planned single dose treatments are provided in Table 6. Eight healthy subjects will be assigned to each of 6 planned SAD cohorts and the BA/FE cohort. Subjects will be randomized within each of the SAD cohorts to receive a single oral dose of BMS-986251 or a matched placebo in a ratio of 3:1. All subjects in the BA/FE cohort will receive BMS-986251. In the first SAD cohort, sentinel dosing will be employed (see Section 8.1).

Within each cohort, safety, tolerability, PK, and PD assessments will be performed at predefined time points. Following completion of each dose cohort there will be a review of blinded study data prior to dose escalation by the Sponsor's dose escalation review group. This group will include the Investigator, PRA Medical Monitor, the BMS Study Director, and additional personnel as deemed necessary by the Sponsor (such as a pharmacokineticist). SAD dose escalation decisions will be based on the safety, tolerability and PK results of the ongoing cohort up to and including Day 7, and on the PD results up to and including Day 5. Medication administration in the next dose cohort will not start until at least 6 subjects have been dosed in the previous dose cohort and the data have been reviewed. The dose escalation

review group will determine whether escalation to the next dose level will occur or whether dose-stopping criteria (presented in Section 8.3.5.5) have been met.

As new safety and/or PK data become available, the dose-escalation scheme may change. Subjects in subsequent dose cohorts may not receive a subsequent higher dose as outlined, but may instead be administered a lower dose than originally planned, repeat a lower dose level, or repeat the same dose of the study drug.

Table 6 IM024 005; Part A Dose Cohorts

Cohort	Number of Subjects (Active / Placebo)	Period	Dose of BMS-986251	Fasted / Fed	Formulation
A1	1 / 1 (sentinel group)	1	2 mg	Fasted	Oral solution
	5 / 1	1	2 mg	Fasted	Oral solution
A2	6 / 2	1	6 mg	Fasted	Oral solution
A3	6 / 2	1	15 mg	Fasted	Oral solution
A4	6 / 2	1	30 mg	Fasted	Oral solution
A5	6 / 2	1	60 mg	Fasted	Oral solution
A6	6 / 2	1	120 mg	Fasted	Oral solution
A7 (BA/FE)	8	1	tbd	Fasted	Oral solution
		2	tbd	Fasted	Oral suspension (under development)
		3	tbd	Fed	Oral suspension (under development)

BA = bioavailability; FE = food effect; tbd = to be determined
Doses may be adjusted based on data obtained in previous cohorts.

8.1.2 Part B MAD, Healthy Volunteers

Part B will be initiated after thorough review of safety, tolerability, PK and PD data from at least the SAD Cohorts A1 up to A4 from Part A.

Subjects enrolled in Part B of the study will be admitted to the CRU on the day prior to first drug administration (Day -1). Subjects will be dosed with BMS-986251 on Days 1-14. During treatment they will remain in the CRU for close observation. Subjects will be discharged on Day 16 (48 hours after the last dose). Subjects will return for ambulatory assessments on Days 18, 20, and 24, including follow-up assessments on Day 24.

The planned multiple dose treatments are provided in Table 7. Eight healthy subjects will be assigned to each of 4 planned dose cohorts. Subjects will be randomized within each dose cohort to receive multiple oral doses of BMS-986251 or a matched placebo in a ratio of 3:1.

Within each cohort, safety, tolerability, PK, and PD assessments will be performed at predefined time points. Following completion of dosing for each MAD dose cohort there will be a short period to review the data and inform dose escalation by the Sponsor's dose escalation review group. MAD dose escalation decisions will be based on the blinded safety, tolerability, PK and PD of the ongoing cohort up to and including Day 14. Ongoing review of SAD safety, tolerability, PK and PD data will also be considered for dose-escalation in

Part B. The dose escalation review group will determine whether escalation to the next dose level will occur or whether dose-stopping criteria (presented in Section 8.3.5.5) have been met.

As new safety and/or PK data become available, the dose-escalation scheme may change. Subjects in subsequent dose cohorts may not receive a subsequent higher dose as outlined, but may instead be administered a lower dose than originally planned, repeat a lower dose level, or repeat the same dose of the study drug.

Table 7 IM024 005; Part B Dose Cohorts

Cohort	Subjects (Active / Placebo)	Dose of BMS-986251	Duration	Fasted/Fed	Formulation
B1	6 / 2	6 mg QD	14 days	Fasted	Oral solution
B2	6 / 2	tbd QD	14 days	Fasted	Oral solution
B3	6 / 2	tbd QD	14 days	Fasted	Oral solution
B4	6 / 2	60 mg QD	14 days	Fasted	Oral solution

QD = once daily; tbd = to be determined upon reviewed data
Doses may be adjusted based on data obtained in previous cohorts.

8.1.3 Part C, Multiple Dose in Psoriasis Patients

Part C will be initiated after thorough review of safety, tolerability, PK and PD data (as available) from Part A and Part B, and after verification that administration of BMS-986251 is safe and tolerable enough to administer in psoriasis patients.

In Part C, a total of 15 patients with moderate-to-severe psoriasis will be enrolled in 2 sub-cohorts: 1 sub-cohort with intensive PK sampling and 1 sub-cohort with sparse PK sampling.

At least 6 patients will be enrolled in the sub-cohort with intensive PK sampling. The patients enrolled in this cohort will be admitted to the CRU on the day prior to first drug administration (Day -1). Patients will be dosed with the first dose of BMS-986251 on Day 1 and will be discharged on Day 2 after intake of the 2nd dose. Between Day 3 and Day 12, the patients will take the medication once daily (QD) at home, except on Day 7. Treatment compliance information will be collected while subject is dosing at-home via dosing diaries. Patients will return to the CRU for an ambulatory visit on Day 7 and will be instructed not to take their morning dose at home, but instead bring their study drug and dosing diaries to the CRU for administration following pre-dose procedures. Should compliance be lower than expected, subjects will be counselled on dose administration. Patients will be re-admitted to the CRU for a second stay on Day 13. Subjects will receive their final dose on Day 14. They will be discharged on Day 15 (24 hours after intake of the last dose). Follow-up assessments will be on Day 28.

Patients who are not available for 2 in-clinic periods will be enrolled in the sub-cohort with sparse PK sampling. These patients will visit the CRU for ambulatory assessments on Day 1 in the morning (first dose) and on Days 7, 14, and 28, with follow-up assessments on Day 28. On Day 1 they will receive the first dose in the CRU. In addition, on Days 7 and 14 the patients will also receive their doses in the CRU. The remaining doses between Days 2-6 and

8-13 will be taken at home. Treatment compliance information will be collected while subject is dosing at-home via dosing diaries.

The planned multiple dose treatment in patients with moderate-to-severe psoriasis is provided in Table 8. A total of 15 patients will be enrolled in one planned dose cohort. Subjects will be randomized to receive multiple oral doses of BMS-986251 or a matched placebo in a ratio of 4:1. The intended dosage form for patients is a tablet formulation, which is currently under development. The final selection of the dose will be made by the Sponsor's dose escalation review group and will be based on the safety, tolerability, PK and PD results of Part A and Part B.

Per protocol amendment the treatment duration may be extended to 12 weeks. Also per protocol amendment, Part C of this study may be extended with further cohorts, receiving lower repeated BMS-986251 dosed than the first cohort. A decision to extend the study with (a) lower-dosed cohort(s) will be based on the preliminary efficacy/safety balance of the 1st patient cohort. A high therapeutic response or, alternatively, poor safety or tolerability observed in the 1st patient cohort may be the basis to amend the study protocol for extension to a lower dosed cohort.

Table 8 IM024 005; Part C Dose Cohort

Cohort	Subjects (Active / Placebo)	Dose of BMS-986251	Duration	Fasted/Fed	Formulation
C1	12 / 3	60 mg QD	14 days	tbd	Oral tablet

QD = once daily; tbd = to be determined upon reviewed data
Dose may be adjusted based on data obtained in previous study parts.

8.2 End of Study Definition

The start of the study is defined as the first visit for first subject screening. The end of the study is defined as the last visit or scheduled procedure shown in the Schedule of Activities (Section 1) for the last subject. Subjects who withdraw early from the study will be requested to complete the study discharge evaluations.

8.3 Study Population

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects. It is imperative that subjects fully meet all eligibility criteria as all arms of the study will be conducted under a "no-waiver" policy.

All screening 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.

To be eligible for the study, subjects must meet the criteria in Sections 8.3.1 and 8.3.2.

8.3.1 Inclusion Criteria

8.3.1.1 Healthy Subjects (Part A and B)

1. Subjects must be willing and able to participate in the study, sign the ICF, and complete all study-specific procedures and visits.
2. Males and females, ages 18 to 55 years, inclusive, at screening.
3. Healthy subjects, as determined by no clinically significant deviations from normal in medical history, physical examination, 12-lead ECGs, vital signs, and clinical laboratory results.
4. Body mass index (BMI) of 18.0 to 30.0 kg/m^2, inclusive, at screening.
   BMI = weight (kg)/height $(m)^2$.
5. Body weight between 55 and 105 kg, inclusive, at screening.
6. Females that meet one of the following:
    a. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test at screening and prior to the start of investigational product (IP) and must agree to follow instructions for method(s) of contraception (Appendix 3) for the duration of the study and a minimum of 3 months after dosing has been completed.
    b. Premenopausal female with 1 of the following:
        i. Documented hysterectomy
        ii. Documented bilateral salpingectomy
        iii. Documented bilateral oophorectomy
        iv. Sexual abstinence as preferred or usual lifestyle of the subject.
    c. Postmenopausal women (12 months or more amenorrhea and over 45 years of age in the absence of other biological or physiological causes). Females under 55 years of age require follicle stimulating hormone (FSH) >40 mIU/mL at screening
7. Women must not be breastfeeding.
8. Males that meet one of the following:
    a. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 3) for the duration of the study and a minimum of 3 months after dosing has been completed. In addition, male subjects must be willing to refrain from sperm donation during this time.
    b. Vasectomized males are exempt from contraceptive requirements.

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.

8.3.1.2 Psoriasis Patients (Part C)

1. Subjects must be willing and able to participate in the study and sign the ICF, and be willing and able to complete all study-specific procedures and visits.
2. Males and females, ages 18 to 70 years, inclusive, at screening.
3. BMI of 18.0 to 35.0 kg/m^2, inclusive, at screening. BMI = weight (kg)/height m^2.
4. Body weight between 55 and 120 kg, inclusive, at screening.

5. Diagnosed with stable chronic plaque psoriasis, for at least 6 months prior to screening and be candidates for either photo-therapy or systemic treatment.
6. Moderate-to-severe intensity of psoriasis as defined by:
    a. Affected body surface area (BSA) of ≥10%.
    b. Psoriasis Area and Severity Index (PASI) ≥12.
    c. Physician Global Assessment (PGA; 6-point scale) ≥3.
7. No clinically significant deviations from normal in medical history, physical examination, 12-lead ECGs, vital signs, and clinical laboratory results, other than abnormalities expected for this patient population, as judged by the Investigator.
8. Females that meet one of the following:
    a. WOCBP must have a negative serum or urine pregnancy test at screening and prior to the start of IP and must agree to follow instructions for method(s) of contraception (Appendix 3) for the duration of the study and a minimum of 3 months after dosing has been completed.
    b. Premenopausal female with 1 of the following:
        i. Documented hysterectomy.
        ii. Documented bilateral salpingectomy.
        iii. Documented bilateral oophorectomy.
        iv. Sexual abstinence as preferred or usual lifestyle of the subject.
    c. Postmenopausal women (12 months or more amenorrhea and over 45 years of age in the absence of other biological or physiological causes). Females under 55 years of age require FSH >40 mIU/mL at screening
9. Women must not be breastfeeding.
10. Males that meet one of the following:
    a. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 3) for the duration of the study and a minimum of 3 months after dosing has been completed. In addition, male subjects must be willing to refrain from sperm donation during this time.
    b. Vasectomized males are exempt from contraceptive requirements.

