Protocol for

Official Title of Study

A Phase 2, Randomized, Double-blinded, Placebo-controlled, 5 Parallel-group Study of BMS-986166 or Branebrutinib for the Treatment of Patients with Moderate to Severe Atopic Dermatitis

NCT05014438

June 30, 2021

REGULATORY AGENCY IDENTIFIER NUMBER(S)

IND: 152413 (BMS-986166); 154998 (BMS-986195)

EudraCT: 2020-004767-77

UTN: U1111-1259-1220

CLINICAL PROTOCOL IM018005

A Phase 2, Randomized, Double-blinded, Placebo-controlled, 5 Parallel-group Study of BMS-986166 or Branebrutinib for the Treatment of Patients with Moderate to Severe Atopic Dermatitis

Short Title:

BMS-986166 or Branebrutinib for Treatment of Atopic Dermatitis

Protocol Amendment 01

Medical Monitoring Contact Information

[redacted]
Bristol Myers Squibb Company
Telephone (office): [redacted]
email: [redacted]

[redacted]
Bristol Myers Squibb Company
Telephone (office): [redacted]
email: [redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]

Bristol-Myers Squibb Company
3401 Princeton Pike
Lawrenceville, NJ 08648

Route 206 & Province Line Road
Lawrenceville, NJ 08543

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 01	30-Jun-2021	[redacted] his amendment also provides updated branebrutinib clinical pharmacology drug-drug interaction (DDI) data. The EudraCT and UTN regulatory agency identifier numbers were also added to the title page.
Original Protocol	23-Mar-2021	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:

[redacted]

The main changes include:

[redacted]

- Addition of visual acuity and optical coherence tomography (OCT) test on Day 57
- Addition of coagulation tests to be performed at screening to ensure normal clotting function upon study entry
- Additional monitoring for the occurrence of known drug reactions associated with other sphingosine-1-phosphate (S1P) receptor modulators
- Added recent clinical pharmacology branebrutinib rosuvastatin (substrate of breast cancer resistance protein [BCRP] drug transporter) drug-drug interaction (DDI) data.

The changes are applicable to all participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
Title Page	The EudraCT and UTN numbers were added to the title page.	To provide all the regulatory agency identifier numbers for the trial.
Section 2 Schedule of Activities Table 2-1 Screening Procedural Outline (IM018005)	Informed Consent notes: added "If re-enrolled, the participant must be reconsented and assigned a new participant number from IRT."	To clarify consent for requirement for re-enrolled participants.
	Added prothrombin time International normalized ratio (PT/INR) test at screening visit.	Additional coagulation tests are to be performed at screening to ensure normal clotting function upon study entry.
	Added "SARS-Cov-2: RT-PCR test or Antigen test" at screening visit.	Added at screening as an exclusion criterion to specifically exclude participants who test positive at screening or baseline.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2 Schedule of Activities Table 2-2 On-treatment Procedural Outline (IM018005)	Added "SARS-Cov-2: RT-PCR test or Antigen test" on or within 3 days of Day 1 dosing.	Added to specifically exclude participants who test positive at screening or baseline.
	Added a Day 57 visual acuity and OCT assessment.	[redacted]
	Updated the Interactive Response Technology (IRT) instructions.	To provide updated information on access/login.
Section 3.2.2.4 Pharmacokinetic Drug Interaction Summary	Added recent clinical pharmacology data for branebrutinib/rosuvastatin (substrate of BCRP drug transporter) (DDI) data.	To include the most recent clinical pharmacology DDI data in the protocol.
Section 3.3.3 [redacted] Section 3.3.3.2 Branebrutinib	Updated the risks for participants receiving branebrutinib with respect to COVID-19.	[redacted]
Section 3.3.3.3 [redacted]	Added text to clarify the timeframe regarding exclusion for COVID-19 infection (suspected or confirmed within 12 weeks of screening, at screening, and Day1).	[redacted]
Section 3.3.3.4 [redacted]	New section added to provide information on vaccination of participants with immune mediated diseases.	[redacted]
Section 5.1.4 Data Monitoring Committee	Added "select efficacy" data to the type of data that the Data Monitoring Committee (DMC) will review.	To clarify that the DMC may review efficacy data to allow the evaluation of safety in the context of benefit.
Section 6.1 Inclusion criteria 2)f) and 2)h)	Added requirement of documented history of inadequate control of atopic dermatitis by a stable regimen. Updated requirement for documentation of positive Varicella Zoster virus (VZV) IgG antibody status or complete VZV vaccination, from 30 days to **90** days prior to randomization.	To align with Table 7.7.1-1 Immunization-live vaccine.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2 Exclusion Criteria 2)h)ii)	Revised existing criteria regarding suspected or confirmed SARS-CoV-2 infection and added 1 additional exclusion criterion regarding SARS-CoV-2 vaccination.	To exclude participants who test positive for protocol-specified SARS-CoV-2 via RT-PCR test or Antigen test and those vaccinated within the screening window.
Section 6.2 Exclusion Criteria 5) vi)	Increased the estimated glomerular filtration rate from < 50 mL/min/1.73m^2 to < **60** mL/min/1.73m^2	[redacted]
Section 7.2 Method of Treatment Assignment	Updated text to describe the treatment assignment and to refer to a separate document for the details.	To remove the details of treatment assignment and instead provide the specifics of treatment assignment in a separate document to be provided to the sites.
Section 7.7.1 Prohibited and/or Restricted Treatments Table 7.7.1-1 Prohibited and Restricted Medications	Added nonlive and live vaccines that are unassociated with influenza or SARS-CoV-2 and those that are associated with influenza or SARS-CoV-2 to the list of example prohibited and restricted medications and modified washout period.	To update and clarify vaccine prohibition for SARS-CoV-2 and influenza.
Section 8.1 Discontinuation from Study Treatment	Added Grade 4 lymphopenia (absolute lymphocyte count [ALC] < 200) with repeat testing within 7 days Added Grade 2 or higher cardiac or bone marrow adverse events (with exception of ALC) Added Grade 3 for other system AEs (according to the common toxicity criteria for AES [CTCAE] version 5.0).	To clarify discontinuation of treatment for lymphopenia and other AEs based upon NCI CTCAE version 5.0 criteria.
Section 9.2 Adverse Events	Deleted "or the participant's legally authorized representative".	This protocol will not allow a legally authorized representative to report AEs or give consent for a participant.
Section 9.2.8 Monitoring of Participants with Adverse Events of Interest (AEIs)	Added malignancies, progressive multifocal leukoencephalopathy (PML), and posterior reversible encephalopathy syndrome (PRES) as potential AEIs to be specifically monitored.	These are added to address an FDA request to monitor for the occurrence of these conditions that are associated with exposure to S1P receptor modulators.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.4 Safety	Added that an external, independent DMC will be empaneled to review safety on a prescheduled and ad-hoc basis, in addition to contemporaneous safety monitoring by the Study Team.	Added for clarification.
Section 9.4.9 Clinical Safety Laboratory Assessments	Added PT/INR test to the coagulation panel and SARS-CoV-2:RT-PCR test or Antigen test to "Other Analyses.".	Coagulation tests are to be performed at screening to ensure normal clotting function upon study entry. SARS-CoV-2 RT-PCR test or Antigen test is added to exclude participants who test positive for COVID-19.
Section 9.8 Biomarkers	Clarified that serum collected at baseline and end of study for SARS-CoV-2 (anti-SARS-CoV-2 IgM and/or IgG and/or IgA) measurements are optional.	To clarify and align with other sections of the protocol stating the analysis is optional.
Section 10.2 Populations for Analyses	Added description to the Safety Population for a participant that is randomized to placebo treatment who then receives non-placebo treatment.	To add clarity to the description of the safety population used in the safety analyses, with regard to exposure to active drug(s).
APPENDIX 2 STUDY GOVERNENCE CONSIDERATIONS	Updated information on the Informed Consent Process and Source documents. Added Information on remote monitoring that will be included in the monitoring plan. Updated "Return of Study Treatment"' Section: Added information on handling of partially used supplies Removed information on the process when on-site drug destruction is not allowed. Added new section 'Study and Site Start and Closure	To align with the current BMS processes. To address the details of remote monitoring if it is utilized in the study. To provide guidance on partially used supplies. The process is not applicable for the sites participating in this study. To provide guidance on study and site closure. Informed consent will be restricted to the study participant; consent by LAR is not allowed.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Removed "legally acceptable representative" (LAR) language. Added new section Dissemination of Clinical Study Data	BMS will make information about clinical research studies and results available to the public as per regulatory and BMS requirements.
APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING	Updated the Assessment of Intensity table. Updated the Serious Adverse Event (SAE) contact information for reporting SAEs.	To clarify expectations and contact information for evaluating and reporting AEs and SAEs.
APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION	Updated description of Appendix 4. Updated the listing of highly effective contraceptive methods that are user dependent.	These updates are to align with the BMS standards of contraceptive methods.
All as applicable	Minor formatting and typographical corrections throughout.	Minor, therefore have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 2, Randomized, Double-blinded, Placebo-controlled, 5 Parallel-group Study of BMS-986166 or Branebrutinib for the Treatment of Patients with Moderate to Severe Atopic Dermatitis

Short Title: BMS-986166 or Branebrutinib for Treatment of Atopic Dermatitis

Study Phase: 2

Rationale:

Atopic dermatitis (AD) is a common, chronic inflammatory skin condition, with approximately 40% of patients meeting the criteria for moderate-to-severe disease. The substantial biological heterogeneity of AD warrants new medications acting through different mechanisms to comprehensively treat patients, such that they all achieve remission or near-remission. Thus, moderate-to-severe AD represents a clear unmet need. Signals transduced by receptors for sphingosine-1-phosphate (S1P) and by Bruton Tyrosine Kinase (BTK) are implicated in the pathobiology of AD, making these pathways attractive targets for potential AD therapies.

Study IM018005 will evaluate the efficacy and safety of BMS-986166 (the prodrug of BMS-986166-P [BMT-121795]), a sphingosine-1-phosphate (S1P) receptor modulator); and of branebrutinib, an oral, potent, and highly selective irreversible inhibitor of BTK. Each will be administered as a single agent to a population of AD participants having moderate-to-severe disease who are intolerant of treatment or inadequately treated and are candidates for systemic therapy. IM018005 is a Phase 2 study to assess the clinical benefit measured primarily by mean percentage change from baseline in Eczema Area and Severity Index (EASI) score provided by each of 3 dose levels of BMS-986166 and of a single dose level of branebrutinib after 16 weeks of treatment. Should this study demonstrate plausible efficacy and safety of either or both of these agents, their evaluation will be expanded with confirmatory studies.