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.

8.3.2 Exclusion Criteria

8.3.2.1 Healthy Subjects (Part A and B)

1. Previous participation in the current study.
2. Participation in a drug study or exposure to any investigational drug or placebo within 2 months prior to (the first) drug administration in the current study. Participation in more than 4 other drug studies in the 12 months prior to (the first) drug administration in the current study.
3. Employees of PRA or the Sponsor and their relatives.
4. Any significant acute or chronic medical condition that presents a potential risk to the subject and/or that may compromise the objectives of the study, including active, or history of, liver disease, or intestinal disorder including irritable bowel syndrome.

5. Current or recent (within 3 months of study treatment administration) gastrointestinal disease that could affect pharmacokinetics; history of cholecystectomy is not allowed.
6. Major surgery within 4 weeks of (first) study treatment administration.
7. History or presence of malignancy including hematological malignancies; subjects with a history of basal cell or squamous cell carcinoma that has been treated with no evidence of recurrence will be allowed for inclusion, as judged by the Investigator.
8. Documented congenital QT syndrome, and/or corrected QT interval (Fridericia correction) at screening or first admission >450 ms.
9. Donation or loss of more than 100 mL of blood within 2 months prior to (the first) drug administration. Donation or loss of more than 1.5 L of blood (for male subjects)/more than 1.0 L of blood (for female subjects) in the 10 months prior to (the first) drug administration in the current study.
10. Inability to be venipunctured and/or tolerate venous access.
11. Subjects who have smoked or used smoking cessation or nicotine containing products (including, but not limited, to e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum, varenicline, bupropion) within 6 months of the first dose of study drug.
12. Abuse or drug addiction (including cannabis products) within one year before screening (Appendix 4).
13. Average intake of more than 24 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine or 35 mL of spirits).
14. Positive drug and alcohol screen (opiates, methadone, cocaine, amphetamines [including ecstasy], cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants and alcohol) at screening or admission to the CRU.
15. Consumption of caffeine or xanthine-containing food or beverages from at least 72 hours prior to admission to the CRU until at least 24 hours after last drug administration.
16. Consumption of any nutrients known to modulate CYP enzymes activity (eg, grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products) within 14 days prior to first administration of study drug until after discharge in the last treatment period.
17. Positive blood screen for hepatitis C antibody, hepatitis B surface antigen (HBsAg), or HIV-1 or -2 antibodies.
18. History of any significant drug and/or food allergies (such as anaphylaxis or hepatotoxicity).
19. Use of any prescription drugs within 4 weeks prior to study drug administration except those medications cleared by the Investigator and PRA Medical Monitor.
20. Use of over-counter (OTC) medications and herbal preparations within 2 weeks prior to study drug administration, except those medications cleared by the Investigator and PRA Medical Monitor.
21. Any history or risk for tuberculosis (TB), specifically subjects with: 1) current clinical, radiographic or laboratory evidence of active TB; 2) history of active TB; 3) positive Quantiferon® test result and history of latent TB, unless subject has documentation of completion of anti-TB treatment.

22. Known or suspected autoimmune disorder, or any history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the subject's immune status (eg, history of splenectomy).
23. Presence of any factors that would predispose the subject to develop infection eg, bronchial asthma, rectal fissures, poor dentition, open skin lesions, and presence of pre-existing skin conditions eg, Behcet's Disease, psoriasis, pustular dermatoses.
24. Any serious (eg, requiring intramuscular or IV antibiotics and/or hospitalization) acute or chronic bacterial, viral or fungal infection (eg, pneumonia, septicemia) within the 3 months prior to screening.
25. Active herpes infection, including herpes simplex 1 and 2 and herpes zoster within 2 months of administration of study medication.
26. History of malaria.
27. History or any evidence of active infection or febrile illness within 7 days of dosing (eg, bronchopulmonary, urinary, or gastrointestinal).
28. History of recurrent or chronic sinusitis, bronchitis, pneumonia, urinary tract infection (recurrent or chronic urinary tract infection is 2 episodes within 6 months).
29. Immunization with live vaccines or live-attenuated within 2 months prior to Day 1.
30. Inability to comply with protocol procedures, assessments, restrictions, and prohibited treatments.
31. Legal incapacity or limited legal capacity.

8.3.2.2 Psoriasis Patients (Part C)

1. Previous participation in the current study.
2. Participation in a drug study or exposure to any investigational drug or placebo within 2 months prior to (the first) drug administration in the current study.
3. Employees of PRA or the Sponsor and their relatives.
4. Any significant acute or chronic medical condition that presents a potential risk to the subject and/or that may compromise the objectives of the study, including active, or history of, liver disease, or intestinal disorder including irritable bowel syndrome.
5. Current or recent (within 3 months of study treatment administration) gastrointestinal disease that could affect pharmacokinetics; history of cholecystectomy is not allowed.
6. Major surgery within 4 weeks of (first) study treatment administration.
7. History or presence of malignancy including hematological malignancies; subjects with a history of basal cell or squamous cell carcinoma that has been treated with no evidence of recurrence will be allowed for inclusion, as judged by the Investigator.
8. Documented congenital QT syndrome, and/or corrected QT interval (Fridericia correction) at screening or first admission >450 ms.
9. Uncontrolled treated/untreated hypertension (defined as a mean of 3 repeated measurements for systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 105 mmHg); current or documented history of repeated clinically significant hypotension or severe episodes of orthostatic hypotension (systolic blood pressure < 90 mmHg and/or diastolic blood pressure < 50 mmHg).
10. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory results beyond what is consistent with the target population, including any of the following laboratory exclusion criteria:

a. Leukopenia defined as absolute WBC count < 3000/mm^3 within 28 days of dosing with study drug on Day 1
b. Lymphopenia defined as absolute lymphocyte count < 500/mm^3 within 28 days of dosing with study drug on Day 1
c. Neutropenia defined as absolute neutrophil count < 1000/mm^3 within 28 days of dosing with study drug on Day 1
d. Moderate to severe thrombocytopenia defined as platelet count < 100,000/mm^3 within 28 days of dosing with study drug on Day 1
e. Moderate to severe anemia defined as hemoglobin < 9 g/dL within 28 days of dosing with study drug on Day 1
f. ALT and/or AST > 3X ULN within 28 days of dosing with study drug on Day 1
g. Total, unconjugated, and/or conjugated bilirubin > 2X ULN within 28 days of dosing with study drug on Day 1

11. Donation or loss of more than 100 mL of blood within 2 months prior to (the first) drug administration. Donation or loss of more than 1.5 L of blood (for male subjects)/more than 1.0 L of blood (for female subjects) in the 10 months prior to (the first) drug administration in the current study.
12. Inability to be venipunctured and/or tolerate venous access.
13. Subjects who have smoked or used smoking cessation or nicotine containing products (including, but not limited, to e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum, varenicline, bupropion) within 6 months of the first dose of study drug.
14. Abuse or drug addiction (including cannabis products) within one year before screening (Appendix 4).
15. Average intake of more than 24 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine or 35 mL of spirits).
16. Positive drug and alcohol screen (opiates, methadone, cocaine, amphetamines [including ecstasy], cannabinoids, barbiturates, benzodiazepines [if not prescribed or otherwise medically indicated, eg for anxiety, insomnia etc., and properly documented in concomitant medication], and alcohol) at screening or admission to the CRU.
17. Consumption of caffeine or xanthine-containing food or beverages from at least 72 hours prior to admission to the CRU and during the stays at the CRU.
18. Consumption of any nutrients known to modulate CYP enzymes activity (eg, grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products) within 14 days prior to first administration of study drug until after discharge in the last treatment period.
19. Subjects diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at the time of the screening visit (eg, eczema) that would interfere with evaluations of the effect of IP on psoriasis.
20. Treatment with experimental or commercially available biological agents such as, but not limited to, etanercept, adalimumab, infliximab, certolizumab pegol within 3 months prior to Day 1.
21. Systemic immunosuppressants (such as, but not limited to, methotrexate, cyclosporine A, mycophenolate, tacrolimus, azathioprine, 6-thiguanine, mercaptopurine

and hydroxyurea), corticosteroids, or phototherapy (UV A light therapy [with or without psoralen], UV B light therapy, or excimer laser) within 1 month prior to Day 1.
22. Topical corticosteroid treatment other than low-strength or lower-mid strength corticosteroids on the face, scalp, axillae, and/or groin within 2 weeks prior to Day 1.
23. Concomitant medications (prescription, OTC, or herbal) outside the stable standard of care regimens for psoriasis administered during the study unless prescribed by the Investigator for treatment of specific clinical events.
24. Positive blood screen for hepatitis C antibody, HBsAg, or HIV-1 or -2 antibodies.
25. History of any significant drug and/or food allergies (such as anaphylaxis or hepatotoxicity).
26. Use of any prescription drugs within 4 weeks prior to study drug administration except those medications cleared by the Investigator and PRA Medical Monitor.
27. Use of OTC medications and herbal preparations within 2 weeks prior to study drug administration, except those medications cleared by the Investigator and PRA Medical Monitor.
28. Concomitant medications that are strong inhibitors or inducers of CYP3A4 or transporters administered within 2 weeks or 5 half-lives, whichever is longer, prior to the start of the study and throughout the study. Patients on stable standard of care medications that are moderate inhibitors or inducers of CYP3A4 or transporters will be cleared for use by the Investigator and PRA Medical Monitor. For guidance, please refer to http://medicine.iupui.edu/clinpharm/ddis/clinical-table or https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm
29. Any history or risk for TB, specifically subjects with: 1) current clinical, radiographic or laboratory evidence of active TB; 2) history of active TB; 3) positive Quantiferon® test result and history of latent TB, unless subject has documentation of completion of anti-TB treatment.
30. Known or suspected autoimmune disorder, except psoriasis, or any history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the subject's immune status (eg, history of splenectomy or diabetes).
31. Presence of any factors that would predispose the subject to develop infection eg, bronchial asthma, rectal fissures, poor dentition.
32. Any serious (eg, requiring intramuscular or IV antibiotics and/or hospitalization) acute or chronic bacterial, viral, or fungal infection (eg, pneumonia, septicemia) within the 3 months prior to screening.
33. Active herpes infection, including herpes simplex 1 and 2 and herpes zoster within 2 months of administration of study medication.
34. History of malaria.
35. History or any evidence of active infection or febrile illness within 14 days of dosing (eg, bronchopulmonary, urinary, or gastrointestinal).
36. History of recurrent or chronic sinusitis, bronchitis, pneumonia, urinary tract infection (recurrent or chronic urinary tract infection is 2 episodes within 6 months).
37. Immunization with live vaccines or live-attenuated within 2 months prior to Day 1.
38. Inability to comply with protocol procedures, assessments, restrictions, and prohibited treatments.
39. Legal incapacity or limited legal capacity.

8.3.3 Lifestyle Restrictions

1. Subjects are to refrain from strenuous exercise and contact sports from 96 hours prior to screening, admission, and for the duration of the study as this could result in abnormal clinical laboratory values.
2. Subjects are not permitted to consume alcohol-containing beverages from 72 hours prior to (first) admission to the CRU until completion of all follow-up visits at study discharge (Part A and B) and from 72 hours prior to each visit to the CRU and during the stays in the CRU (Part C).
3. Subjects are not permitted to consume caffeine-containing food or beverages from 72 hours prior to admission to the CRU until 24 hours after the last dose (Part A and B), and from 72 hours prior to admission to the CRU and during the stays in the CRU (Part C).
4. Subjects are not permitted to consume any nutrients known to modulate CYP enzymes activity (eg, grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products) within 14 days prior to first administration of study drug until after discharge in the last treatment period.
5. Subjects are not allowed to smoke or use smoking cessation or nicotine containing products (including, but not limited to, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum, varenicline, bupropion) within 6 months of the first dose of study until after discharge in the last treatment period.
6. Subjects are required to fast overnight with an additional 4 hours of fasting post-dose on the following study days: Day 1 (Part A), Day 1 and Day 14 (Part B and Part C [intensive PK sampling sub-cohort only]).
7. Subjects should refrain from consumption of any foods containing poppy seeds within 48 hours (2 days) prior to screening and admission to the clinical research center to avoid false positive drug screen results.

8.3.4 Screen Failures and Rescreening

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 information includes date of consent, demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

The study permits the rescreening (after the end of the initial 3-week screening period) of a subject who discontinues the study as a pretreatment failure (ie, the subject failed screening and has not been treated). The subject must be re-consented and will be assigned a new identification number, and a full screening visit must be performed again.

Screening assessments and/or laboratory parameters (Section 1) may be repeated at the Investigator's discretion, in an effort to find all possible well-qualified subjects. Consultation

with the PRA Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

8.3.5 Withdrawal and Replacement of Subjects

8.3.5.1 Discontinuation of Treatment

Subjects MUST discontinue IP or study procedures (in case of single dose treatments) for any of the following reasons:

- Subject's request to stop study treatment. Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information.
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Termination of the study or program by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Abnormal liver tests suggestive of drug-induced liver injury (DILI) as defined in Section 8.5.2.1.7.
- Inability to comply with protocol.
- Stopping rules as defined in Section 8.3.5.5 are met.
- Discretion of the Investigator.

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 electronic case report form (eCRF) page. As indicated, appropriate follow-up and/or alternate medical care must be arranged for the subject.

Refer to the Schedule of Activities (Section 1) 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 study treatment should comply with protocol specified follow-up procedures as outlined in Section 1. 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 described in Section 8.3.5.4.

To the greatest extent possible, subjects who discontinue study treatment will remain in the study for continued follow-up.

In the case of pregnancy (Section 8.5.2.1.5), the Investigator must immediately notify the BMS Study Director and PRA Medical Monitor or designee of this event. In the event a normal healthy female subject becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Study Director and PRA Medical Monitor within 24 hours of awareness of the pregnancy.

8.3.5.2 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. 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. Expectations are as follows:

- 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, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate eCRF page.
- In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

The following procedures must be performed upon subject withdrawal:

- Assessments for the end of treatment visit must be performed, provided that the subject has not withdrawn consent for these activities.
- All required eCRF pages must be completed, including the date of and explanation for the withdrawal.

8.3.5.3 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 as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

The site staff 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.

8.3.5.4 Replacement of Subjects

Rescreening is discussed in Section 8.3.4.

Subjects will not be replaced if they are discontinued from the study secondary to an AE unless the AE can be determined to be unrelated to treatment. Subjects who are discontinued from the study for reasons not related to an adverse or other safety observation may be replaced. The replacement subject will receive the same treatment as the subject being replaced.

8.3.5.5 Stopping Rules for Part A and Part B

In the assessment whether AE related criteria for halting or stopping are met, special attention will be paid to any AE that is classed by the investigator as:

- A sign or symptom of bacterial, fungal or viral infection.
- An intestinal disorder.
- A hematological abnormality.

Dosing within a dose cohort will be stopped and further dosing will be halted until unblinded safety information (of the subject with the event) can be reviewed in case of one or more of the following occurring at any time during the observation period in the ongoing cohort:

1. A clinically significant AE that in the opinion of the Investigator, BMS Study Director and PRA Medical Monitor, indicates that the limits of safety and tolerability have been met, and precludes further safe dosing of subjects.
2. Two or more subjects with a severe or serious AE considered to be related to the study drug.
3. Two or more subjects with a serious infection event or 1 subject with opportunistic infection requiring systemic therapy (assessed as related to study drug).
4. Two or more subjects with liver function test elevations (confirmed by repeat) in the absence of an alternative explanation, including:
    - aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN)
    - AST or ALT > 3 x ULN with symptoms consistent with hepatic inflammation
5. One or more subjects with liver function test elevations (confirmed by repeat) consistent with drug-induced liver injury, in the absence of an alternative explanation, including:
    - AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
6. Two or more subjects have a greater than 60 msec increase in QTcF from the baseline value or a QTcF of > 500 msec (confirmed by repeat ECG).

Pending review of all pertinent information collected to date, one of the following decisions may be made:

- To continue dosing the remaining subjects of the cohort as planned, or
- To reduce the dose and continue dosing the remaining subjects of the cohort at the modified dose level (or placebo), or
- To terminate further dosing in the ongoing cohort.

In case of one or more occurrences as listed above, **dose escalation** will be halted until unblinded safety information for the subject(s) in the last completed cohort and with the event(s) can be reviewed. Pending review of all pertinent information collected to date, one of the following decisions may be made:

- To escalate to the next dose level as planned, or
- To escalate to a lower dose level than planned, or
- To extend the last cohort with more subjects exposed to the same dose level (or placebo), or
- To de-escalate, and to dose the next cohort to a lower dose than evaluated in the last cohort (or placebo), or
- To terminate further dose escalations in the relevant study part; subsequent study parts may be continued with amended dose level(s).

In addition, the Sponsor and Investigator may decide to halt dosing within a panel or dose-escalation for reasons not defined above, including but not limited to observing trends in a given dose panel and/or across dose panels.

If any of the above criteria are met within a dose level, dosing will be put on hold and all safety data available across the study will be evaluated to estimate the risk of continuing dosing at the current level and/or proceeding to the higher dose level. The review may include unblinding of the subject(s) that experienced AEs listed above. In addition, the unblinded data set may include subjects from a dose panel, or if appropriate, all treated subjects to date. Unblinding recommendation must be approved by the Sponsor's safety physician.

The maximum acceptable dose will be the dose level below the dose level at which the stopping criteria are met, unless it is determined that a lower dose should be designated as the maximum acceptable dose.

8.4 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 may include both IP and non-IP and is described in Table 9. In this protocol only administration of IP is planned.

An IP, also known as Investigational Medicinal Product (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 preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, will be considered as non-IPs.

Table 9 Study Treatments for IM024 005

Product Description / Class and Dosage Form	Study Part/Cohort	Potency	IP/Non-IP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986251 / oral solution	Part A and Part B	1 mg/mL and 20 mg/mL	IP	Blinded	On-site compounded solution#	Refer to the label on container and/or pharmacy manual
Placebo for BMS-986251 / oral solution	Part A and Part B	N/A	IP	Blinded	On-site compounded solution#	Refer to the label on container and/or pharmacy manual
BMS-986251 / oral suspension (under development)	Part A – BA/FE cohort only	Depending on final formulation	IP	Open label	Depending on formulation*	Refer to the label on container and/or pharmacy manual
BMS-986251 / tablet (under development)	Part C	Depending on final formulation	IP	Blinded	Formulated tablet in a bottle	Refer to label on container and/or pharmacy manual
Placebo for BMS-986251 / tablet (under development)	Part C	N/A	IP	Blinded	Formulated tablet in a bottle	Refer to label on container and/or pharmacy manual

IP = investigational product; N/A = not applicable.

The composition of the oral solution vehicle and placebo is 50/15/35 %w/w PEG-400 (polyethylene glycol-400)/TPGS (Tocopherol Polyethylene Glycol Succinate)/200mM Tris (trisaminomethane) buffer pH 9.

* The suspension formulation is under development. All excipients will be of compendial grade.

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8.4.1 Treatments Administered

The Investigator must ensure that the IP will be used only in accordance with the protocol.

8.4.1.1 Part A – SAD in Healthy Volunteers

In the morning of Day 1, after fasting for at least 10 hours, each subject will receive a single oral dose of BMS-986251 or placebo at approximately 9:00 AM as an oral solution of up to a planned volume of 6 mL, depending on the dose level. The medication time is provided as an indication only (for scheduling purposes).

Subjects enrolled in the BA/FE cohort will receive a second single oral dose of BMS-986251 at approximately 9:00 AM on the morning of Day 1 of Period 2, as an oral suspension (under development; representative for the solid dosage form to be used in Part C), after a 10-hour overnight fast. These subjects will receive a third single oral dose of BMS-986251 at approximately 9:00 AM on the morning of Day 1 of Period 3, as an oral suspension, 30 minutes after start of consumption of a high-fat breakfast. The high-fat breakfast (see Appendix 5) has to be consumed completely in 20 minutes. The exact time of start and end of breakfast and the exact time of dosing will be recorded in the eCRF. Washout between single dose administrations will be at least 2 weeks, based on an anticipated terminal half-life of BMS-986251 of approximately 40 hours.

In all study periods, at the time of dosing, a total of 240 mL of water will be administered to the subjects in all cohorts along with his/her dose of study drug. The time of BMS-986251/placebo administration will be called “0” hour. The exact time of dosing will be recorded in the eCRF. Subjects will remain fasted until at least 4 hours after administration. Water is allowed during fasting, except for 2 hours before and 1 hour after administration.

8.4.1.2 Part B – MAD in Healthy Volunteers

In the morning of Days 1-14, each subject will receive a single oral dose of BMS-986251 or placebo at approximately 9:00 AM as an oral solution of up to a planned volume of 6 mL, depending on the dose level. The medication time is provided as an indication only (for scheduling purposes). On Days 1 and 14, subjects will fast for at least 10 hours prior to dosing. At the time of dosing, 240 mL of water will be administered to the subject along with his/her dose of study drug. The time of first dose administration will be called “0” hour; all other time points will be relative to time “0”. The exact time of dosing will be recorded in the eCRF. On Days 1 and 14, subjects will remain fasted until at least 4 hours after administration. Water is allowed during fasting, except for 2 hours before and 1 hour after administration.

On Days 2 to 13, BMS-986251 or placebo will be administered in the fasted state. After dosing, subjects will continue their fast until breakfast. The breakfast will be provided approximately 2 hours after dosing. Water is allowed during fasting, except for 2 hours before and 1 hour after administration.

8.4.1.3 Part C – Multiple Dosing in Psoriasis Patients

Sub-cohort with intensive PK sampling
On Days 1 and 14, subjects will be dosed in the CRU following an overnight stay. They will receive a single oral tablet dose of BMS-986251 or placebo at approximately 9:00 AM in the morning, after an overnight fast of at least 10 hours prior to dosing. The medication time is provided as an indication only (for scheduling purposes). At the time of dosing, 240 mL of water will be administered to the subject along with his/her dose of study drug. The time of first dose administration will be called "0" hour; all other time points will be relative to time "0". The exact time of dosing will be recorded in the eCRF. On Days 1 and 14, subjects will remain fasted until at least 4 hours after administration. Water is allowed during fasting, except for 2 hours before and 1 hour after administration.