Study Population:

Males and females aged 18 (or local age of majority) to 65, inclusive, with confirmed moderate-to-severe AD who are candidates for systemic therapy.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of BMS-986166 and of branebrutinib, each versus placebo, at Week 16 in participants with moderate-to-severe AD.	• Mean percentage change from baseline in EASI score at Week 16
Secondary	
• To further evaluate the efficacy of BMS-986166 and of branebrutinib, each versus placebo, at Week 16 in participants with moderate-to-severe AD.	• Proportion of participants exhibiting a vIGA-AD score of 0 (cleared) or 1 (almost cleared) AND a ≥ 2 point reduction from baseline at Week 16 • Proportion of participants exhibiting a ≥ 50% (EASI-50) reduction from baseline in EASI score at Week 16 • Proportion of participants exhibiting a ≥ 4-point improvement from baseline in Pruritus NRS at Week 16 • Mean percentage change from baseline in Pruritus NRS at Week 16 • Mean change from baseline in percentage of affected BSA at Week 16
• To assess the safety and tolerability of BMS-986166 and of branebrutinib in participants with moderate-to-severe AD.	• Incidence and severity of all AE and SAE • Incidence and severity of clinically significant changes in vital signs, ECG, OCT, PFT, and safety laboratory tests

Abbreviations: AD = atopic dermatitis; AE = adverse event; BSA = body surface area; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; NRS = numerical rating scale; SAE = serious adverse event; OCT = optical coherence tomography; PFT = pulmonary function test; vIGA-AD = Validated Investigator Global Assessment Scale for Atopic Dermatitis

Overall Design:

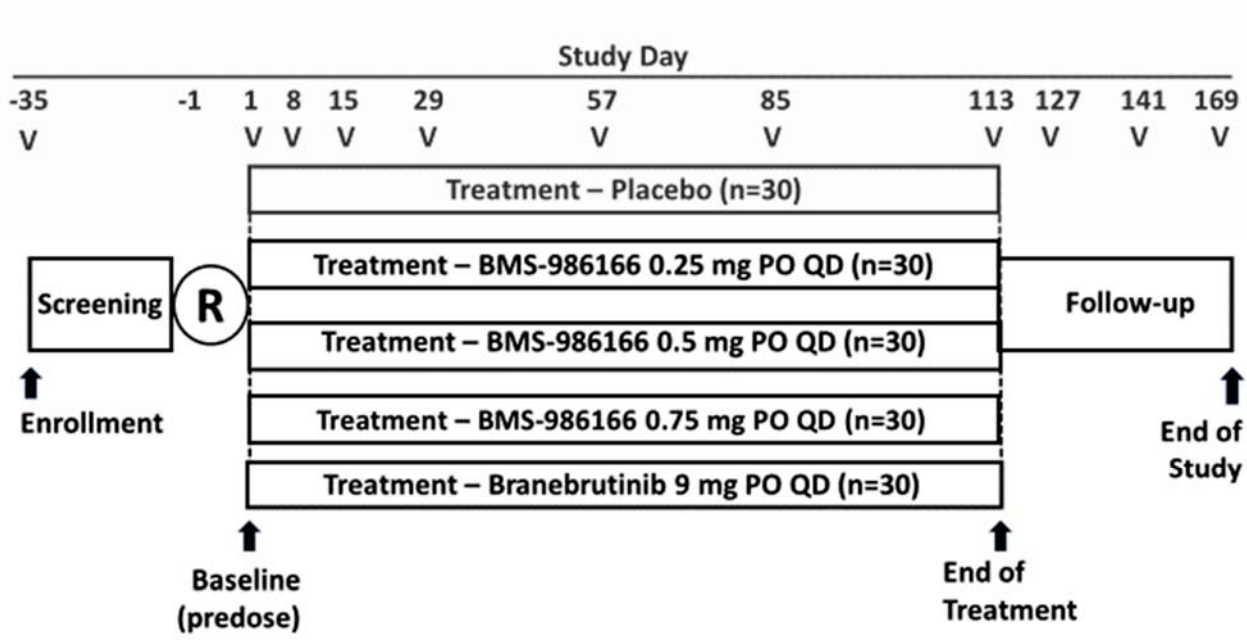
This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, 5 parallel-group study of BMS-986166 or branebrutinib for the treatment of moderate-to-severe AD. The overall study design is outlined in Figure 1-1.

Participants will have confirmed moderate-to-severe AD. Participants will be assessed for clinical responses to placebo, BMS-986166, or branebrutinib for 16 weeks and monitored for treatment-emergent safety outcomes for a total of approximately 29 weeks.

White blood cell (WBC) counts and lymphocyte counts will be monitored centrally and will not be provided to the site to prevent potential unblinding of the investigator.

An external independent Data Monitoring Committee (DMC) will be empaneled to monitor for safety with periodic and as-needed review.

Figure 1-1: Study Design Schematic



Abbreviations: n = number of participants; PO = taken orally; QD = once daily; R = randomization; V = visits
Study day visits will be ± 3 days, except for Day 8 visit (± 1 days).

Screening Period Days -35 to -1

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity, and safety assessments. Screening and randomization must be completed within 35 days of signing the informed consent form. Participants who experience an AD flare, defined as doubling of the EASI score between Screening and Baseline, or worsening that requires administration of prohibited medications within 3 weeks of randomization should be discontinued from the study.

Treatment Period, Days 1 to 113

On Day 1, eligible participants will be randomly allocated to receive: placebo, BMS-986166 0.25 mg orally (PO) once daily (QD), BMS-986166 0.5 mg PO QD, BMS-986166 0.75 mg PO QD, or branebrutinib 9 mg PO QD for 16 weeks. Randomization will be in a 1:1:1:1:1 ratio.

Participants will visit the clinic 7 times (including baseline) during the treatment period. Safety and efficacy will be assessed at each of these visits. This visit density is intended to balance, on the one hand, monitoring of sufficiently high resolution to detect infections, excessively low leukocyte counts, inefficacy and/or flares, and other problems in a timely fashion; with on the other hand, subject burdens and potential risk of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) exposure associated with clinic visits. This frequency reflects customary practice in the field, as reflected in other clinical studies of medicines having similar mechanisms.

Topical rescue treatments may be provided at the discretion of the investigator to alleviate intolerable AD symptoms. Participants escalating to systemic rescue medications or not responding adequately after at least 7 days of topical rescue treatment will be immediately discontinued from study treatment and considered treatment failures for categorical endpoints.

Follow-up Period, Days 114 to 169

Follow-up after dosing cessation is planned for approximately 60 days (5x mean half-life for BMS-986166), with visits on Days 127, 141 and 169; participants will be followed for disease activity, safety, and washout of pharmacodynamics (PD) effects. If applicable, participants will be followed until absolute neutrophil count (ANC) > 1500/μL and absolute lymphocyte count (ALC) > 1000/μL – demonstrating sufficient washout of pharmacodynamics (PD) effects to permit discharge from the study.

Number of Participants:

Approximately 150 participants will be randomized 1:1:1:1:1 into 5 parallel treatment groups.

Treatment Arms and Duration:

Participants will be randomized to one of the following dose levels of BMS-986166 or branebrutinib or placebo in blinded fashion:

- BMS-986166 0.25 mg PO QD
- BMS-986166 0.50 mg PO QD
- BMS-986166 0.75 mg PO QD
- Branebrutinib 9 mg PO QD
- Placebo PO QD
- The first dose of double-blind study medication (BMS-986166 or branebrutinib or placebo) will be taken in the morning on Day 1 after fasting for at least 8 hours.
- Study medication should be taken at approximately the same time each day.
- Participants will take 3 capsules each day, one from each of 3 distinct bottles.

Study Treatment				
Treatment Group	**Double-blind Kit**	**Bottle A**	**Bottle B**	**Bottle C**
Placebo	Each kit contains Bottle A, Bottle B, Bottle C	Placebo capsule	Placebo capsule	Placebo capsule
`166 0.25 mg QD		`166 capsule, 0.25 mg	Placebo capsule	Placebo capsule
`166 0.5 mg QD		`166 capsule, 0.25 mg	`166 capsule, 0.25 mg	Placebo capsule
`166 0.75 mg QD		`166 capsule, 0.25 mg	`166 capsule, 0.25 mg	`166 capsule, 0.25 mg
BRA 9 mg QD		BRA capsule, 3 mg	BRA capsule, 3 mg	BRA capsule, 3 mg

Abbreviations: ‘166 = BMS-986166-04; BRA = branebrutinib; QD = once daily
Note: all capsules are identical in size (size 0).

Data Monitoring Committee: Yes

Statistical Considerations:

The sample size calculation is driven by the power to compare mean percentage change from baseline in EASI score at Week 16 between BMS-986166 or branebrutinib versus placebo. Thirty participants per group will provide 84% power to detect a treatment difference (versus placebo) of 30% at the type I error of $\alpha = 0.05$ (1-sided), assuming a common standard deviation of 43%. The assumed treatment difference of 30% is similar to the mean difference observed from historical data on approved drugs across different mechanism of actions. No adjustment will be made for multiplicity.

Assuming a 15% dropout rate (ie, the fraction of participants not completing Week 16 assessment), 25 participants per group will still provide 78% power to detect a treatment difference of 30%.

An interim analysis (IA) may be performed when approximately 50% of the participants have reached Week 16 or discontinued. Safety and efficacy analysis will be performed to accelerate internal decision making. The IA will be performed by individuals or vendor independent of the study team. The study team will remain blinded during IA.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (IM108005)

Procedure	Screening Visit (Day -35 to -1)	Notes
Administrative and Historical Assessments		
Informed Consent	X	A participant is considered enrolled when a protocol-specific informed consent form (ICF) is signed. If re-enrolled, the participant must be reconsented and assigned a new participant number from IRT.
Optional ICFs	X	• AD-related Genomics and Pharmacogenetics • 12-hour Pharmacokinetics sample • Skin Biopsy
Enrollment in the IRT System	X	Contact IRT for participant number. If participant does not meet eligibility criteria, contact IRT to screen-fail participant.
Inclusion/Exclusion Criteria	X	
Demographics Collection	X	
Atopy History with Targeted Questionnaire; AD-related Treatment	X	
Medical History	X	
Prior and Concomitant Medication Use	X	Includes prescription, over-the-counter medications, and herbal supplements. All concomitant medications to be reviewed by the Medical Monitor and clinical pharmacology asset lead.
Disease Assessment		
DLQI	X	Patient reported 10 item questionnaire to evaluate the impact of skin condition on health related quality of life over the past week. (Appendix 12)
POEM	X	Patient reported 7-item questionnaire to evaluate atopic dermatitis symptoms in the past 7 days. (Appendix 13)
EASI	X	EASI score 12 or higher at screening (Appendix 9)
vIGA-AD	X	vIGA-AD ≥ 3 (Appendix 8)
BSA Assessment	X	BSA ≥ 10% affected (Appendix 10)

Table 2-1: Screening Procedural Outline (IM108005)

Procedure	Screening Visit (Day -35 to -1)	Notes
Pruritus and Sleep Quality NRS	X	Participants will be trained at Screening, and will be familiarized with its use at that time. The diary will be completed every day at waking thenceforth. Data collected starting on Day -6 will be used for analysis. (Appendix 11)
Safety Activities		
Counseling on Contraception Use	X	
Vital Signs	X	Includes body temperature, respiratory rate, blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been supine quietly for at least 5 minutes.
Complete Physical Examination	X	Includes height and weight. See Section 9.4.1.
12-lead ECG	X	ECGs should be recorded after the participant has been supine for 5 to 10 minutes. Lab work must be done after the ECG.
SAE Assessment	X	SAEs must be collected from the time of signing the ICF, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation of dosing or participation in the study if the last scheduled visit occurs at a later time.
Chest Radiography	X	PA & lateral CXR
Pulmonary Function Test	X	FEV1, FVC, and DLCO
Visual Acuity Testing and Optical Coherence Tomography	X	
Laboratory Tests		
Hematology	X	CBC with differential
Chemistry Panel	X	Includes liver function testing
Lipid Panel	X	Non-fasting
Hemoglobin A1c	X	
Coagulation Panel	X	PT and INR
Screening for Drugs of Abuse (urine or serum)	X	Performed locally and entered by the site into the eCRF
eGFR Calculation	X	
Urinalysis (UA)	X	Abnormal results trigger reflex microscopic exam

Table 2-1: Screening Procedural Outline (IM108005)

Procedure	Screening Visit (Day -35 to -1)	Notes
Pregnancy Test	X	WOCBP only; performed locally
Follicle Stimulating Hormone (FSH)	X	For select women only, serum FSH level will be determined to confirm menopausal status
FSH and LH, and Total Testosterone	X	Male participants only. Samples should be taken in the morning
Hepatitis and HIV Screening	X	Includes HCV antibody, HBsAg, HBcAb, and HIV antibodies
QuantiFERON-TB Gold test	X	
SARS-CoV-2: RT-PCR test or Antigen test	X	
COVID-19 Mitigation	X	Measures (eg, viral testing, temperature readings, interviews, social distancing, PPE, etc.) required by the clinical research site will be implemented according to approved institutional procedures.