On Day 2 subjects will be dosed in the CRU, after an overnight fast. Breakfast will be given after dosing. The minimum time between dosing and breakfast will be determined based on the results of the FE investigation in Part A. Prior to discharge, subjects will be given a dosing diary and study drug will be dispensed for at-home administration in the mornings on Days 3-6 and 8-13. Study treatment will be supplied as tablets in a bottle. Subjects will be instructed to take study drug at approximately the same time every morning on an empty stomach and are instructed to record the time of their taken dose in their dosing diary. Results from the FE investigation in Part A may lead to different dosing instructions. If a subject forgets a dose, but remembers within approximately 12 hours of the expected dose, the dose should be taken. If it is past 12 hours, that dose should be missed and the next expected dose should be taken at the usual time.

On Day 7, subjects will not take their morning dose at home, but instead bring their study drug and dosing diaries to the CRU for administration of the dose after completion of pre-dose procedures.

Sub-cohort with sparse PK sampling
Patients enrolled in the sub-cohort with sparse PK sampling will receive the first dose of study drug in the CRU. The study drug will be taken with 240 mL of water. In addition, on Days 7 and 14 the patients will also receive their doses in the CRU. The remaining doses between Days 2-6 and 8-13 will be taken at home. On Day 1, subjects will be given a dosing diary and study drug will be dispensed for at-home administration in the mornings on Days 3-12. Study treatment will be supplied as tablets in a bottle. Subjects will receive the same dosing instructions for dosing at home as above.

8.4.2 Method of Treatment Assignment

Within each cohort (excluding the BA/FE cohort of Part A), subjects will be randomized to receive either BMS-986251 or placebo. All subjects who sign informed consent and are enrolled (including those not subsequently randomized or treated) will be assigned sequential subject numbers. Eligible subjects will be randomized according to a computer-generated randomization scheme. Subjects in Cohort A7 in Part A will be assigned sequential subject

numbers in the order of enrollment. Eligible subjects will be treated in accordance with the study design.

Sealed code break envelopes will be provided prior to the start of the study.

Part A, SAD in Healthy Volunteers:
Approximately 48 subjects (8 in each cohort) enrolling in Cohorts A1 to A6 will be randomized to BMS-986251 or matching placebo in a 3:1 randomization ratio. All subjects in BA/FE Cohort A7 will receive BMS-986251.

Part B, MAD in Healthy Volunteers:
Approximately 32 subjects will be enrolled in 4 dose cohorts during the MAD study. Each dose cohort will randomize 8 subjects in a 3:1 ratio to receive BMS-986251 or matching placebo.

Part C, Multiple Dosing in Psoriasis Patients:
Approximately 15 subjects in one planned dose cohort will be randomized in a randomization ratio of 4:1 to receive BMS-986251 or matching placebo.

Enrolled subjects meeting all of the inclusion and none of the exclusion criteria will be eligible to be dosed.

Subjects may be replaced under some circumstances (Section 8.3.5.4).

8.4.3 Blinding of Study Medication

8.4.3.1 Maintaining the Blind

As all parts of this Phase 1 FIH study are double blind (with the exception of the BA/FE cohort), the CRU staff, clinical research associates, Sponsor and designated personnel, study subjects, and their families will remain blinded to treatment assignments.

An unblinded PRA statistician will generate the treatment randomization schedule for each part of the study separately and the randomization schedules will be stored with restricted access.

An unblinded PRA pharmacist will prepare all study doses, however the CRU staff administering study medication will remain blinded. An unblinded CRA may be assigned if needed for drug accountability checks.

8.4.3.2 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 PRA Medical Monitor, but the Investigator always has ultimate authority for the decision to unblind. The 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 may open the emergency unblinding envelope to reveal the identity of the medication for that subject. If such unblinding occurs, the Investigator shall notify the BMS Study Director and PRA Medical Monitor immediately. This information, including the reason for the blind being broken, must be recorded on the appropriate study status page of the eCRF. In addition, the information that is requested on the emergency unblinding envelope must be completed.

In cases of accidental unblinding, contact the BMS Study Director and PRA Medical Monitor and ensure every attempt is made to preserve the blind. Any request to unblind a subject for non-emergency purposes should be discussed with the BMS Study Director and PRA Medical Monitor.

Within each cohort, safety, PK, and PD assessments will be performed. The bioanalytical personnel responsible for performing the analyses of the PK samples will be unblinded throughout the study to prevent unnecessary analysis of placebo samples. Following completion of each dose panel, there will be a review period between panels, during which all available safety, tolerability, PK, and PD data (as applicable) will be reviewed by the Sponsor's dose escalation review group. Limited designated staff of BMS and/or PRA can be unblinded at this time to prepare preliminary summaries of PK, PD and safety data. These summaries will not reveal individual subjects' treatment assignments and will include summaries and figures of mean data (as applicable). The Sponsor's dose escalation review group will review the data and will determine whether escalation to the next dose level will occur, or whether dose-stopping criteria have been met. The pharmacist at the site and/or designate will be unblinded to the randomized treatment assignments in order to dispense treatment from bulk supplies, as needed. Except as noted above, other members of BMS Research and Development and PRA will remain blinded.

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

8.4.4 Study Treatment Preparation, Handling, Storage, and Accountability

The IP should be stored in a secure area according to local regulations and site SOPs. It is the responsibility of the Investigator to ensure that 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 pharmacy 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 contacted immediately.

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

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

Compounding instructions will be provided separately to sites.
Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

Further guidance and information for final disposition of unused study treatment are provided in Appendix 1.

8.4.4.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

8.4.5 Dose Modification

No dose reductions or modifications are allowed for a subject.

8.4.6 Treatment Compliance

8.4.6.1 Part A and B

Study drug will be administered in the CRU. After administration, an examination of the oral cavity is required to verify that a subject has swallowed the BMS-986251 or matching placebo. The subjects should drink the entire aliquot of water given with the oral solution. Date and time of dosing will be recorded in the eCRF.

8.4.6.2 Part C

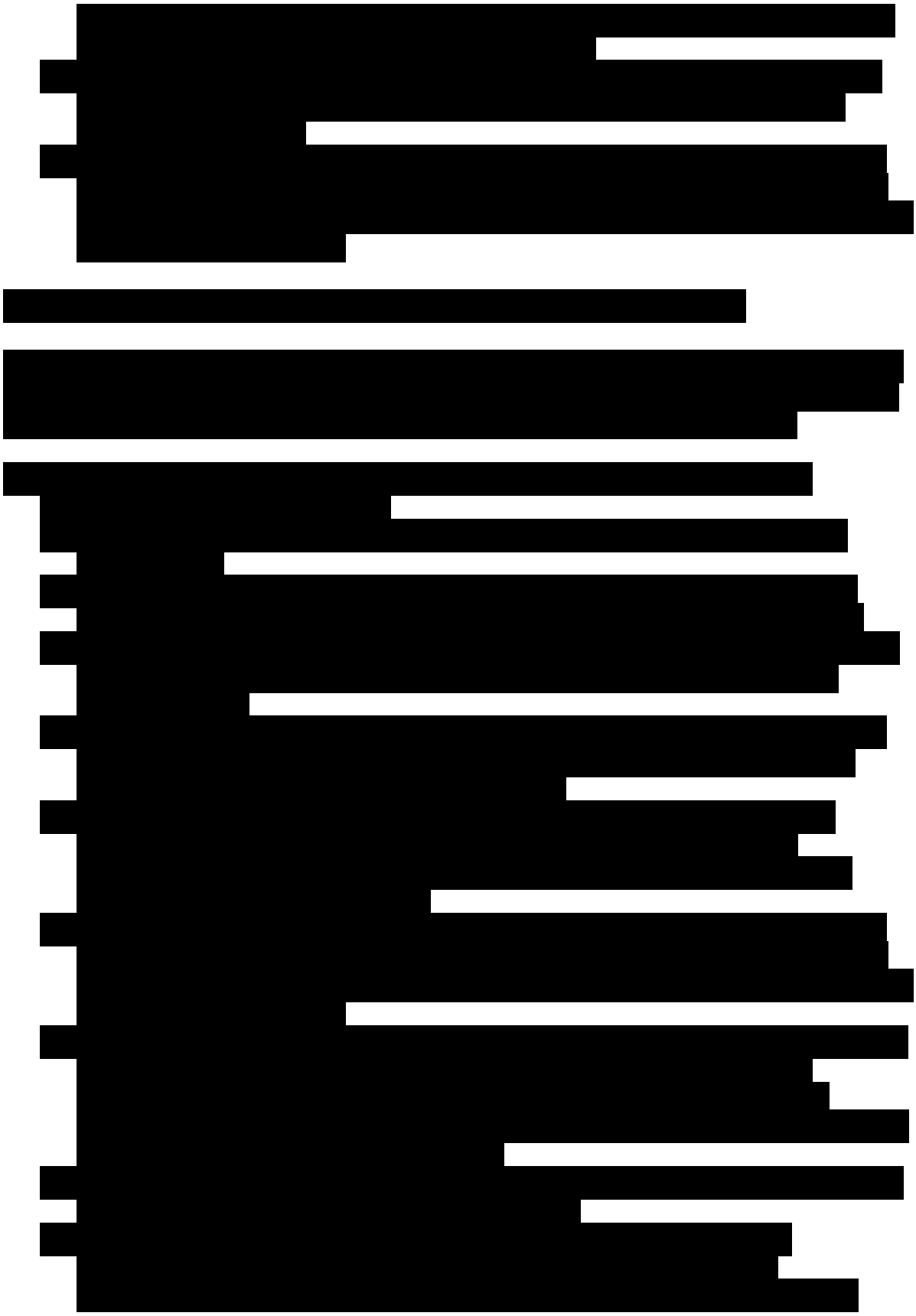
During confinement and ambulatory visits, administration of the study drug will be supervised by the Investigator or authorized designee to ensure treatment compliance as described in Section 8.4.6.1. Date and time of dosing will be recorded in the eCRF.

In the sub-cohort with intensive PK sampling, subjects will be dispensed blinded study drug for daily at-home administration on Day 2, prior to discharge from the CRU. Compliance to study drug during at-home administration will be monitored through the use of a subject dosing diary. Date and time of drug intake will be recorded daily, starting on Day 3 and up to and including Day 13 (with the exception of Day 7).

In the sub-cohort with sparse PK sampling, subjects will be dispensed blinded study drug for daily at-home administration on Day 1, after administration of the first dose in the CRU during an ambulant visit. Compliance to study drug during at-home administration will be monitored through the use of a subject dosing diary. Date and time of drug intake will be recorded daily starting on Day 2 and up to and including Day 13 (with the exception of Day 7).

Subjects will be asked to bring all unused study drug to the CRU at each ambulatory study visits. Study site personnel will review subjects' dosing diaries and if non-compliance is noted, site personnel will re-train subjects on protocol of at-home dosing. Study site personnel must make reasonable efforts to obtain unused study drugs from subjects who do not routinely return them at study site visits. Unreturned drug will be considered to have been taken.

Compliance will further be confirmed by bioanalytical assessment of BMS-986251 in plasma samples taken during confinement and ambulatory visits.



8.4.8 Treatment After the End of the Study

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

Sponsor/PRA 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 or other reasons; b) the development of BMS-986251 for treatment of psoriasis is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives. In all cases Sponsor/PRA will follow local regulations.