Abbreviations: AD = Atopic Dermatitis; BSA = Body Surface Area; CBC = Complete Blood Count; COVID-19 = coronavirus disease 2019; CXR = Chest X-ray; DLCO = Diffusion Capacity; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eCRF = Electronic Case Report Form; eGFR = estimated Glomerular Filtration Rate; FEV1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; FSH = Follicle Stimulating Hormone; HBcAb = Hepatitis B core antibody; HBsAb = Hepatitis B surface antibody; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; HIV = Human Immunodeficiency virus; ICF = Informed Consent Form; INR = international normalized ratio; IRT = Interactive Response Technology; LH = Luteinizing hormone; NRS = Numerical Rating Scale; PA = Posteroanterior; POEM = Patient Oriented Eczema Measure; PPE = Personal Protective Equipment; PT = prothrombin time; RT-PCR = Reverse transcriptase polymerase chain reaction; SAE = Serious Adverse Event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = Tuberculosis; UA = urinalysis; vIGA-AD = validated Investigator Global Assessment scale for Atopic Dermatitis; WOCBP = Women of Childbearing Potential.

Table 2-2: On-treatment Procedural Outline (IM018005)

Procedure	Day 1[a] (Rand)	Day 8 W1 (± 1 days)	Day 15 W2 (± 3 days)	Day 29 W4 (± 3 days)	Day 57 W8 (± 3 days)	Day 85[a] W12 (± 3 days)	Day 113 (EOT) W16 (± 3 days)	Notes
Administrative and Historical Assessments								
Inclusion/Exclusion Criteria	X							Review of inclusion/exclusion criteria that are specified on or defined relative to the randomization day
Randomization via IRT	X							
Disease/Efficacy Assessment								
EASI	X	X	X	X	X	X	X	EASI at baseline must be ≥ 16 (prior to randomization).
vIGA-AD	X	X	X	X	X	X	X	
BSA Assessment	X	X	X	X	X	X	X	
Pruritus and Sleep Quality NRS	X	X	X	X	X	X	X	Will be collected daily in an electronic diary – represents preceding 24 hours. Data will be collected at each specified visit.
DLQI	X	X	X	X	X	X	X	Data will be collected at each specified visit.
POEM	X	X	X	X	X	X	X	
PGI-S	X	X			X		X	
PGI-C		X			X		X	
Pulmonary Function Test				X			X	FEV1, FVC & DLCO may be collected within a window of ± 5 days of visit.
Visual Acuity Testing and Optical Coherence Tomography					X		X	May be collected within a window of ± 7 days of visit.
Safety Activities								
Body Weight	X						X	

Table 2-2: On-treatment Procedural Outline (IM018005)

Procedure	Day 1[a] (Rand)	Day 8 W1 (± 1 days)	Day 15 W2 (± 3 days)	Day 29 W4 (± 3 days)	Day 57 W8 (± 3 days)	Day 85[a] W12 (± 3 days)	Day 113 (EOT) W16 (± 3 days)	Notes
Vital Signs	X[b]	X	X	X	X	X	X	Includes body temperature, respiratory rate, blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been supine for at least 5 minutes.
Complete Physical Examination	X						X	Includes height and weight. See section 9.4.1
Targeted Physical Examination		X	X	X	X	X		See section 9.4.1 for assessed organ systems.
12-lead ECG	X[c]	X	X	X	X	X	X	The duration of the Day 1 visit will be approximately 7 hours, except at select sites.
AE and SAE Assessment	X	X	X	X	X	X	X	AEs and SAEs must be collected from the time of the first dose of the study drug through the date of the follow-up or last visit.
SARS-CoV-2: RT-PCR test or Antigen test	X							Participants must have a negative SARS-CoV-2 PCR test result within 3 days prior to Day 1 dosing in accordance with site standard practices.
COVID-19 Mitigation	X	X	X	X	X	X	X	Measures (eg, temperature readings, interviews, social distancing, PPE, etc.) required by the clinical research site will be implemented according to approved institutional procedures.
Concomitant Medication Use	X	X	X	X	X	X	X	
Laboratory Tests								
Hematology (CBC)	X	X	X	X	X	X	X	
Chemistry Panel	X	X	X	X	X	X	X	

Table 2-2: On-treatment Procedural Outline (IM018005)

Procedure	Day 1[a] (Rand)	Day 8 W1 (± 1 days)	Day 15 W2 (± 3 days)	Day 29 W4 (± 3 days)	Day 57 W8 (± 3 days)	Day 85[a] W12 (± 3 days)	Day 113 (EOT) W16 (± 3 days)	Notes
eGFR calculation	X	X	X	X	X	X	X	
Urinalysis (UA)	X						X	Abnormal results trigger reflex microscopic exam.
Pregnancy Test	X	X	X	X	X	X	X	WOCBP only; performed locally.
Drugs of abuse (urine or serum)	X							Predose, performed locally and entered into the eCRF by the site
FSH, LH, and Total Testosterone				X			X	Male participants only. Samples should be taken in the morning.
SARS-CoV-2 Serology	X							Serum to be collected for optional measurements of anti-SARS-CoV-2 IgM and/or IgG and/or IgA.
Pharmacokinetics Assessments								
Collect Blood or Plasma Samples for PK	See Table 9.5.1-1							
Biomarkers Assessments and Pathway Engagement								
Biomarker samples collection	See Table 9.8-1							
Study Treatment								
Access/Login IRT	X			X	X	X		Register visit in the IRT every 4 weeks (± 3 days).
Study Drug Dispensing	X			X	X	X		Dispense study drug every 4 weeks (± 3 days).

Table 2-2: On-treatment Procedural Outline (IM018005)

Procedure	Day 1[a] (Rand)	Day 8 W1 (± 1 days)	Day 15 W2 (± 3 days)	Day 29 W4 (± 3 days)	Day 57 W8 (± 3 days)	Day 85[a] W12 (± 3 days)	Day 113 (EOT) W16 (± 3 days)	Notes
Study Drug Compliance Check		X	X	X	X	X	X	Participants must bring their pill bottles with them for pill counts and compliance queries.

[a] The visit duration on Days 1 and 85 will be approximately 7 hours for either PK and/or 12-lead ECG collection. At selected sites, the visit duration will be approximately 12 hours for PK.

[b] Day 1 visit to include vital signs recorded predose then hourly at 1, 2, 3, 4, 5, and 6 hours (± 10 minutes) post-dose.

[c] Day 1 predose 12-lead ECG will be performed, and following dosing, participants will have ECGs recorded at 1, 2, 4, and 6 hours (± 10 minutes) post-dose.

Abbreviations: AD = atopic dermatitis; AE = adverse event; BSA = body surface area; CBC = complete blood count; COVID-19 = coronavirus disease 2019; DLCO = Diffusion Capacity; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eGFR = estimated Glomerular Filtration Rate; EOT = end of treatment; FEV1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; FSH = Follicle Stimulating Hormone; ICF = informed consent form; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IRT = Interactive Response Technology; LH = Luteinizing hormone; NRS = Numerical Rating Scale; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; POEM = Patient Oriented Eczema Measure; RT-PCR = Reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UA = urinalysis; vIGA-AD = Validated Investigator Global Assessment scale for Atopic Dermatitis; W = week; WOCBP = Women of Childbearing Potential.

Table 2-3: Post-treatment Follow-up and Additional Visit Types

Procedure	Day 127 (± 3 days) W18	Day 141 (± 3 days) W20	Day 169 (± 3 days) W24 EOS[a]	Study Withdrawal	Unscheduled[b]	Notes
Administrative Activities						
Contact IRT for EOS			X	X		
Disease/Efficacy Assessment						
EASI	X	X	X	X	X	
vIGA-AD	X	X	X	X	X	
BSA assessment	X	X	X	X	X	
Pruritus and Sleep Quality NRS	X	X	X	X		Will be collected daily in an electronic diary – represents preceding 24 hours. Data will be collected at each specified visit.
DLQI	X	X	X	X	X	Data will be collected at each specified visit.
POEM	X	X	X	X	X	
PGI-S			X			
PGI-C			X			
Pulmonary function test			X	X		
Visual Acuity Testing and Optical Coherence Tomography			X	X		
Safety Activities						
Body Weight			X	X	X	Data will be collected at each specified visit.
Vital Signs	X	X	X	X	X	Body temperature, blood pressure, respiratory rate, and heart rate. Data will be collected at each specified visit.

Table 2-3: Post-treatment Follow-up and Additional Visit Types

Procedure	Day 127 (± 3 days) W18	Day 141 (± 3 days) W20	Day 169 (± 3 days) W24 EOS[a]	Study Withdrawal	Unscheduled[b]	Notes
Complete Physical Examination			X	X		Data will be collected at each specified visit.
Targeted Physical Examination	X	X			X	Data will be collected at each specified visit.
12-lead ECG	X	X	X	X	X	Data will be collected at each specified visit.
AE and SAE Assessment	X	X	X	X	X	Data will be collected at each specified visit.
Concomitant Medication Use	X	X	X	X	X	Data will be collected at each specified visit.
Laboratory Tests						
Hematology (CBC)	X	X	X	X	X	Data will be collected at each specified visit.
Chemistry Panel	X	X	X	X	X	Data will be collected at each specified visit.
eGFR calculation	X	X	X	X	X	Data will be collected at each specified visit.
Urinalysis (UA)			X	X	X	Abnormal results trigger reflex microscopic exam. Data will be collected at each specified visit.
Pregnancy Test	X	X	X	X		WOCBP only; performed locally. Data will be collected at each specified visit.
FSH and LH, and Total Testosterone			X	X		Male participants only. Samples should be taken in the morning.
SARS-CoV-2 Serology			X	X		For contingent/optional analysis

Table 2-3: Post-treatment Follow-up and Additional Visit Types

Procedure	Day 127 (± 3 days) W18	Day 141 (± 3 days) W20	Day 169 (± 3 days) W24 EOS[a]	Study Withdrawal	Unscheduled[b]	Notes
Biomarker Assessments and Pathway Engagement						
Biomarker samples collection	See Table 9.8-1					

[a] Participants follow-up may be extended as needed until absolute lymphocyte count is > 1000/μL and absolute neutrophil count is > 1500/μL.

[b] Ad hoc safety procedures required to address the circumstances and if applicable EASI, vIGA, BSA and DLQI assessments

Abbreviations: AD = Atopic Dermatitis; AE = Adverse Event; BSA = Body Surface Area; CBC = Complete Blood Count; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eGFR = estimated Glomerular Filtration Rate; EOS = end of study; FSH = Follicle Stimulating Hormone; ICF = Informed Consent Form; IRT = Interactive Response Technology; LH = Luteinizing hormone; NRS = Numerical Rating Scale; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PK = pharmacokinetics; POEM=Patient Oriented Eczema Measure; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UA = urinalysis; vIGA-AD = validated Investigator Global Assessment scale for Atopic Dermatitis; WOCBP = women of childbearing potential.

When multiple assessments are conducted at a single visit, the following is the order in which they should be performed:

1) Safety assessments (eg, vitals, electrocardiograms [ECG], adverse events [AEs])
2) Laboratory tests (eg, safety laboratory tests, pharmacokinetic assessments, biomarker assessments)
3) Clinical efficacy assessments
4) Treatment dosing

3 INTRODUCTION

IM018005 is a Phase 2 study to assess the clinical benefit provided by each of 3 dose levels of BMS-986166, a modulator of sphingosine-1-phosphate receptor 1 (S1PR1), and of a single dose level of branebrutinib (an inhibitor of Bruton Tyrosine Kinase [BTK]) in participants with moderate-to-severe atopic dermatitis (AD).

Interventions that are safe and highly effective in a large majority of AD patients with moderate or severe disease remains an unmet medical need (Section 3.1.1). Despite the recent approval of dupilumab (anti-interleukin-4 receptor alpha monoclonal antibody) for the treatment of AD, after 16 weeks of treatment, approximately 40% of patients with moderate or severe AD, demonstrated a reduction of the Investigators' Global Assessment (IGA) to either 1 (almost clear) or 0 (clear). The substantial biological heterogeneity of AD warrants development of new medications acting through different mechanisms to treat patients, so that all may achieve remission or near-remission.

Signals transduced by receptors for sphingosine-1-phosphate (S1P) and by BTK are implicated in the pathobiology of AD (Section 3.1.2), making these pathways attractive targets for potential AD therapies.

BMS-986166 and branebrutinib demonstrated satisfactory safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) in Phase 1 clinical studies following extensive and promising nonclinical evaluations (Section 3.2). Thus, they are being evaluated in this Phase 2 study for their initial safety and efficacy in participants with moderate or severe AD.

3.1 Study Rationale

3.1.1 Disease Rationale

AD is one of the most common inflammatory skin diseases, affecting 3% to 10% of the US population.[1] Worldwide, it affects up to 20% of children and 3% of adults, with higher prevalence in younger children (ages 6 years to 7 years as compared with ages 13 years to 14 years) and also in some countries which have emerged as regions of relatively high prevalence.[2] In the majority of cases, AD has an onset before age 5 years, and prevalence data in children show a slight female to male preponderance (1.3 to 1).[3] Persistent AD may be present in approximately 50% of patients diagnosed with atopic dermatitis during childhood.[4,5] Of those affected, about 40% have moderate-to-severe disease.[6] Beyond the characteristic skin pathology, AD is associated with increased anxiety, depression, sleep disorders, reduced productivity, and impaired activity – all of

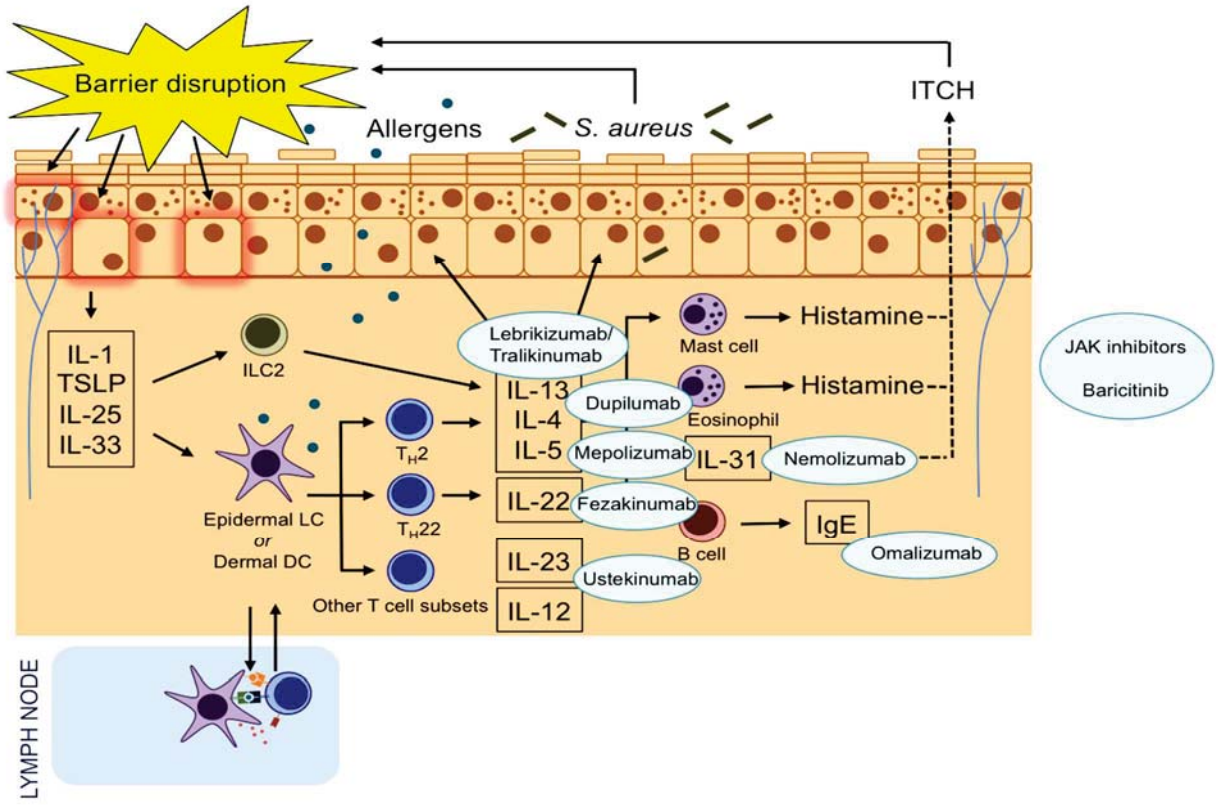
approximately equivalent magnitudes to those observed in psoriasis.[7] Patients with AD have increased risk of other atopic disorders, including asthma, allergic rhinitis, and chronic sinusitis with nasal polyposis.[8,9,10] Taken together, the burdens of AD resulted in an estimated > $5B in societal costs in 2016.[11]

A multiplicity of factors, including epidermal barrier defects, dysregulation of innate immune responses, and altered Type 2 immunity, are implicated in the pathogenesis of AD, culminating in an inflammatory response involving multiple cell types, cytokines, and chemokines. The epidermis of patients with AD is characterized by a genetically impaired skin barrier function with increased transepidermal water loss. These abnormalities may be present at birth and predict the development of AD in the first year of life.[12] Higher levels of transepidermal water loss in patients with AD have been associated with greater disease severity.[13,14] Enhanced allergen/antigen penetration through an impaired skin barrier resulting in a type 2 helper T-lymphocyte (Th2)-type milieu has been proposed as a critical link between the primary barrier defect in patients and Th2 polarization.[15] Th2 differentiation of naive CD4+ T-cells predominates in AD causing an increased production of interleukins (IL), primarily IL- 4, IL-5, and IL-13 (Figure 3.1.1-1), which then leads to an increased level of immunoglobulin E (IgE), and corresponding inhibition of type 1 helper T-lymphocyte (Th1) differentiation. In 80% of AD patients, the disease is associated with hypersensitivity to environmental or food allergens, increased specific serum IgE levels, and eosinophilia.[16,17] Thus, AD is often part of (even the first manifestation of) a multi-system, Th2-dependent disease constellation that can include allergy, elevated IgE, and asthma.[18,19,27] The barrier defects, other genetic and environmental factors, and exaggerated Th2 biology also involve activation of dermal keratinocytes and Langerhans cells, accompanied by in situ lymphocyte proliferation and activation – potentially accompanied by allergic phenomena in many cases[20] and possibly immune -mediated phenomena in a fraction of cases.[21] This pathobiology further worsens barrier function and causes the chronic, self-sustaining syndrome of skin rash, pruritus, xerosis, and gram-positive skin dysbiosis that imposes the personal and societal burdens summarized above (Figure 3.1.1-1).

Until recently, treatment for moderate or severe AD involved hydration of the skin, and/or application of topical treatments such as glucocorticoids, calcineurin inhibitors, phosphodiesterase 4 (PDE4) inhibitors, tar, vitamin D, or dilute bleach. Severe, complex, or refractory cases invoked wet-wrap dressings, phototherapy, or systemic treatment with glucocorticoids, cyclosporine, and azathioprine -- for most patients, these approaches were, at best, partially satisfactory.[10] More recently, biologic and small molecule therapies have proven to be promising investigational treatments for AD (Figure 3.1.1-1).[22] In particular, the recent European Medicines Agency (EMA) and FDA approvals of dupilumab (anti-IL-4Rα monoclonal antibody) represent a significant advance for AD patients.[29] Nevertheless, AD exhibits biological and clinical heterogeneity,[23,24] and new medications employing different mechanisms are needed to provide a complete treatment armamentarium; indeed, the placebo-adjusted fraction of patients with moderate or severe AD demonstrating a reduction of Investigators' Global Assessment (IGA) to either 1 (almost clear) or

0 (clear) after 16 weeks of dupilumab treatment is only ~36%.[25,26] Furthermore, dupilumab requires periodic injections which may be associated with inconvenience, discomfort, and injection-site reactions. New treatments for moderate and severe AD thus still represent a clear unmet need.

Figure 3.1.1-1: Schematic of Selected Immune Mechanisms in Atopic Dermatitis



Abbreviations: DC = dendritic cell; IgE = immunoglobulin E; IL = interleukin; ILC2 = type 2 innate lymphoid cell; LC = Langerhans cell; S. aureus = Staphylococcus aureus; TSLP = thymic stromal lymphopoietin. Schematic model of interplay between microbiome, skin barrier, and immunity in atopic dermatitis highlighting targets of novel biologic agents.[22]

3.1.2 Rationale for Study Drug Mechanisms

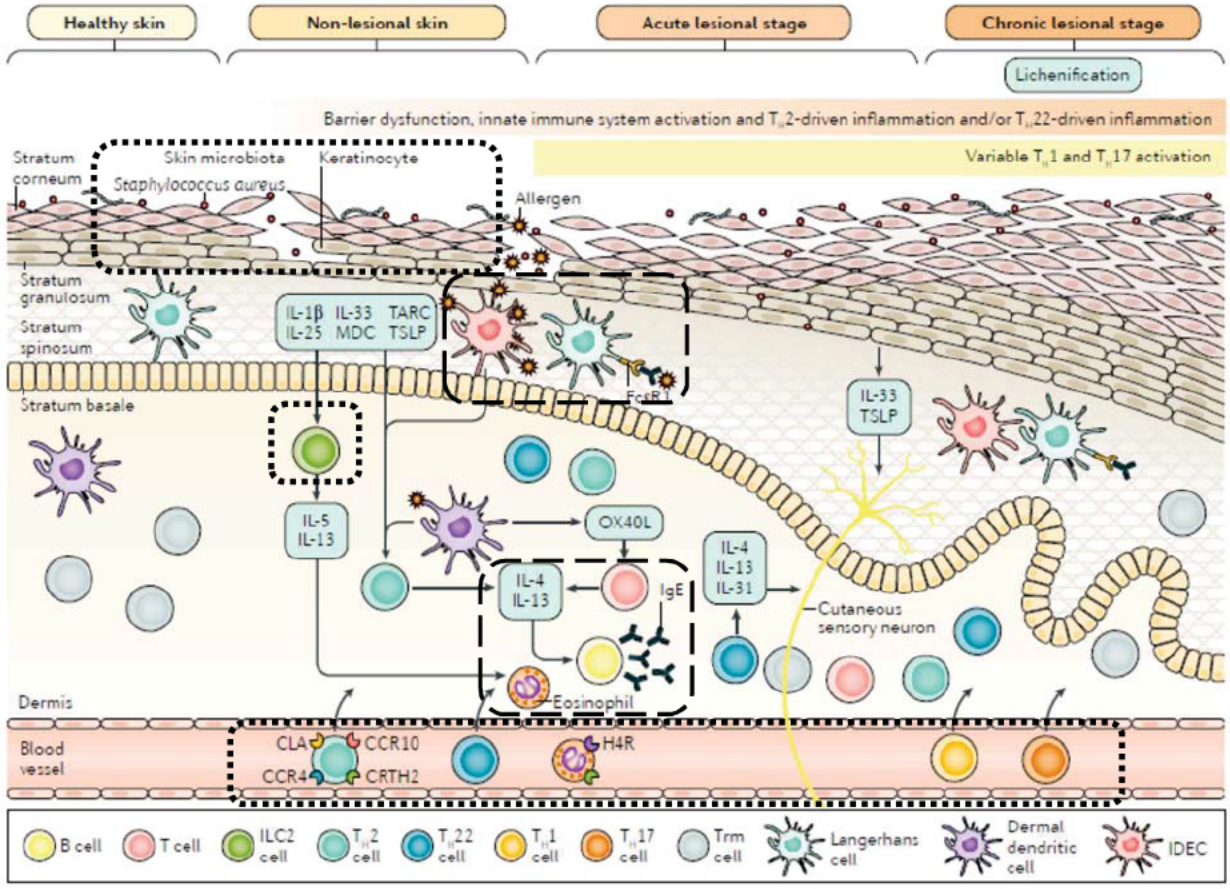
Exaggerated activation, local proliferation, and in-migration of leukocytes in the skin characterize AD (Figure 3.1.2-1).[27,28] Th2 cells contribute by producing IL-4, -5, and -13, which, amongst other effects, recruit and activate eosinophils. Together, the Th2 cells and eosinophils directly and indirectly contribute to multiple phenomena associated with AD – including IL-31 production, which helps drive the intense itch associated with the disease. Products of these cells are validated targets of both approved and experimental treatments for AD, including dupilumab (anti-IL-4Rα);[29] and nemolizumab (anti-IL-31).[30,31] Th2 cells and a subset of myeloid dendritic cell (DC) also play significant roles; their function and products have likewise been targeted by experimental therapies (Figure 3.1.1-1).