8.5 Efficacy and Safety Assessments

Study procedures and timing are summarized in the Schedule of Activities (Section 1). Waivers or exemptions from protocol-required evaluations are not allowed.

8.5.1 Efficacy Assessments

Preliminary efficacy assessments will be performed in Part C only and will consist of evaluation of PASI scores, PGA scores, and Dermatology Life Quality Index (DLQI) scores. Planned time points for all preliminary efficacy assessments are listed in the Schedule of Activities (Section 1).

8.5.1.1 Psoriasis Area and Severity Index Scoring (PASI)

The PASI is a physician assessed index that measures psoriasis severity and evaluates erythema, infiltration, and desquamation (scaling) on different body areas including the head, upper extremities, the trunk, and lower extremities. The area affected is included in this index as well. The PASI provides a clinical summary of psoriasis disease activity, as well as a means to assess treatment efficacy in psoriasis and is considered a reliable measure for disease severity. Further details are provided in Appendix 7.

8.5.1.2 Physician Global Assessment (PGA)

The Physician's Global Assessment evaluates the overall severity of disease on a 6-point scale based on plaque elevation, scaling and erythema. The same observer should evaluate the score throughout the study for a particular subject. Further details are provided in Appendix 8.

8.5.1.3 Dermatology Life Quality Index (DLQI)

The DLQI[4] has been the most widely used measure for assessing quality of life related to skin disease in psoriasis trials. This instrument consists of 10 questions covering six domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and bother with psoriasis treatment). The DLQI can be found in Appendix 9.

8.5.2 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 1). All urgent safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.

Safety evaluations that will be performed in addition to AE monitoring are physical examinations, vital signs, 12-lead ECGs, concomitant medication use, clinical laboratory tests, and continuous cardiac monitoring (Holter monitoring; Part A and B only).

8.5.2.1 Adverse Events

The definitions of an AE or SAE can be found in Appendix 2.

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 2.

8.5.2.1.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

The collection of non-serious AE information should begin at initiation of study treatment until the follow-up visit, at the time points specified in the Schedules of Activities (Section 1). Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

After the subject's written consent to participate in the study is obtained, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol specified procedure. The Investigator must report any SAE that occurs after this time period and that is believed to be related to study drug or protocol-specified procedure.

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 intensity and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 2.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 2.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

8.5.2.1.2 Method of Detecting Adverse Events and Serious Adverse Events

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.

8.5.2.1.3 Follow-up of Adverse Events and Serious Adverse Events

- Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 2).
- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious AE page of the eCRF. Completion of supplemental eCRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 8.3.5.3).
Further information on follow-up procedures is given in Appendix 2.

8.5.2.1.4 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards 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 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 Suspected Unexpected Serious Adverse Reaction (SUSAR) is a subset of SAEs and will be reported to the appropriate regulatory authorities and Investigators following local and global guidelines and requirements.

8.5.2.1.5 Pregnancy

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 (ie, those that have a failure rate of < 1% when used consistently and correctly; Appendix 3).

If, following initiation of the study treatment, it is subsequently discovered that a subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the Investigator must immediately notify the BMS Study Director, PRA Medical Monitor or designee of this event and complete and forward a Pregnancy Surveillance Form to BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 2.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Study Director within 24 hours of awareness of the pregnancy.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

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

8.5.2.1.6 Laboratory Test Result Abnormalities

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

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

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

8.5.2.1.7 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Appendix 2 for reporting details).

Potential DILI is defined by presence of all of the following characteristics:

- ALT or AST elevation > 3 × ULN.
- Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase).
- No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.5.2.1.8 Other Safety Considerations

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

8.5.2.2 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see Appendix 2).

In the event of an overdose, the Investigator should do the following:

1. Contact the medical monitor immediately.
2. Closely monitor the subject for AEs/SAEs and laboratory abnormalities until BMS-986251 can no longer be detected systemically (at least 3 days).
3. Obtain an additional plasma sample for PK analysis if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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.

8.5.2.3 Physical Examinations

Schedules for physical examinations are provided in Section 1. Complete and/or targeted physical examinations will be performed according to the CRO's standard operating procedures (SOPs). In addition, body weight and height will be measured according to CRO SOPs.

Symptom-directed, targeted physical examinations are not listed in the schedules in Section 1, but will be conducted as needed/appropriate, at the Investigator's discretion. Documentation of who performed the examination is to be recorded in source notes. A targeted physical examination may note any changes in the subject's condition (body systems) since the last assessment and does not preclude examination of any of the other

body systems as clinically indicated. Every effort should be made to ensure the same evaluator will complete the examination for each subject at all visits throughout the study.

8.5.2.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report. A local laboratory will perform the analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed on Day -1 must be available prior to first dosing.

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the eCRF or by another mechanism as agreed upon between the Investigator and BMS (eg, provided electronically). In case of unexplained or unexpected clinical laboratory test values, the tests will be repeated as soon as possible and followed up until the results have returned to the normal range and/or an adequate explanation for the abnormality is found. The clinical laboratory will clearly mark all laboratory test values that are outside the normal range and the Investigator will indicate which of these deviations are clinically significant. Any abnormal laboratory test result considered clinically significant by the Investigator must be recorded on the appropriate AE page of the eCRF (Section 8.5.2.1.6).

Samples for clinical laboratory will be taken in the fasted state (at least 4 hours).

Table 10 Clinical Laboratory Assessments

Hematology

Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count
Red blood cell count
Reticulocyte count

Chemistry

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Lactate dehydrogenase (LDH)
Creatinine
Urea
Uric acid
Fasting glucose
High sensitivity C-reactive protein (hs-CRP)
Total protein
Albumin
Sodium
Potassium
Chloride
Calcium
Inorganic phosphate
Magnesium
Creatine kinase
Creatinine clearance (CLcr)- screening only
Cholesterol
Triglycerides
High-density lipoprotein (HDL)
Low-density lipoprotein (LDL)

Urinalysis

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

Serology

Serum for hepatitis C antibody, HBsAg, and HIV-1 and -2 antibody (at screening only)

Quantiferon Gold test® for tuberculosis (TB) (at screening only)

Other Analyses

Urine test for alcohol (see Table 1 through Table 4)
Urine test for drugs of abuse (see Table 1 through Table 4)
Pregnancy test (females only; see Table 1 through Table 4)
FSH (screening only; test will be performed in all females for logistical purposes)

8.5.2.5 Vital Signs

Systolic and diastolic blood pressure and pulse will be recorded after the subject has been resting for at least 5 minutes in the supine position. These assessments will be made using an automated device. Body temperature and respiratory rate will be measured subsequently.

8.5.2.6 12-Lead Electrocardiogram

Standard 12-lead ECG will be recorded in triplicate (3 measurements within 5 minutes) after the subject has been resting for at least 5 minutes in the supine position. All ECG recordings will be performed using a standard high-quality, high-fidelity machine equipped with computer-based interval measurements and automated interpretation. The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, QTc-interval (Fridericia's) and the interpretation of the ECG profile by the Investigator. Changes of the T-wave and U wave morphology will be documented. Source documentation for ECG recordings will be kept.

8.5.2.7 Continuous Cardiac Monitoring (Holter Monitoring)

Continuous ECG monitoring will be performed to help monitor patient safety; primarily to detect ventricular and atrial arrhythmias. The site will follow their normal operating procedures established for ECG monitoring. Clinically significant findings from the monitoring will be recorded as AEs and SAEs per the Investigator's decision, and at the Investigator's discretion the study drug may be discontinued for clinically significant arrhythmias.

The ECGs collected by continuous monitoring will be stored for potential later use. These ECGs may or may not be analyzed for the purpose of Concentration Effect Modelling, based on future development decisions for BMS-986251. If analyzed, results of the modeling will not be included in the clinical study report, but will be included in a separate report.

8.5.3 Pharmacokinetics

Pharmacokinetic variables will be the plasma concentrations and urine concentrations (Part A and B only) of BMS-986251 and derived PK parameters. The PK parameters to be assessed for BMS-986251 include but are not limited to the parameters given below. Some of the listed parameters may only be calculated for specific parts of the study; this includes the assessment of urinary excretion of parent compound and metabolites in urine, which may be limited to the higher dosed cohorts in Part A and B. The relevant PK parameters to be calculated for each study part and study day are listed in Section 9.3.1.

C_{pre}	Pre-dose plasma concentration
C_{max}	Maximum observed plasma concentration
t_{max}	Time of maximum observed plasma concentration
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC_{0-inf}	Area under the plasma concentration-time curve from time zero extrapolated to infinite time
AUC_{0-24}	Area under the concentration-time curve over 24 hours (one dosing interval)
AR_{Cmax}	Accumulation ratio: ratio of C_{max} following last dose (Day 14) to C_{max} following first dose (Day 1)
$AR_{AUC0-24}$	Accumulation ratio: ratio of AUC_{0-24} following last dose (Day 14) to AUC_{0-24} following first dose (Day 1)
k_{el}	Terminal elimination rate constant
$t_{1/2}$	Terminal elimination half-life, calculated as $0.693/k_{el}$
CL/F	Apparent (oral) clearance, calculated as dose/AUC_{0-inf} for single dose (Part A, Day 1) or dose/AUC_{0-24} for multiple dose (Part B and C, Day 14)
V_z/F	Apparent volume of distribution at terminal phase
Ae_t	Cumulative urinary excretion (of the unchanged drug) (Part A and B only)
$Fe_{urine}\%$	Amount excreted unchanged in urine (% of dose) (Part A and B only)
CL_R	Renal clearance (Part A and B only)

Individual subject PK parameter values will be derived by non-compartmental methods by a validated PK analysis program. Actual times of sample collection will be used for the analyses. Table 11 (Part A), Table 12 (Part B), Table 13 (Part C, sub-cohort with intensive PK sampling), and Table 14 (Part C, sub-cohort with sparse PK sampling) list the sampling schedule to be followed for the assessment of PK in plasma (all study parts) and in urine (Part A and B only). In addition, exploratory metabolite profiling may be evaluated in select dose cohorts in blood and urine. No separate blood samples are planned for this, but residual plasma samples may be used for this purpose. An additional urine sample from each collection interval will be aliquoted for this purpose.

If deemed necessary by the Investigator or the Sponsor, the number and/or volume of blood samples per assessment may be increased as long as the total volume of blood drawn for a subject does not surpass 500 mL (except when extra blood samples need to be taken for safety reasons).

Blood and urine collection, processing, and shipping details will be outlined in the Laboratory Manual.

The plasma will be analyzed for BMS-986251 by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay by PRA. The urine (Part A and B only) will be analyzed for BMS-986251 by a validated LC-MS/MS assay by PRA.

Residual plasma and urine samples for exploratory metabolite profiling will be analyzed by an exploratory LC-MS/MS assay by BMS or BMS contracted laboratories.

Table 11 Pharmacokinetic Sampling Schedule; Part A

Sample Collection Time		Time (relative to dosing) hour:min	Blood Sample	Urine Sample
Study Day	**Time (event)**		**PK Blood Sample**	**Collection Interval**
-1	NA	NA		X
1	0 h (pre-dose)	00:00	X	
1	0.5 h	00:30	X	X (0-12 h)
1	1 h	01:00	X	
1	1.5 h	01:30	X	
1	2 h	02:00	X	
1	3 h	03:00	X	
1	4 h	04:00	X	
1	6 h	06:00	X	
1	8 h	08:00	X	
1	12 h	12:00	X	X (12-24 h)
2	24 h	24:00	X	
2	36 h	36:00	X	X (24-48 h)
3	48 h	48:00	X	
4	72 h	72:00	X	X (48-72 h)
5	96 h	96:00	X	X (72-96 h)
6	120 h	120:00	X	X (96-120 h)
7	144 h	144:00	X	X (120-144 h)
9	192 h	192:00	X	
11	240 h	240:00	X	

h = hour; min = minute; PK = pharmacokinetic.