S1P is a lysophospholipid mediator that evokes a variety of cellular responses by the stimulation of 5 members of a G-protein coupled receptor family: S1PR1, 2, 3, 4, 5.[32] S1PR1 is ubiquitously distributed across multiple tissues, notably endothelial cells and lymphoid cells. Among its numerous biological activities, S1PR1 controls the egress of lymphocytes from peripheral lymphoid organs and their subsequent peripheral localization. Thus, S1PR1 has been targeted in the treatment of immune-mediated diseases.[33] In particular, S1P also figures prominently in the migratory behavior and activation states of the cells operative in AD;[34] and is important to keratinocyte homeostasis,[35,36] accordingly, S1PR modulation is a promising approach for the treatment of AD. The dotted boxes in Figure 3.1.2-1 highlight S1P-associated elements of AD pathobiology. Hence, the second-generation S1PR agonist (S1PR1 full agonist, S1PR4/5 partial agonist) etrasimod is already being studied in a Phase 2 study for this indication.[37]

BMS-986166 (henceforth meaning either the parent or its phosphorylated derivative, depending on context) differentiates from other S1PR drugs by virtue of its partial agonist activity on S1PR1 (Section 3.2) – leading to reduced macular, pulmonary, and cardiac liabilities both in vivo nonclinical and in vitro pharmacology models.[38] Furthermore, the safety data for BMS-986166 from two Phase 1 studies of healthy participants (IM018001 and IM018003) demonstrated no significant effects on ECG (after the first dose or after multiple doses), vital signs, and clinical laboratory parameters at the doses to be tested in this study.

Based on the preceding, BMS-986166 is an appropriate investigational drug for AD. For justification of doses, refer to Section 5.5.1.

Figure 3.1.2-1: Schematic Model of Leukocyte Roles in Atopic Dermatitis



Abbreviations: IgE = immunoglobulin E; IL = interleukin; ILC = innate lymphoid cell; IDEC = inflammatory dendritic epidermal cell; Th = helper T-cell; Trm = resident T memory cell; TSLP = thymic stromal lymphopoietin
Dotted boxes highlight targets of S1PR1 modulators; Dashed boxes highlight targets of Bruton Tyrosine Kinase inhibitors.[28]

Similarly to the S1P signaling axis, kinases that regulate cellular activities associated with AD pathobiology also represent promising therapeutic targets, as demonstrated by the reported efficacy of the Janus kinase inhibitors abrocitinib and upadacitinib.[39,40,41] BTK is a member of the Tec family of nonreceptor tyrosine kinases and is expressed in all hematopoietic cells, except T-cells and terminally-differentiated plasma cells.[42] The underlying pathobiology of several immune-mediated diseases involves signaling pathways associated with BTK activation.

In B-cells, BTK helps mediate B-cell receptor (BCR) responses to autoantigens and pro-inflammatory signaling.[43] BTK also plays a role in signaling via the Fc gamma receptor (FcγR)IIa and FcγRIIIa receptors (low affinity activating receptors for immune complexes [ICs] containing immunoglobulin [Ig]G on myeloid cells and dendritic cells)[44,45,46] which may play a critical role in the immunopathology of immune-mediated disorders. Of added relevance to AD, BTK is also critical for signaling via the high-affinity IgE receptor (FcεRI) expressed on the mast cells, eosinophils, and inflammatory dendritic epidermal cells (IDEC) cells that feature prominently in AD pathobiology. The dashed boxes in Figure 3.1.2-1 highlight BTK-associated elements of AD pathobiology.

BTK inhibition is thus expected to block antigen-dependent B-cell signaling and function without depleting B-cells[43], lead to decreases in IC-mediated production of pro-inflammatory cytokines, reduce IC signaling to monocytic cells, and block FcεRI-mediated activation of basophils and eosinophils by allergen-specific IgE.[47] Many of the processes mediated by BTK are shared across immune-mediated diseases, including AD,[48] making it a plausible target for the treatment of multiple immune-mediated disorders, including AD.

Branebrutinib is an oral, potent, and highly selective, irreversible inhibitor of BTK that covalently modifies a cysteine residue within the active site of the enzyme; it is thus an appropriate investigational drug for AD in this study. For justification of dose, refer to Section 5.5.2.

3.1.3 Rationale for Study Population

Mild AD generally responds well to skin hydration and topical agents.[10] Treatment of moderate-to-severe AD, however, still represents a significant unmet need because the majority of patients do not achieve durable clear or almost-clear status in investigator assessments, despite topical treatment or systemic therapy (Section 3.1.1).

AD, like most inflammatory disorders, exhibits a waxing and waning course; thus, careful patient selection is required to avoid unexpected "regression to the mean" and other confounding effects in clinical studies. This study will recruit adult participants with moderate or severe chronic AD of at least 2-years duration. They must also demonstrate Eczema Area and Severity Index (EASI) score ≥ 16, validated Investigator Global Assessment Scale for Atopic Dermatitis (vIGA-AD) ≥ 3, and ≥ 10% body surface area (BSA) affected by AD at baseline visit. In addition, a stable regimen (≥ 4 weeks) of topical corticosteroids, calcineurin inhibitors or biologics must have failed to provide adequate response within the 6 months prior to randomization. Consistent use of additive-free, basic bland emollients twice-daily for ≥ 7 days before the baseline visit and throughout the treatment period will be mandatory. These factors will minimize selection of patients with inconsistent or exceptionally variable disease. Only adults will be studied due to the early developmental phases of both active investigational products.

3.1.4 Rationales for Primary and Secondary Efficacy Endpoints

The primary efficacy endpoint is mean percentage reduction from baseline in EASI score at Week 16. The EASI is a widely used clinical study endpoint in AD. Thus, it allows contextualization with the full spectrum of approved and experimental drugs – offering maximum opportunity for benchmarking and modeling of the relationships between PK, PD, safety, and efficacy. This study will use it on a continuous scale to maximize statistical efficiency – though the categorical endpoints of EASI-50/75/90 will be assessed as secondary/exploratory endpoints. (Table 4-1)

The secondary endpoints include the mean reduction in affected BSA, the proportion of participants achieving EASI-50, and the proportion of participants achieving a score of "cleared" or "almost cleared" on the vIGA-AD and pruritus NRS (4-point improvement and mean % change). These endpoints are important adjuncts to the continuous-scale EASI and can provide insight into the registrational plausibility of the study drugs. The FDA, in particular, has assigned significant weight to the vIGA-AD response in registrational packages of other compounds.

3.1.5 Research Hypothesis

Inhibition of S1PR1, 4, 5 or BTK with BMS-986166 or branebrutinib, respectively, will safely reduce disease activity in participants with moderate-to-severe AD.

3.2 Background

3.2.1 BMS-986166

A detailed description of pharmacology, toxicology, and clinical safety can be found in BMS-986166 investigator brochure.[38] Key highlights are provided below.

3.2.1.1 In Vitro Pharmacology

BMS-986166 is a novel prodrug that is phosphorylated to its pharmacologically active moiety, BMS-986166-P (BMT-121795). BMS-986166-P is a sphingosine 1 phosphate (S1P) receptor modulator; a biased agonist of S1PR1, with agonist activity for S1PR4 and S1PR5. BMS-986166-P relies predominantly on sphingosine kinase 2 (SphK2), similar to fingolimod (FTY-720, GILENYA®). Importantly however, BMS-986166-P differentiates from fingolimod phosphate (FTY-P) and other S1PR1 agonists in its differential effects on various signaling pathways downstream of S1PR1, ie, it is a biased ligand.[49]

BMS-986166-P fully displaces S1P binding to S1PR1 transfected Chinese hamster ovary (CHO) cells with an half maximal inhibitory concentration (IC50) of 0.014 nM, and acts as a full agonist in a cyclic adenosine monophosphate (cAMP) assay in these cells with an EC50 of 0.0079 nM, comparable to fingolimod phosphate. In an S1PR1 GTPγS binding assay in S1PR1/CHO cells, however, BMS-986166-P acts as a partial agonist with maximum efficacy that reaches only 79% of the maximum efficacy of endogenous ligand S1P. In an S1PR1 internalization assay (in S1PR1/CHO/ green fluorescent protein [GFP] cells), BMS-986166-P also acts as a partial agonist with an efficacy that reaches 72% of maximum effect observed with S1P. This partial agonism is unique to BMS-986166-P, as fingolimod phosphate and S1PR1 selective agents (eg, BAF-312, KRP-203, and CS-0777) are S1PR1 full agonists in both the GTPγS and the internalization assays. Lastly, in an S1PR1 extracellular signal-related kinase (ERK)-phosphorylation assay (in S1PR1/CHO cells), BMS-986166-P is shown to be a full agonist but with an EC50 more than 100-fold higher than the EC50 of fingolimod phosphate. Taken together, the above demonstrate the biased agonism properties of BMS-986166-P.

Despite the above-mentioned differences in receptor pharmacology in S1PR1/CHO cells, BMS-986166-P completely blocks S1P-induced T-cell chemotaxis in a primary T-cell system, similar to fingolimod phosphate. Lastly, similar to fingolimod phosphate, BMS-986166-P is a potent agonist for S1PR4 and S1PR5 receptors with EC50 values comparable to fingolimod phosphate: 3.4 and 2.47 nM vs. 1.6 and 0.67 nM, correspondingly. Similar to second-generation S1P-1 modulators, BMS-986166-P is inactive in S1P-3R GTPγS assays with an EC50 greater than 1 μM.

In summary, BMS-986166-P appears to be a biased ligand of S1PR1 based on its partial agonist activity in the S1PR1 internalization assay (S1PR1/CHO cells) and right-shifted potency in ERK

phosphorylation assays (vs. fingolimod phosphate). BMS-986166 thus demonstrates differentiated in vitro pharmacology relative to prior-generation S1PR1 modulators, offering promise for improved clinical performance.

3.2.1.2 In Vivo Pharmacology

S1PR1 agonists cause lymphocyte sequestration in lymphoid organs, which results in rapid lymphopenia. Accordingly, in rats receiving vehicle or escalating doses of BMS-986166, BMS-986166 reduces lymphocyte counts in a dose-dependent manner at 24 hours post-dose, achieving a decline of ~80% compared with vehicle-treated controls. The EC50 was determined to be 6.5 nM in rats.[38]

Mouse skin contact hypersensitivity models share many of the features of human atopic dermatitis. Accordingly, contact hypersensitivity was induced in BALB/c mice by sensitizing the flanks with 0.5% fluorescein isothiocyanate (FITC) on Days 0 and 5 of the study and challenging the ears with the same solution on Days 11, 12, and 13. Treatments included BMS-986166 administered via oral gavage at 0.1, 0.5, or 2 mg/kg/day or dexamethasone at 1 mg/kg/day with first dose initiated on the day before sensitization. BMS-986166 demonstrated robust efficacy in this 14-day FITC-induced AD model based on the dose-dependent reduction in 1) ear swelling, 2) total serum IgE levels, 3) ear histology scores, 4) scratching events, 5) skin inflammatory cytokine gene expression (Th1, Th2, Th17, Th22), and 6) the numbers of infiltrating immune cells.[50] The effect for BMS-986166 at 2 mg/kg was comparable to that of the dexamethasone positive control. BMS-986166 thus modulates the complex inflammatory pathways involved in this model of AD disease pathogenesis.