Table 12 Pharmacokinetic Sampling Schedule; Part B

Sample Collection Time		Time (relative to dosing) hour:min	Blood Sample	Urine Sample
Study Day	**Time (event)**		**PK Blood Sample**	**Collection Interval**
-1	NA	NA		X
1	0 h (pre-dose)	00:00	X	
1	0.5 h	00:30	X	
1	1 h	01:00	X	
1	1.5 h	01:30	X	
1	2 h	02:00	X	
1	3 h	03:00	X	
1	4 h	04:00	X	
1	6 h	06:00	X	
1	8 h	08:00	X	
1	12 h	12:00	X	
2-13	0 h (pre-dose)	0:00	X	
2-13	4 h	4:00	X	
14	0 h (pre-dose)	0:00	X	X (0-24 h on Day 14)
14	0.5 h	00:30	X	
14	1 h	01:00	X	
14	1.5 h	01:30	X	
14	2 h	02:00	X	
14	3 h	03:00	X	
14	4 h	04:00	X	
14	6 h	06:00	X	
14	8 h	08:00	X	
14	12 h	12:00	X	
15	24 h	24:00	X	
16	48 h	48:00	X	
18	96 h	96:00	X	
20	144 h	144:00	X	
24	240 h	240:00	X	

h = hour; min = minute; NA = not applicable; PK = pharmacokinetic.

Table 13 Pharmacokinetic Sampling Schedule; Part C (Sub-Cohort with Intensive PK Sampling)

Sample Collection Time		Time (relative to dosing) hour:min	Blood Sample
Study Day	Time (event)		PK Blood Sample
1	0 h (pre-dose)	00:00	X
1	0.5 h	00:30	X
1	1 h	01:00	X
1	1.5 h	01:30	X
1	2 h	02:00	X
1	3 h	03:00	X
1	4 h	04:00	X
1	6 h	06:00	X
1	8 h	08:00	X
1	12 h	12:00	X
2	0 h (pre-dose)	0:00	X
7	0 h (pre-dose)	0:00	X
14	0 h (pre-dose)	0:00	X
14	0.5 h	00:30	X
14	1 h	01:00	X
14	1.5 h	01:30	X
14	2 h	02:00	X
14	3 h	03:00	X
14	4 h	04:00	X
14	6 h	06:00	X
14	8 h	08:00	X
14	12 h	12:00	X
15	24 h	24:00	X
28	NA	NA	X

h = hour; min = minute; NA = not applicable; PK = pharmacokinetic.

Table 14 Pharmacokinetic Sampling Schedule; Part C (Sub-Cohort with Sparse PK Sampling)

Sample Collection Time		Time (relative to dosing) hour:min	Blood Sample
Study Day	Time (event)		PK Blood Sample
1	0 h (pre-dose)	00:00	X
7	0 h (pre-dose)	00:00	X
14	0 h (pre-dose)	00:00	X

h = hour; min = minute; NA = not applicable; PK = pharmacokinetic

8.5.4 Pharmacodynamics

Planned time points for all PD assessments are listed in the Schedule of Activities (Section 1).

The following PD assessment is planned in this study:

- Blood sampling for ex-vivo inhibition (I) of IL-17 secretion in whole blood (all study parts)

In addition, the following exploratory PD assessments are planned in this study:

- Blood sampling for IL-17, IL-22, β-defensin, and erythropoietin concentrations in serum or plasma (Part B and Part C).
- Blood sampling for TBNK cells, γδ T cells, T cell subsets (Part B and Part C).
- Plaque biopsy for immunochemistry and RNA analysis (Part C).

Table 15 (Part A), Table 16 (Part B), Table 17 (Part C, sub-cohort with intensive PK sampling), and Table 18 (Part C, sub-cohort with sparse PK sampling) list the sampling schedule to be followed for the (exploratory) PD assessments. Further details of whole blood, plasma, and plaque biopsy collection and processing will be provided in a separate Laboratory Manual.

For the ex-vivo inhibition of IL-17 secretion in whole blood, PD parameters will be calculated as listed below. Some of the listed parameters may only be calculated for specific parts of the study. The relevant PD parameters calculated for each study part and study day are listed in Section 9.3.2.

I_{pre}	Pre-dose inhibition
I_t	Inhibition at time t
I_{max}	Maximum observed inhibition
t_{Imax}	Time of maximum observed inhibition
$t_{I>50\%}$	Time of inhibition above 50%
$t_{I>90\%}$	Time of inhibition above 90%

Table 15 Pharmacodynamic Sampling Schedule; Part A

Sample Collection Time		Time (relative to dosing) hour:min	Blood Samples
Study Day	**Time (event)**		**Ex-vivo IL-17 Inhibition in Whole Blood**
-1	Admission	NA	X
1	0 h (pre-dose)	00:00	X
1	1 h	01:00	X
1	2 h	02:00	X
1	4 h	04:00	X
1	12 h	12:00	X
2	24 h	24:00	X
3	48 h	48:00	X
5	96 h	96:00	X
7	144 h	144:00	X
11	240 h	240:00	X

h = hour; IL-17 = interleukin-17; min = minute; NA = not applicable.

Table 16 Pharmacodynamic Sampling Schedule; Part B

Sample Collection Time		Time (relative to dosing) hour:min	Blood Sample		
Study Day	Time (event)		Ex-vivo IL-17 inhibition in whole blood	IL-17, IL-22, β-defensin, and erythropoietin concentrations	T, B, and NK cells (TBNK), γδ T cells, T cell subsets
-1	Admission	NA	X		
1	0 h (pre-dose)	00:00	X	X	X
1	1 h	01:00	X		
1	2 h	02:00	X		
1	4 h	04:00	X		
1	12 h	12:00	X		
2	0 h (pre-dose)	0:00	X		
4	0 h (pre-dose)	0:00	X		
7	0 h (pre-dose)	0:00	X		
14	0 h (pre-dose)	0:00	X		
14	1 h	01:00	X		
14	2 h	02:00	X		
14	4 h	04:00	X		
14	12 h	12:00	X		
15	24 h	24:00		X	X
16	48 h	48:00	X		
20	144 h	144:00	X		
24	240 h	240:00	X	X	X

h = hour; IL-17 = interleukin-17; IL-22 = interleukin-22; min = minute; NA = not applicable; NK = natural killer.

Table 17 Pharmacodynamic Sampling Schedule; Part C (Sub-Cohort with Intensive PK Sampling)

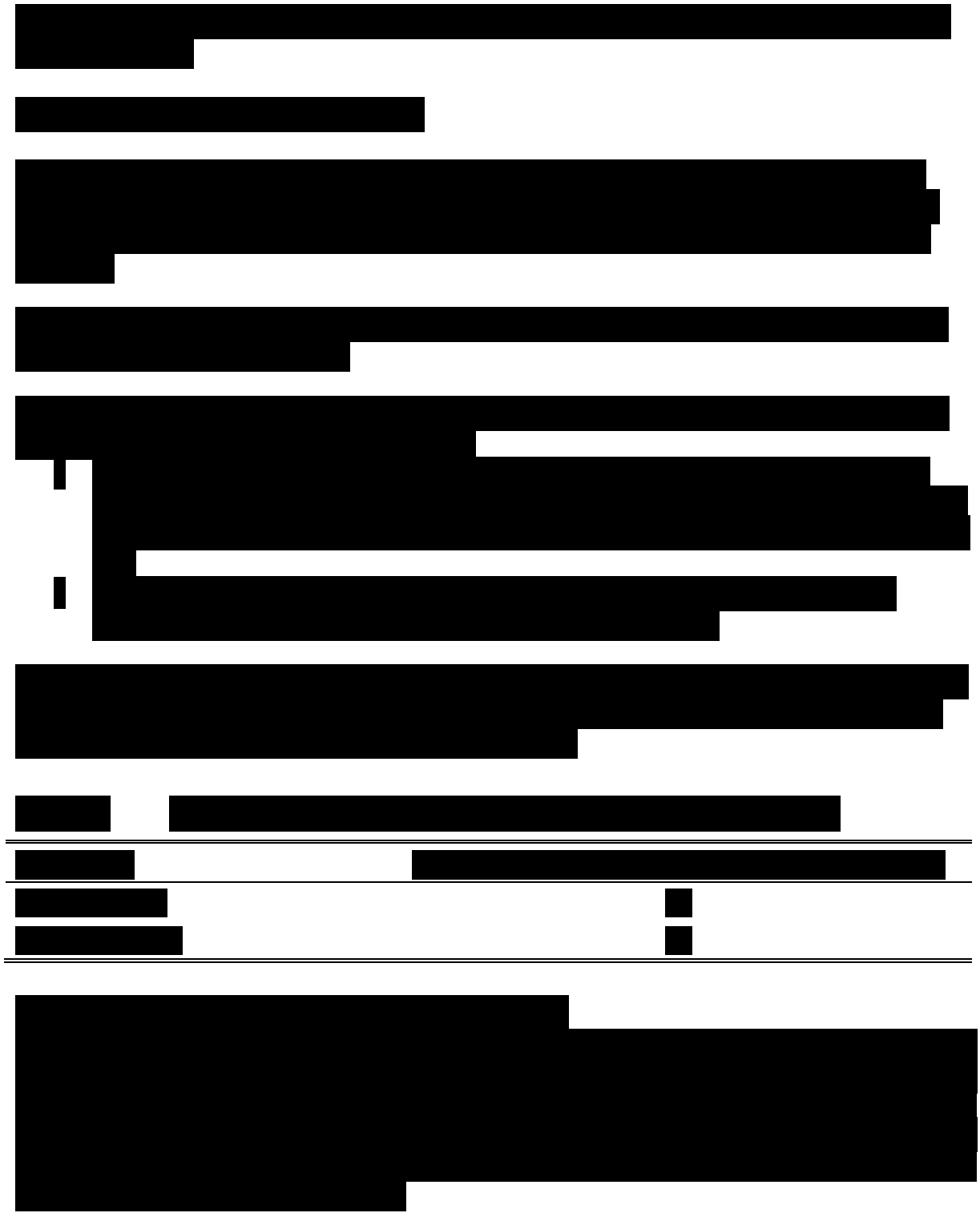
Sample Collection Time		Time (relative to dosing) hour:min	Blood Sample			Plaque Biopsy
Study Day	Time (event)		Ex-vivo IL-17 inhibition in whole blood	IL-17, IL-22, β-defensin, and erythropoietin concentrations	T, B, and NK cells (TBNK), γδ T cells, T cell subsets	Immuno-chemistry and RNA analysis
-1[a]	Admission	NA	X			X
1	0 h (pre-dose)	00:00	X	X	X	
1	1 h	01:00	X			
1	2 h	02:00	X			
1	4 h	04:00	X			
1	12 h	12:00	X			
2	0 h (pre-dose)	0:00	X			
7	0 h (pre-dose)	0:00		X	X	
14	0 h (pre-dose)	0:00	X	X	X	
14	1 h	01:00	X			
14	2 h	02:00	X			
14	4 h	04:00	X			X
14	12 h	12:00	X			
15	24 h	24:00	X			
28	NA	NA	X	X	X	

h = hour; IL-17 = interleukin-17; IL-22 = interleukin-22; min = minute; NA = not applicable; NK = natural killer.

Table 18 Pharmacodynamic Sampling Schedule; Part C (Sub-Cohort with Sparse PK Sampling)

Sample Collection Time		Time (relative to dosing) hour:min	Blood Sample[a]			Plaque Biopsy
Study Day	Time (event)		Ex-vivo IL-17 inhibition in whole blood	IL-17, IL-22, β-defensin, and erythropoietin concentrations	T, B, and NK cells (TBNK), γδ T cells, T cell subsets	Immuno-chemistry and RNA analysis
1	0 h (pre-dose)	00:00	X	X	X	X
7	0 h (pre-dose)	00:00	X	X	X	
14	0 h (pre-dose)	00:00	X	X	X	X
28	NA	NA	X	X	X	

[redacted]



8.5.6 Total Blood Volume to be Collected (Part A and Part B)

The number and volume of blood samples and the total volume of blood that will be collected throughout the study per subject is given in Table 20 (Cohorts A1 to A6) and Table 21 (Cohort A7) for Part A, and in Table 22 for Part B.

If deemed necessary by the Investigator or the Sponsor, the number and/or volume of blood samples per assessment may be increased as long as the total volume of blood drawn for a subject does not surpass 500 mL (except when extra blood samples need to be taken for safety reasons).

Table 20 Number and Volume of Blood Samples and Total Blood Volume Collected per Subject (Part A, Cohorts A1-A6)

Assessment	Maximum # samples	Volume of blood per sample (mL)	Total volume of blood (mL)
Pharmacokinetics - BMS-986251 in plasma	19	5	95
Pharmacodynamics - Ex vivo inhibition of IL-17 secretion in whole blood	11	1	11
Whole blood for potential analysis of DNA variants in ADME-related genes	1	6	6
Clinical chemistry	6	3.5	21
Hematology	6	3	18
Serology	1	5	5
QuantiFERON® test	1	4	4
Total volume of blood drawn			**160**

Table 21 Number and Volume of Blood Samples and Total Blood Volume Collected per Subject (Part A, Cohorts A7)

Assessment	Maximum # samples	Volume of blood per sample (mL)	Total volume of blood (mL)
Pharmacokinetics - BMS-986251 in plasma	57	5	285
Pharmacodynamics - Ex vivo inhibition of IL-17 secretion in whole blood	11	1	11
Whole blood for potential analysis of DNA variants in ADME-related genes	1	6	6
Clinical chemistry	14	3.5	49
Hematology	14	3	42
Serology	1	5	5
QuantiFERON® test	1	4	4
Total volume of blood drawn			**402**

Table 22 Number and Volume of Blood Samples and Total Blood Volume Collected per Subject (Part B)

Assessment	Maximum # samples	Volume of blood per sample (mL)	Total volume of blood (mL)
Pharmacokinetics - BMS-986251 in plasma	49	5	245
Pharmacodynamics - Ex vivo inhibition of IL-17 secretion in whole blood - IL-17, IL-22, β-defensin, erythropoietin [redacted]	17 4 4	1 2.5 5	17 10 20
Whole blood for potential analysis of DNA variants in ADME-related genes	1	6	6
Clinical chemistry	8	3.5	28
Hematology	8	3	24
Serology	1	5	5
QuantiFERON® test	1	4	4
Total volume of blood drawn			**359**

9. STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

Part A and B – SAD and MAD cohorts
The current design of 8 subjects per cohort with 6 subjects assigned to active treatment is a commonly used design for SAD and MAD studies and is considered sufficient to achieve the study objectives. Although this number of is not based on statistical power considerations, administration of BMS-986251 to 6 subjects in each dose cohort provides approximately 80% probability of observing at least one occurrence of any AE which would occur with approximately 24% incidence in the population from which the sample is drawn.

Part A – BA/FE cohort
The planned number of 8 subjects on active treatment to be enrolled in the BA/FE cohort (in which BA and FE of an oral suspension will be evaluated in a 3-period sequential design), has not been based on formal statistical sample size calculations. This number of subjects is a commonly accepted number of subjects for this type of exploratory study and is considered sufficient to achieve the study objectives.

Part C – Psoriasis patients
Like Parts A and B, Part C is also an exploratory study. Therefore, no formal statistical sample size calculation has been performed and the sample size is not based on a power calculation. The planned number of 15 subjects with 12 subjects on active treatment is a commonly accepted number of subjects for this type of exploratory study. Formal statistical hypotheses were not set up. Any statistical test performed will be exploratory.

9.2 Populations for Analyses

The following populations are defined for each part of the study and will be used for analysis purposes:

Population	Description
Enrolled	All subjects who sign informed consent.
Randomized	All subjects who are randomized to a treatment, analyzed as per randomized treatment.
Safety	All subjects who had received at least one dose of BMS-986251 or placebo.
Pharmacokinetic (PK)	All subjects who receive at least 1 dose of BMS-986251 and have any available concentration-time data. Additionally, the evaluable PK population is defined as subjects who have adequate PK profiles.

Population	Description
Pharmacodynamic (PD)	All subjects who receive at least 1 dose of BMS-986251 or placebo and have any available concentration-time data for the PD assessments. Additionally, the evaluable PD population is defined as subjects who have adequate PD profiles.
Efficacy	All subjects who receive at least 1 dose of BMS-986251 or placebo and have available data for the efficacy assessments at baseline and the last visit at a minimum.

9.3 Endpoints

9.3.1 Primary Endpoints

The primary objective to assess the safety, tolerability and PK of single and multiple oral doses of BMS-986251 in healthy subjects and in patients with moderate-to-severe psoriasis will be measured by the following primary endpoints:

Safety and tolerability

- Number and percent of subjects that experience the following: SAE, death or an AE leading to study discontinuation, during the study participation or up to 1 month post discontinuation of dosing or last participation in the study for SAE.
- Number and percent of subjects with potentially clinically significant changes in ECG parameters, vital signs, or clinical laboratory parameters from Day 1 through the final follow visit.

Other safety measures collected during the study are not considered among the primary endpoint and will be summarized as safety endpoints. Stopping rules for safety are discussed in Section 8.3.5.5.

Pharmacokinetics

PK parameters will be derived from BMS-986251 concentration versus time data measured at the time points specified in the schedule of assessments for each part of the study. The PK parameters to be assessed are listed in Section 8.5.3. The PK parameters to be evaluated in each part include but are not limited to the following:

- Part A: C_{max}, t_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $t_{1/2}$, CL/F, V_z/F, Ae_t, Fe_{urine}%, CL_R
- Part B:
  Day 1: C_{max}, t_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$
  Days 2-14: C_{pre}
  Day 14: C_{max}, t_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, CL/F, V_z/F, $t_{1/2}$, $AR_{AUC0\text{-}24}$, $AR_{Cmax,}$ Ae_t, Fe_{urine}%, CL_R
- Part C (intensive PK sampling sub-cohort):
  Day 1: C_{max}, t_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$

Days 2-14: C_{pre}
Day 14: C_{max}, t_{max}, AUC_{0-t}, AUC_{0-24}, CL/F, V_z/F, $t_{1/2}$, $AR_{AUC0-24}$, AR_{Cmax}

- Part C (sparse PK sampling sub-cohort):
  Days 7 and 14: C_{pre}

9.3.2 Secondary Endpoints

The secondary objective to assess PD of single and multiple oral doses of BMS-986251 in healthy subjects and in patients with moderate-to-severe psoriasis will be measured by evaluating the percentage ex-vivo inhibition (I) of IL-17 secretion in whole blood. PD parameters will be derived from inhibition versus time data measured at the time points specified in the schedule of assessments for each part of the study. The PD parameters to be assessed are listed in Section 8.5.4. The PD parameters to be evaluated in each part include:

- Part A: I_{max}, t_{Imax}, $t_{I>50\%}$, $t_{I>90\%}$
- Part B: I_{max}, t_{Imax}, $t_{I>50\%}$, $t_{I>90\%}$ (Day 1 and Day 14); I_{pre} (Days 2, 4, 7, and 14); I_t (Days 16, 20, and 24)
- Part C (intensive PK sampling sub-cohort): I_{max}, t_{Imax}, $t_{I>50\%}$, $t_{I>90\%}$ (Day 1 and Day 14); I_{pre} (Days 1, 2, and 14); I_t (Days 15 and 28)
- Part C (sparse PK sampling sub-cohort): I_{pre} (Days 1, 7 and 14); I_t (Day 28)

The secondary objectives to evaluate the oral BA of an oral suspension of BMS-986251 relative to a liquid dosage form at a single dose level in healthy subjects, and to evaluate the effect of a high-fat meal on the PK of an oral suspension of BMS-986251 at a single dose level in healthy subjects will be evaluated by comparing the PK parameters listed for the SAD part in Section 9.3.1.

The secondary objective to evaluate the efficacy of multiple doses of BMS-986251 in patients with moderate-to-severe psoriasis will be evaluated by evaluating the following endpoints:

- PASI score at baseline, and Days 7, 14, and 28
- PGA score at baseline, and Days 7, 14, and 28
- DLQI at baseline, and Days 7, 14, and 28

[redacted]

9.4 Statistical Analyses

A statistical analysis plan (SAP) will be developed and finalized prior to database lock and will provide detailed specifications of the analysis of all study endpoints.

Descriptive summaries will be presented for continuous variables using number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum. In addition geometric mean and coefficient of variation (CV) will be reported for selected variables as appropriate. Descriptive summaries for categorical variables will utilize counts (N) and percentages (%).

Each part of the study will be summarized separately. Subjects receiving placebo in any cohort will be pooled into a single placebo group.

9.4.1 Efficacy Analyses

Efficacy analyses will be performed using the efficacy population. Efficacy assessments will be summarized descriptively. Descriptive statistics of PASI, PGA, and DLQI scores will be provided for each time point. In addition, exposure-response analysis (if sufficient data are available) or dose–response analysis (in case more dose cohorts are included in Part C) may be performed of the percent change from baseline in PASI score on Days 7, 14, and 28 and for the percentage of active-treated patients per cohort with 75% reduction in PASI score (PASI75) on Day 28 versus baseline. Exposure-response analysis (if sufficient data are available) or dose–response analysis (in case more dose cohorts are included in Part C) of change in PGA and DLQI on Days 7, 14 and 28 may be performed as well. Further details of the exploratory efficacy analyses may be added to the protocol via protocol amendment prior to start of Part C and will also be provided in the SAP.

9.4.2 Safety Assessments

Safety analyses will be performed using the safety population.

9.4.2.1 Adverse Events

All recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment for each part of the study. Coding will be performed according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Adverse events which occur on or after the first dose of study treatment through study participation will be considered treatment emergent and will be summarized. Serious AEs will be recorded from signing of the ICF up to 1 month after the last dose of study treatment or last

participation in the study (whichever is longer) and will be included in summary statistics. Adverse events leading to discontinuation or death will be listed.

9.4.2.2 Vitals Signs and ECGs

Vital sign measurements and 12-lead ECG test results will be listed and summarized.

Vital sign parameters (temperature, SBP, DBP respiratory rate and heart rate) at each collected time point during the study period will be summarized for each treatment by study part. Change from baseline will be derived for each time point and will be summarized. If considered informative, plots of the mean change from baseline for each parameter versus time since dosing may be presented by treatment.