BMS-986166 has also demonstrated maximal lymphopenia and efficacy in the experimental allergic encephalomyelitis rodent model of MS, and the MRL/lpr mouse lupus model -- similar to that of fingolimod, and efficacy superior to anti-tumor necrosis factor (TNF)α antibody in oxazolone-induced mouse colitis models. Although these models differ phenomenologically from those of AD, the latter share key cellular and molecular mechanisms with the former,[51] as demonstrated by published reports of beneficial pharmacologic S1PR1 modulation in murine AD models.[52]

Taken together, the in vivo pharmacology properties of BMS-986166 support efficacy testing in human immune-mediated diseases, including AD.

3.2.1.3 Nonclinical Toxicology

A comprehensive nonclinical toxicology program was executed for BMS-986166 and is summarized in BMS-986166 Investigator Brochure (IB).[38] Results of 6-month and 9-month good laboratory practice (GLP) toxicity studies in rats and dogs, respectively, are highlighted below.

In a 6-month repeat dose, oral GLP toxicity study in rats with an 8-week recovery period, BMS-986166 was administered at doses of 0 (vehicle), 1, 3, or 10 mg/kg/day to groups of 25 rats/sex. Potential effects of BMS-986166 on mating and fertility in male rats and early embryonic development of their offspring were also evaluated.[53] BMS-986166 was well tolerated

at doses of up to 10 mg/kg/day with no BMS-986166-related clinical observations or effects on physical and ophthalmologic examinations, NCV measurements, male reproductive performance and early embryonic development of their offspring, and coagulation and urinalysis parameters. Findings consistent with the intended pharmacology of BMS-986166 were observed at all doses (≥ 1 mg/kg/day; mean sex-combined AUC[0-24] ≥ 1.13 µg·h/mL), including decreased lymphocytes in blood and lymphoid tissue. All BMS-986166-related changes were partially or completely reversible following the 8-week post-dose recovery period. As there were no adverse findings at any dose, the NOAEL was considered to be 10 mg/kg/day (mean sex-combined AUC[0-24h] 7.29 µg·h/mL for BMS-986166 and AUC[0-24h] 22.3 µg·h/mL for BMS-986166-P).

In a 9-month repeat dose, oral GLP toxicity study in dogs with a 12-week recovery period, BMS-986166 was administered by oral gavage at doses of 0 (control; males/females), 0.1 (males), 0.3 (males/females), 1 (males/females) and 3 (females) mg/kg/day to groups of 4 to 6 dogs per sex.[54] BMS-986166 was clinically well tolerated when administered at an oral dose of ≤ 1 mg/kg/day in males (mean AUC[0-24h] 4.44 µg·h/mL), and ≤ 3 mg/kg/day in females (mean AUC[0-24h] 7.51 µg·h/mL) with no drug-related clinical observations or effects on neurological, ECG or ophthalmic examinations; respiratory assessments; coagulation, urinalysis or urine chemistry parameters; and organ weights or gross pathology. Findings consistent with the intended pharmacology were observed at all doses included decreases in lymphocytes in blood and lymphoid tissue. There were no adverse BMS-986166-related findings at 0.1 mg/kg/day in males and ≤ 3 mg/kg/day in females; however, adverse changes of seminiferous tubule degeneration/atrophy of the testis that were reversible were observed in males at 0.3 mg/kg/day and 1 mg/kg/day. Therefore, the NOAEL was considered to be 0.1 mg/kg/day in males and 3 mg/kg/day in females (AUC[0-24h] 0.528 µg·h/mL and 7.51 µg·h/mL, respectively, for BMS-986166, and AUC[0-24h] 2.16 µg·h/mL for males at 0.1 mg/kg/day, and 25.3 µg·h/mL for females at 3 mg/kg/day for BMS-986166-P).

3.2.1.4 Pharmacokinetic Drug Interaction Summary

A complete summary of the nonclinical PK of BMS-986166 can be found in the IB. Drug-drug interaction (DDI) potential of BMS-986166 is briefly discussed in this section. In vitro data in human liver microsomes suggested that BMS-986166 is metabolized via cytochrome P450 (CYP)3A4/3A5 (~68%) and CYP2C8 (~36%).[55] Thus, the PK of BMS-986166 may be altered when co-administered with CYP3A4/3A5 inhibitors or inducers.

In vitro studies with recombinant enzymes showed that BMS-986166 did not inhibit uridine diphosphate glucuronosyltransferase (UGT)1A1 at clinically relevant concentrations.[56] In human liver microsomes, BMS-986166 was not a reversible or time-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 (IC50 > 6 µM).[56] In cryopreserved human hepatocytes, BMS-986166 was not an inducer of CYP1A2, CYP2B6, or CYP3A4 (EC50 > 2.5 µM).[56]

BMS-986166 did not inhibit digoxin transport in Caco-2 cells (IC50 > 15 μM),[56] suggesting that it is not a P-glycoprotein (P-gp) inhibitor. In vitro studies with cells expressing single transporters showed that BMS-986166 is not an inhibitor of various human transporters including breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP1)B1, OATP1B3, bile salt export pump, organic anion transporter (OAT)1, OAT3, sodium taurocholate co-transporting polypeptide, or multidrug resistance-associated protein 2 (IC50 > 16.7 μM).[56]

Overall, the present results indicate that the potential for BMS-986166 as a perpetrator of DDI is minimal. There have been no formal clinical DDI studies with BMS-986166.

3.2.1.5 Clinical Safety

Clinical safety of BMS-986166 has been evaluated in 2 studies performed in healthy participants.

Study IM018001

Study IM018001 was a randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, PK, and PD of single ascending doses (SAD) of BMS-986166 and an ascending dose titration of BMS-986166 over 16 days, as well as the effect of food and pH on the relative bioavailability of BMS-986166. It was performed in healthy women not of childbearing potential (WNOCBP) and in males. BMS-986166 was administered as SAD (Panels 1-3), an intrasubject ascending dose titration (Panel 4), and as a single fixed dose with or without food and famotidine (Panel 5a/b/c).

- In Panels 1-3, eligible participants were randomized in a 4:1 ratio to receive an oral solution formation of BMS-986166 or placebo. The doses for Panels 1, 2, and 3 were 0.75 mg, 2.0 mg, and 5.0 mg, respectively.
- Panel 4 enrolled 16 participants who were randomized in a 3:1 ratio to receive double-blind treatment with an oral solid dosage formulation of BMS-986166 or placebo. Participants randomized to BMS-986166 received increasing daily doses of 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, and 1.5 mg.
- Panel 5 enrolled 24 participants who were randomized in a 1:1:1 ratio to receive a single dose of 2.0 mg BMS-986166 solid dosage formulation in the fasted state (Panel 5a), in the fed state (Panel 5b), or 2 hours following administration of 40 mg famotidine (Panel 5c). Panel 5 did not include a placebo lead-in period.

Sixty participants received BMS-986166 in this study. Single oral doses of BMS-986166 were administered to 48 participants at doses of 0.75 mg (8 participants), 2.0 mg (32 participants), or 5.0 mg (8 participants). The other 12 participants received multiple oral doses of BMS-986166, which were titrated from 0.25 mg to 1.5 mg over a dosing period of 16 days. BMS-986166 was administered as an oral solution formulation to 24 participants (8 participants each at doses of 0.75 mg, 2.0 mg, or 5.0 mg) and as a capsule formulation in the other 36 participants. Ten participants received matching placebo.

BMS-986166 was well tolerated by the healthy participants in this study when administered as single oral dose from 0.75 mg to 5.0 mg, or as multiple oral doses with titration from 0.25 mg to

1.5 mg over 16 days. All AEs reported in the study were assessed as non-serious, mild in intensity (Grade 1), and unrelated to study treatment. There were no deaths, SAEs, or treatment discontinuations due to AEs. Treatment-emergent AEs were reported with similar frequency for BMS-986166-treated participants (any dose) and placebo participants. Among participants receiving BMS-986166, there were no dose-related trends in the frequency of AEs, nor were there any meaningful differences in the AE profile when BMS-986166 was administered as a solid dosage versus solution formulation or following administration of BMS-986166 with a high-fat meal or famotidine compared with administration of BMS-986166 alone under fasting conditions.

Transient, dose-dependent reductions in mean absolute lymphocyte count (ALC) deemed not clinically relevant were observed following treatment with BMS-986166 compared with placebo, an effect that was expected based on the mechanism of action of BMS-986166 and that was evaluated as a PD endpoint in this study. Furthermore, no subject experienced an infection that was attributed to study treatment and could potentially be related to lymphopenia.

Cardiac monitoring and frequent ECG analyses were performed throughout the study. Though dose-dependent decreases in hourly heart rate (HR) were observed following administration of single doses of BMS-986166, no adverse treatment-related reductions in HR or other ECG abnormalities were identified. For the interval from 0 to 12 hours post-dose, the time-matched, placebo-corrected, median largest decreases in hourly HR were -0.29 beats per minute (bpm), -6.38 bpm, and -8.37 bpm for the 0.75, 2.0, and 5.0 mg dose panels, respectively. The 2 highest dose panels met the prospective definition for treatment-related bradycardia during the 0 to 12-hour and/or 0 to 24-hour time intervals (ie, median time-matched largest decrease from baseline in hourly HR showed a $\geq$ 7 bpm difference for active relative to placebo); however, no subject had a reduction in HR below an absolute value of 45 bpm, and no subject experienced an AE of syncope, dizziness, atrioventricular (AV) block, or other event that could be attributed to a reduction in HR. It is important to note that the 2.0 mg and 5.0 mg doses administered in Study IM018-001 are well above the dose levels to be administered in this Phase 2 study (IM018-005). Section 5.5.1 details the relationship between dose and HR expected for the present study.

A similar effect on hourly HR was not observed following dose titration of BMS-986166 up to 1.5 mg in Panel 4. In addition, an evaluation of ECG HR during treadmill testing in Panel 4 did not indicate any clinically meaningful effect on the target physiologic HR achieved during exercise following dose titration of BMS-986166. A concentration-response analysis of ΔQTcF interval versus plasma concentration of BMS-986166 or BMS-986166-P did not show any trends toward increases in QTcF with increasing concentration of either analyte; the apparent slight decrease in QTcF with increasing concentration of BMS-986166 was not deemed clinically relevant.

In summary, the safety data from Study IM018001 indicated that single doses of BMS-986166 up to 5.0 mg were generally safe and well-tolerated, and did not suggest association with unexpected infection risk, or an increased risk of clinically significant bradycardia, AV conduction delays/blocks, or hypotension.

Study IM018003

Study IM018003 was a randomized, double-blind, placebo-controlled study designed to assess the safety, tolerability, PK, and PD of MAD of BMS-986166 for 28 days in healthy male or female (WNOCBP) participants. There were 3 sequential multiple-dose panels designated as Panels 1, 2, and 3. A total of 32 participants received QD doses of blinded study treatment for 28 days; 24 participants received BMS-986166 at doses of 0.25, 0.75, or 1.5 mg (8 participants per dose), and 8 participants received placebo.