ECG parameters (heart rate, QTcF, PR, QRS) will be summarized using descriptive statistics. Each parameter and the corresponding change from baseline will be summarized by treatment and time point in each part of the study. Electrocardiogram readings will be evaluated by the Investigator and abnormalities, if present, will be listed.

The baseline value is defined as the Day 1 (pre-dose) value, or the last assessment obtained prior to study drug administration.

9.4.2.3 Clinical Laboratory Data

Clinical laboratory data will be listed and summarized by treatment and time point. Change from baseline will also be displayed. Shift tables and graphical presentation of laboratory values over time may be provided (absolute values and/or change from baseline). Baseline value is defined as the last result obtained prior to study drug administration (Day -1 or Day 1 [pre-dose], whichever is the last result obtained).

Abnormal test results will be listed.

9.4.2.4 Physical Examination

Abnormal physical examination findings will be collected and listed by treatment and dosing cohort.

9.4.3 Pharmacokinetics

All available concentration-time data from subjects who receive BMS-986251 will be reported.

All available derived PK parameters will be included in the PK data set and reported, but only subjects with adequate PK profiles will be included in the summary statistics and statistical analysis.

BMS-986251 plasma concentrations and derived PK parameters (see Section 8.5.3) will be listed and summarized descriptively by study part, treatment, and study day/time point (where appropriate) in tabular and/or graphical form using appropriate descriptive statistics. Details will be provided in the SAP.

Dose-linearity analysis will be performed of C_{max}, AUC_{0-t}, and AUC_{0-inf} (Part A), and C_{max} and AUC_{0-24} (Days 1 and 14) (Part B). Scatter plots of the appropriate PK parameters versus dose will be presented. Dose proportionality will be assessed by estimating the slope of the linear regressions of log[AUC_{0-t}], log[AUC_{0-inf}], and log(C_{max}) on log(dose). The power model described by Gough et al[5] will be used to assess the dose proportionality of BMS-986251. Details on the analysis will be provided in the SAP.

To assess the relative BA (C_{max}, AUC_{0-t}, and AUC_{0-inf}) and change in t_{max} comparing an oral suspension (under development; representative for a solid dosage form to be used in Part C; Cohort A7, Period 2) and a liquid dosage form (Cohort A7, Period 1), linear mixed model analyses will be performed. Point estimates and 90% confidence intervals will be constructed for the ratios of oral suspension to liquid dosage form geometric means. Treatment differences on the log-scale will be exponentiated to obtain estimates for ratios of geometric means on the original scale. Details on these statistical analyses will be provided in the SAP.

To evaluate the effect of food on the PK of BMS-986251 given as an oral suspension (Cohort A7, Periods 2 and 3), linear mixed model analyses will be performed. Point estimates and 90% confidence intervals will be constructed for the ratios of fed (Period 3) to fasted (Period 2) geometric means. Treatment differences on the log-scale will be exponentiated to obtain estimates for ratios of geometric means on the original scale. Details on these statistical analyses will be provided in the SAP.

Individual PK parameters from the 3 periods will be plotted versus treatment (liquid dosage form fasted, oral suspension fasted, or oral suspension fed).

If warranted, analysis of PK and exposure-response relationships of BMS-986251 will be conducted using a population approach as appropriate and reported separately from the clinical study report.

9.4.4 Pharmacodynamics

Percentage of inhibition of ex-vivo IL-17 secretion in whole blood and derived PD parameters (see Section 8.5.4) will be listed and summarized by treatment and time point collected in tabular and/or graphical form using appropriate descriptive statistics. Results of exploratory PD assessments will be listed and summarized descriptively as well. Details will be provided in the SAP.

Dose-response analysis will be performed of I_{max}, $t_{I>50\%}$, and $t_{I>90\%}$ for inhibition of ex-vivo stimulated IL-17 secretion in whole blood. Concentration-effect modeling will be performed for BMS986251 plasma concentrations versus PD, including exploratory PD assessments. PK and exploratory PD profiles will be compared on Days 1 and 14 (Parts B and C). Time-dependent changes will be evaluated. Details on these analyses will be provided in the SAP.

9.4.5 Interim Analysis

Dose escalation reports will be prepared after each cohort in Parts A and B after completion of each cohort. Safety and preliminary PK and/or PD data from Parts A and B will be summarized as an interim report prior to initiation of Part C. The report will be submitted to the relevant health authorities.

11. APPENDICES

APPENDIX 1 STUDY GOVERNANCE CONSIDERATIONS

The term 'Subject' used in the eCRF is intended to refer to a person who has consented to participate in the clinical research study.

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 on Harmonisation (ICH);
- the ethical principles underlying European Union-Clinical Trial Directive (EU-CTD) 2001/20/EC;
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50); and
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent form (ICF) will receive approval/favorable opinion by the Independent Ethics Committee (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).

INDEPENDENT ETHICS COMMITTEE

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IEC for the protocol, ICF, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the 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 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 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:

- 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 IEC 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 ICF must be revised and submitted to the IEC 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 IEC.

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.

Sponsor or designee will provide the Investigator with an appropriate (ie, Global or Local) sample 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 non-technical and easily understood.
- Allow time necessary for subject to inquire about the details of the study.
- Obtain an ICF 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 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.
- Revise the ICF 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 Health Insurance Portability Act Authorization.

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

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

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, adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • 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 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 drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers

If	Then
	• 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 eCRF 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 Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by sponsor or designee.

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 Sub-Investigator and who is delegated this task on the Delegation of Authority Form. Sub-Investigators in Japan may not be delegated the CRF approval task. 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

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.

In addition, the study may be evaluated by sponsor or designee internal auditors and government inspectors who must be allowed access to eCRFs, 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 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 must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator 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). 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) (eg,study treatments sourced from the sites' stock or	It is the Investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and

commercial supply, or a specialty pharmacy)	procedures.

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

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

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

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

CLINICAL STUDY REPORT AND PUBLICATIONS

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

For this single site protocol, the Principal Investigator for the site will sign the clinical study report.

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 governing study site 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 2 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.

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/incapacity
Is a congenital anomaly/birth defect

Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [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 8.5.2.1.7) for the definition of potential DILI).

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study treatment is an SAE.

Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs (see Section 8.5.2.1.5 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 • Moderate • Severe
Assessment of Causality
The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following: • Related: There is a reasonable causal relationship between study drug administration and the AE. • Not related: There is not a reasonable causal relationship between study drug administration and the AE. The term “reasonable causal relationship” means there is evidence to suggest a causal relationship.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. Note: Follow-up SAE reports must include the same investigator term(s) initially reported. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study drug, and pregnancies must be reported to PRA Drug Safety within 24 hours of awareness of the event.
- SAEs must be recorded on the Safety Report Form; pregnancies on the Pregnancy Surveillance Form (paper forms) and entered on the eCRF.
- The preferred method for SAE/pregnancy data reporting collection is through the paper SAE/pregnancy surveillance forms. The paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

When paper forms are used, the original paper forms are to remain on site.

APPENDIX 3 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 participant's medical records, medical examination, or medical history interview.

Postmenopausal female

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

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout periods 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 PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the methods of contraception listed below is required for the duration of treatment with BMS-986251 until at least 3 months post treatment completion.

- Non-hormonal intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Complete abstinence as defined below
- Vasectomized partner with documented azoospermia 3 months after procedure

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

"Highly effective" denotes methods with a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

"Less than highly effective" denotes methods with a failure rate of > 1% per year when used consistently and correctly.

Highly Effective Contraceptive Methods That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation: oral or injectable Note: Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the study drug 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.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation (see above note about potential for interaction of study drug and hormonal methods) • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion Note: IUDs and IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from IUDs do not alter contraception effectiveness.

• Vasectomized partner: A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. o It is not necessary to use any other method of contraception when complete abstinence is elected. o WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 1. o Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence o The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject
Less Than Highly Effective Contraceptive Methods That Are User Dependent
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and a minimum of 3 months after dosing has been completed.

- Female partners of males participating in the study to consider use of effective methods of contraception for the duration of the study and a minimum of 3 months after dosing has been completed.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and a minimum of 3 months after dosing has been completed.
- Male participants must refrain from donating sperm for the duration of the study and a minimum of 3 months after dosing has been completed.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 8.5.2.1.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and Procedures for Evaluating, Follow-up, and Reporting (Appendix 2).

APPENDIX 4 DIAGNOSTIC CRITERIA FOR DRUG AND ALCOHOL ABUSE

The following is taken from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition:

DIAGNOSTIC CRITERIA FOR PSYCHOACTIVE SUBSTANCE DEPENDENCE

A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by 3 (or more) of the following, occurring at any time in the same 12-month period:

1) Tolerance, as defined by either of the following:
   a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b) Markedly diminished effect with continued use of the same amount of the substance
2) Withdrawal, as manifested by either of the following:
   a) The characteristic withdrawal syndrome for the substance
   b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3) The substance is often taken in larger amounts or over a longer period than was intended
4) There is a persistent desire or unsuccessful efforts to cut down or control substance use
5) A great deal of time is spent in activities necessary to obtain the substance (eg, visiting multiple doctors or driving long distances), use the substance (eg, chain-smoking), or recover from its effects
6) Important social, occupational, or recreational activities are given up or reduced because of substance use
7) The substance use is continued despite knowledge of having a persistent or recurring physical or psychological problem that is likely to have been caused or exacerbated by the substance (eg, current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption.)

CRITERIA FOR SEVERITY OF PSYCHOACTIVE SUBSTANCE DEPENDENCE

Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others.
Moderate: Symptoms or functional impairment between “mild” and “severe.”
Severe: Many symptoms in excess of those required to make the diagnosis, and the symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.
In Partial Remission: During the past 6 months, some use of the substance and some symptoms of dependence.
In Full Remission: During the past 6 months, either no use of the substance, or use of the substance and no symptoms of dependence.

DIAGNOSTIC CRITERIA FOR PSYCHOACTIVE SUBSTANCE ABUSE

A. A maladaptive pattern of psychoactive substance use, leading to clinically significant impairment or distress as manifested by 1 (or more) of the following, occurring at any time in the same 12-month period:
   1) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (eg, repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school, neglect of children or household)
   2) Recurrent substance use in situations in which it is physically hazardous (eg, driving an automobile or operating a machine when impaired by substance use)
   3) Recurrent substance-related legal problems (eg, arrests for substance-related disorderly conduct)
   4) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (eg, arguments with spouse about consequences of intoxication, physical fights)
B. The symptoms have never met the criteria for substance dependence for this class of substance

APPENDIX 5 REPRESENTATIVE STANDARD HIGH FAT AND HIGH CALORIE MEAL

STANDARD HIGH-FAT AND HIGH-CALORIE MEAL

The standard FDA high-fat breakfast of 918 kcal consists of:

- 2 fried eggs (in 15 g butter/margarine) (approximately 100 g)
- 1 portion of bacon (40 g)*
- 1 portion of fried potatoes (115 g)
- 2 slices of (toasted) (wheat) bread with 15 g margarine
- 1 glass of high fat milk (240 mL)

* For vegetarians bacon may be replaced by brie 60+

The total of 918 kcal (vegetarian version 915 kcal) can be broken down as follows:

- 39 g protein = 156 kcal
- 59 g fat = 527 kcal
- 59 g carbohydrates = 235 kcal