- Multiple oral doses of BMS-986166 up to 1.5 mg QD for 28 days were safe and generally well tolerated in the healthy participants in this study.
- No drug-related SAEs or deaths occurred during this study. One subject administered placebo had an SAE reported as vasovagal symptoms graded as moderate (Grade 2).
- Twenty-two of 24 participants (91.7%) experienced AEs following administration of BMS-986166, and 6 of 8 participants (75.0%) had AEs following administration of placebo. The most frequently occurring AEs during BMS-986166 administration were lymphopenia (N=15; 62.5%) versus 0 in placebo arm, which is consistent with the pharmacology of the drug; contact dermatitis at the site of the ECG monitoring electrode deemed unrelated (N=8; 33.3%) versus 1 (12.5%) in placebo group, increased blood creatine phosphokinase (N=7; 29.2%) versus 3 (37.5%) in placebo group, and headache (N=5; 20.8%) versus 1 (12.5%) in placebo group.
- Eighteen of 24 participants (75.0%) administered BMS-986166 experienced AEs assessed as drug-related by investigators, all graded as mild (Grade 1). The most frequent were lymphopenia (N=15; 46.9%), headache (N=3; 9.4%), and alanine aminotransferase (ALT) increased (N=3; 9.4%), which were generally dose dependent.
- Of the 32 participants treated, 2 participants (6.3%) discontinued treatment due to AEs. One subject (12.5%) in the 1.5 mg BMS-986166 QD dose group had a single premature ventricular contraction (PVC) with retrograde sinus node activation (listed as sinus node exit block), which was followed by a 3-beat run of non-sustained ventricular tachycardia (NSVT) and 4 isolated PVCs lasting less than 1 minute on continuous clinical monitoring. This event was asymptomatic and graded as mild. One subject in the placebo group had a decrease in serum testosterone lasting 38 days.
- There was a dose-related trend in the AE observance of mild lymphopenia, the intended mechanism of action of BMS-986166, occurring after multiple oral doses of BMS-986166 $\geq$ 0.75 mg QD. There were no other treatment, or dose-related trends in the frequency of clinical laboratory abnormalities after multiple oral doses of BMS-986166 up to 1.5 mg QD for 28 days.
- There were no apparent dose-related trends in the 12-lead ECG parameters (ie, HR; and PR, QRS, QTcF, and QT intervals).
- There was a dose-related decrease in mean HR, recorded by continuous cardiac monitoring on Day 1, after administration of BMS-986166 compared with placebo in a time-matched analysis. No arrhythmias of high-grade AV block were noted. There were no differences in AEs of dizziness, syncope, pre-syncope, and fatigue between the drug and the placebo arms. Overall, in the study, there was 1 subject who had symptoms of pre-syncope at the 0.25 mg

dose and 1 subject with dizziness at the 0.75 mg dose. In the placebo arm, there was 1 subject with dizziness and 1 subject with pre-syncope.

- Statistical analysis of continuous cardiac monitoring data identified no treatment-related bradycardia (ie, maximal median HR decrease of ≥ 7 bpm compared with time-matched predose levels vs placebo participants) in hourly HR at nadir following multiple oral doses up to 1.5 mg BMS-986166.
- Results from the BMS-986166 treatment panels over the 0 to 672 hour (Day 28) study interval yielded largest decreases in nadir hourly HR (time matched) from placebo of 0.83 bpm, 3.46 bpm, and 5.54 bpm at the 0.25 mg, 0.75 mg, and 1.5 mg dose levels, respectively.
- There were no clinically meaningful changes in vital signs or physical examination findings (see Section 9.2.8).

In summary, the safety data from Study IM018003 indicated that (1) multiple ascending doses of BMS-986166 up to 1.5 mg were generally safe and well-tolerated, and with no association with unexpected infection risk, or an increased risk of symptomatic bradycardia, AV conduction delays/blocks, or hypotension; and (2) no dose initiation titration is required.

Taken together, results of Phase 1 studies with BMS-986166 demonstrate a satisfactory safety profile for its investigation in patients with immune-mediated diseases.

3.2.2 Branebrutinib

A detailed description of pharmacology, toxicology, and clinical safety can be found in the branebrutinib IB.[47] Key highlights appear below.

3.2.2.1 In Vitro Pharmacology

Branebrutinib is a potent inhibitor of BTK (IC50 = 0.1 nM) that covalently modifies a cysteine residue (Cys-481) within the active site of the enzyme. Against a panel of 245 kinases, the compound was shown to inhibit BTK with greater than 5,000-fold selectivity over all but 4 kinases. The highly related kinase Tec was inhibited 9-fold less potently than BTK. Of particular note, branebrutinib was > 10,000-fold selective over members of the epidermal growth factor receptor (EGFR) family of kinases. In contrast, ibrutinib inhibited these EGFR kinase family members with much greater potency, with only 10- to 110-fold selectivity for BTK.[57] Ibrutinib shows 3-fold selectivity for BTK over Tec.

Branebrutinib potently inhibited multiple functional endpoints in primary human B-cells stimulated through the BCR (IC50 values < 1 nM), including production of inflammatory cytokines, cell proliferation, and surface expression of CD86. Branebrutinib also inhibited FcγR (FcγRIIa and FcγRIIIa)-dependent IL-6 production stimulated from peripheral blood mononuclear cells (PBMCs) stimulated by IgG-containing ICs with a potency (IC50 = 0.3 nM) equivalent to those measured against BCR-dependent endpoints in B-cells. In assays using human whole blood, branebrutinib was shown to inhibit BCR-stimulated expression of CD69 on B-cells with an IC50 value of 11 nM. Measurements of BTK inactivation in human whole blood showed a similar IC50 value of 5 nM. Branebrutinib rapidly inactivated BTK in a time-dependent and concentration-

dependent manner when added to human whole blood. The second-order rate constant for the inactivation of BTK in human whole blood by branebrutinib was determined to be 3.5×10^{-4} $nM^{-1} \cdot min^{-1}$. This represents a rate of inactivation 3 times faster than that measured with ibrutinib (1.2×10^{-4} $nM^{-1} \cdot min^{-1}$).[57]

3.2.2.2 *In Vivo Pharmacology*

A single oral administration of branebrutinib at 1 mg/kg to mice resulted in BTK inactivation of 89%, 82%, and 72% in blood, popliteal lymph nodes, and spleens, respectively, at 4 hours post-dose. The compound dose-dependently inactivated BTK in whole blood after a single oral administration, with the dose producing 50% effect (ED50) values of 0.12 and 0.07 mg/kg PO at 4 hours and 24 hours post-dose, respectively. Ibrutinib at 1 mg/kg provided only 37% and 42% BTK inactivation at 4 and 24 hours, respectively, in the same experiment, and demonstrates the considerably greater potency of branebrutinib in vivo. After 24 hours, the recovery of available BTK active sites in both blood and spleens due to new protein synthesis was measured at a rate of 25% to 35% per day.[58]

Branebrutinib was highly effective in New Zealand black/white lupus-prone mice -- dose-dependently inhibiting the increase in severe proteinuria, a measure of the underlying nephritis. All dose levels also protected from the disease-related death in these mice over the course of treatment. Serum anti-double-stranded deoxyribonucleic acid (anti-dsDNA) titers, which progressively increased over the course of the study in vehicle control mice, were also inhibited in a dose-dependent manner by treatment with branebrutinib.

Branebrutinib also demonstrated robust efficacy in the mouse collagen-induced arthritis and collagen antibody-induced arthritis models, demonstrating its ability to attenuate Fc receptor and B-cell receptor signaling associated with disease biology, including clinically evident disease, histological joint damage, and bone mineral density loss. In both models, maximal efficacy was observed with ≥ 95% inactivation of BTK in vivo.

In summary, branebrutinib is a potent and highly selective small-molecule, irreversible inhibitor of BTK that blocks antigen receptor-dependent signaling and functional endpoints in human B-cells, including the production of proinflammatory cytokines, co-stimulation molecule (eg, CD86) expression, and proliferation with IC50 values of < 1 nM. The compound also potently inhibited BTK-dependent cytokine production from PBMCs stimulated through the low-affinity activating FcγRs. In human whole blood, branebrutinib rapidly inactivated BTK. Branebrutinib was highly efficacious in all tested murine models of immune-associated diseases. Many of the BTK-associated pathobiologic mechanisms common to these mouse autoimmunity models apply to AD as well (Section 3.1).

3.2.2.3 *Nonclinical Toxicology*

Branebrutinib was studied in a comprehensive nonclinical toxicology program. Results of 6-month and 9-month GLP toxicity studies in rats and dogs, respectively, are highlighted below.

In a 6-month oral toxicity study in rats with a 5-week recovery,[59] branebrutinib was administered by daily oral gavage at doses of 0 (vehicle), 1, 5, or 20 mg/kg/day to groups of 25 rats/sex. Satellite

animals consisting of 25 naïve female rats (untreated) per group were used for mating and fertility assessment of the males in each dose group.

Branebrutinib was clinically well tolerated by rats for 6 months at oral doses ≤ 20 mg/kg/day with no BMS-986195-related effects on survival; body weight or food consumption; physical or ophthalmic examinations; male reproductive performance (mating and fertility) or early embryonic development of the offspring sired by treated males; coagulation, urinalysis or urine chemistry parameters; or organ weights. The suppression of T cell-dependent antibody response (TDAR) to keyhole limpet hemocyanin (KLH) and decreases in B lymphocytes at all doses were consistent with the pharmacologic activity of branebrutinib. The primary effects were noted in the pancreas at all doses and were characterized microscopically by islet fibrosis, peri-islet pigment, islet hemorrhage, mononuclear cell infiltration, and acinar atrophy. These pancreatic findings were not considered adverse, as they represent exacerbation of an age-related background pancreatic finding specific to rats, which has been reported from emerging literature for this class of compound.[60] Comparing the pancreatic findings across studies, there was no progression of the lesions, in terms of severity, after 6 months of dosing, when compared with the lesions seen in studies of shorter duration (2 weeks[61] and 1 month of dosing[62,63]). For these reasons, it was considered unlikely that the pancreatic lesions observed in rats treated with BTK inhibitors would have any relevance to the safety assessment for human participants treated with this drug class, and this was acknowledged by the FDA. As a result, conclusions from earlier studies of shorter duration that these findings were adverse in the rat should not preclude dosing at equivalent exposures in humans. Therefore, the NOAEL was considered to be the high dose of 20 mg/kg/day (mean sex-combined AUC[0-24h] 61.9 µg·h/mL).

In a 9-month oral toxicity study in dogs with a 4-week recovery,[64] branebrutinib was administered by oral gavage at doses of 0 (vehicle), 0.5, 3, or 15 mg/kg/day to groups of 6 dogs per sex.

Overall, branebrutinib was tolerated by dogs for 9 months at oral doses ≤ 15 mg/kg/day with no branebrutinib-related clinical observations, effects on body weights and body weight gains, food consumption, physical and ophthalmic examinations, electrocardiology, urinalysis and urine chemistry parameters, organ weights changes and gross pathology findings. Consistent with the expected pharmacology of branebrutinib, the primary findings at ≥ 0.5 mg/kg/day were minimal to mild or moderate germinal center lymphoid depletion in lymph nodes, spleen, and/or gut-associated lymphoid tissue (GALT), and suppression of TDAR to KLH. Based on the absence of adverse findings at any dose tested, the NOAEL was considered to be 15 mg/kg/day (mean sex-combined AUC[0-24h] 113 µg·h/mL at Week 39).

3.2.2.4 Pharmacokinetic Drug Interaction Summary

Data from the in vitro DDI interaction studies of branebrutinib with multiple CYP and UGT enzymes and multiple drug transporters predicted DDI potential with substrates of CYP3A4 (both as inhibitor and inducer), CYP2C8 enzymes, and BCRP drug transporter. In the clinical DDI studies, co-administration of branebrutinib (9 mg QD for 14 days, Study IM014013) did not have an effect on the exposures of the corresponding substrates of multiple CYP enzymes, including the PK of midazolam (sensitive substrate of CYP3A4) or pravastatin (OATP1B1 and OATP1B3),

but led to weak interaction with montelukast (CYP2C8) with mild increase in its exposure (1.556× Cmax and 1.270× AUC[INF]). Additionally, a mild increase in digoxin (P-gp substrate) Cmax (1.565×), and AUC (1.209× AUC[INF]) were also observed in the clinical DDI study with branebrutinib. Overall, the data suggest that CYP3A4 inhibitory and induction properties of branebrutinib may "balance" each other in vivo and co-administration of branebrutinib with substrates of P-gp (such as digoxin) or CYP2C8 with narrow therapeutic index should be avoided or restricted or their serum concentrations be monitored in the presence of branebrutinib.

Furthermore, in clinical DDI studies (IM014013, IM014023), branebrutinib showed no clinically relevant interactions either with oral contraceptives (ethinylestradiol/norethindrone) or with methotrexate. In another clinical DDI study (IM014032), the effect of coadministration of multiple oral doses (9 mg, QD) of branebrutinib on the single-dose PK of rosuvastatin (10 mg) in healthy participants was assessed. Rosuvastatin is a sensitive substrate of the BCRP drug transporter. Despite in vitro DDI data that showed branebrutinib to inhibit BCRP with an IC50 of 1.8 μM, preliminary results from this clinical DDI study showed that the concomitant administration of branebrutinib at steady-state resulted in no clinically meaningful effect on the plasma exposure of rosuvastatin following a single dose in healthy volunteers.

On the other hand, a human absorption, distribution, metabolism, and excretion (ADME) study (IM014016) showed the major metabolic clearance pathway for branebrutinib to be enzyme-mediated glutathione conjugation catalyzed by multiple glutathione-S-transferase (GST) enzymes (please refer to the IB for details). Therefore, clinically significant effect on branebrutinib exposure is not likely to occur when co-administrated with other agents that are inhibitors of major drug-metabolizing enzymes such as CYPs and UGTs.

In summary, branebrutinib is unlikely to be a clinically significant victim of PK drug interactions. It also has low likelihood of being a PK drug-interaction perpetrator through most metabolic enzymes and transporters. However, it may act as a weak inhibitor of CYP2C8 and P-gp at clinically relevant concentrations.

3.2.2.5 Clinical Safety

Clinical safety of branebrutinib has been evaluated in 4 studies performed in healthy participants. Currently 2 studies are ongoing: IM014029 (a Phase 2a study of branebrutinib in systemic lupus erythematosus, primary Sjogren's syndrome, and rheumatoid arthritis), and IM014032 (a Phase 1 study of drug interactions between branebrutinib and rosuvastatin); neither of these 2 studies currently have sufficient data to report.

Studies IM014001, IM014013, IM014016, and IM014023

The FIH study in healthy participants (Study IM014001)[65] included a randomized, placebo-controlled, double-blind, SAD (Part A) and MAD (Part B; 14 days) - study (non-Japanese descent); a randomized, placebo-controlled, double-blind, MAD study (Japanese descent; Part C); and an open-label, non-randomized, single-sequence relative bioavailability and food effect study (4 single doses, 4 days apart; Part D). Evaluations included safety and tolerability, PK, PD, target engagement characteristics, effects in Japanese participants, and clinical pharmacology

assessments of food effect and bioavailability of a suitable formulation for use in patients with rheumatoid arthritis (RA). Doses and dose escalation were planned so that the projected mean AUC would not exceed the proposed maximum AUC (5400 ng·hr/mL), providing approximately a 10-fold safety margin from the AUC in rats (20 mg/kg/day).

There were no deaths in the study. [redacted] Other than this event, there were no AEs leading to discontinuation, and all AEs were mild or moderate in intensity. In the SAD panels (Part A), 30 participants received branebrutinib (0.3, 1, 3, 10, or 30 mg as oral solution) and 10 received placebo. Eighteen participants (60%) who received branebrutinib experienced at least 1 AE. AEs that occurred for > 1 subject were: headache (4), upper respiratory tract infection (3), dizziness (3), nausea (2), rash (2), throat irritation (2), myalgia (2), and dysmenorrhea (2). Nine participants who received branebrutinib had AEs classified as related to study drug by the investigator as follows: headache (2); rash (2); and dizziness, dysgeusia, oral herpes, influenza-like illness, malaise, hot flush, nausea, tongue ulceration, and dry lips (1 each). Among the 10 participants who received placebo in Part A, 5 (50.0%) experienced at least 1 AE; headache was reported for 3 participants, and epistaxis was reported for 2 participants (other events were reported for 1 subject each).

In the MAD panels (Part B), 24 participants received branebrutinib (0.3, 1, 3, or 10 mg as oral solution) and 8 received placebo QD for 14 days. Seventeen participants (70.8%) of 24 who received branebrutinib experienced at least 1 AE. The most frequently reported AEs were headache (8); upper respiratory tract infection (4); oral herpes (3); abdominal pain (2); nausea (2); and tension headache (2). The abdominal pain events were not associated with abnormalities in amylase or lipase values. They were considered unrelated to branebrutinib and they resolved without treatment. Ten participants who received branebrutinib experienced at least 1 AE that was classified as related to study drug by the investigator as follows: headache (5), oral herpes (3, all had history of oral ulcers), abdominal pain, chills, conjunctivitis allergic, cough, dry skin, dyspepsia, eye irritation, mouth ulceration, nasal congestion, nausea, oropharyngeal pain, tension headache, and upper respiratory tract infection (1 each). Among the 8 participants who received placebo in Part B, 7 (87.5%) experienced at least 1 AE (only musculoskeletal pain [2] was reported for more than 1 subject).

In Part C, 9 participants (Japanese MAD) had AEs: 7 participants (38.9%) following treatment with branebrutinib; and 2 participants (33.3%) after having received placebo. In Part D, 14 participants received 4 doses of branebrutinib 10 mg as follows: solution formulation under fasted condition on Day 1, solution/fed on Day 5, suspension/fasted on Day 9, and suspension/fed on Day 13. Six participants (42.9%) experienced at least 1 AE during any period. The most frequently reported AE was chest discomfort (2). The AEs of chest discomfort (2) and influenza-like illness were assessed as related to branebrutinib by the investigator.

Overall, in Study IM014001, no clinically meaningful safety signals were identified based on assessments of AEs, ECGs, vital signs, and clinical laboratory tests. There was no relationship of frequency and severity of AE with dose levels. Safety and tolerability of branebrutinib are favorable, based on the observed data from the FIH study.

In Study IM014013, a DDI study in 26 healthy male participants to assess the effects of co-administration of branebrutinib on the PK of methotrexate (MTX) and on a cocktail of probe substrates, there were no deaths and no other SAEs, other significant AEs, or AEs leading to discontinuation. Caffeine, montelukast, flurbiprofen, omeprazole, midazolam, pravastatin, and digoxin (probe substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4, OATP1B1, OATP1B3, and P-gp, respectively) alone, and in combination with branebrutinib were generally safe and well tolerated in healthy male participants.

In Study IM014016, an ADME study in 9 healthy male participants who received [^{14}C]branebrutinib, there were no deaths and no other SAEs, other significant AEs, or AEs leading to discontinuation. A total of 3 AEs was reported by 3/9 (33.3%) participants. No treatment-emergent adverse events (TEAEs) were considered related to branebrutinib, and all TEAEs were considered mild in severity and were resolved by end of study. There were no clinically relevant changes in laboratory results, ECG intervals, or vital signs reported.

In Study IM014023, a study in 24 healthy female participants designed to investigate the effects on PK, as well as the safety and tolerability of branebrutinib co-administered with the high-dose OC Loestrin®, there were no deaths and no other SAEs, other significant AEs, or AEs leading to discontinuation. Overall, 34 TEAEs were reported in 16 participants. All TEAEs were considered to be mild in severity. The most common TEAEs were headache (5 participants); hepatic enzyme increased (3 participants); and ALT increased, back pain, dry eye, nausea, and rash papular (all reported in 2 participants each). Hepatic marker measurements showed no elevations in total bilirubin and alkaline phosphatase but did include elevations of aspartate aminotransferase (AST). All changes in ALT and AST were < 3× the upper limit of normal (ULN) and most were < 2× ULN. They did not require discontinuation of treatment of the study drug and resolved without treatment.

Taken together, results of Phase 1 studies with branebrutinib demonstrate a satisfactory safety profile for its investigation in patients with immune-mediated diseases.

3.3 Benefit/Risk Assessment

AD is a common, chronic, or recurrent inflammatory skin condition with significant associated social and financial burden. AD affects adults and children with worldwide prevalence rates of 1% to 20%. Using US census estimates, based on recent epidemiologic data, 16.5 million adults would have a diagnosis of AD, with 6.6 million meeting criteria for moderate-to-severe disease.[6] Characterized by often disabling pruritus, scaling, xerosis, and eczematous lesions whose features include erythema, induration/papulation, excoriations, and lichenification, severe disease can be debilitating due to several factors: psychiatric disorders, sleep loss, and impaired quality of life (QOL). The majority of AD patients exhibit hypersensitivity to environmental or food allergens characterized by increased serum IgE levels and eosinophilia.[16,17,66] Compromised skin barrier

function and a dysregulated immune system also render AD patients more susceptible to contact irritants and sensitizers, and to skin infections.

Topical corticosteroids have been the mainstay of treatments for AD. However, for patients with moderate-to-severe AD, topical therapies have limited efficacy, and long-term application of topical corticosteroids carries the risk of side-effects of acneiform eruptions, dyspigmentation, skin atrophy, and risks associated with systemic absorption.[67] Systemic immunosuppressant drugs are generally more effective than topical treatments, but they are associated with more substantial toxic effects, including diabetes, hypertension, and osteoporosis.[67] Moreover, systemic cyclosporin and corticosteroids may result in prominent rebound effects after treatment discontinuation. Subsequently, cyclosporine is dosed for a limited duration, with a requirement of monitoring of renal function and hypertension.[68] Other immunosuppressants such as azathioprine (AZA), mycophenolate mofetil (MMF), and methotrexate MTX, are also used with caution in severe refractory patients, due to less evident efficacy and potential serious adverse effects.

An unmet need therefore remains for effective and safe, long-term oral medications for patients with moderate-to-severe AD. Given the supportive mechanistic biology of the 2 agents being evaluated in this study (Section 3.1.2), it is hypothesized that participants will benefit from participation by experiencing reductions in disease activity and associated discomfort.

Furthermore, nonclinical and Phase 1 results with both molecules (Sections 3.2.1 and 3.2.2) suggest that this reduction in disease activity can be undertaken safely. Appropriate safety monitoring, frequent visits, and other risk-minimization measures such as ongoing safety review and Data Monitoring Committee (DMC) oversight will be implemented to ensure that the safety of the participants is adequately monitored (Section 9.4). In summary, the Sponsor believes that the -benefit-risk relationship of participation is favorable for patients with moderate or severe AD.

3.3.1 BMS-986166

Assessments of benefit and risk rely on nonclinical data and on data from completed Phase 1 studies in healthy volunteer participants. The proposed dosing regimens of 0.25 mg, 0.5 mg, and 0.75 mg QD reflect implementation of adequate safety margins compared to the projected steady state AUC at the clinical dose of 0.75 mg (approximately 23× in rats and female dogs, or 2× in male dogs for BMS-986166; or approximately 112× in rats, 127× in female dogs, or 11× in male dogs for BMS-986166-P) based on the AUC at the NOAEL in the 6- and 9-month rat and dog studies (10 mg/kg/day in rats and 0.1 mg/kg/day or 3 mg/kg/day in male and female dogs, respectively) and is within the range of doses tested in MAD study IM018003.

The potential beneficial effects of S1PR1 have been documented in pharmacology studies, demonstrating its potential benefit for disorders of immune activation (Section 3.2.1). Moreover fingolimod (Gilenya) is an S1P receptor-analogue, acting as a nonselective potent agonist of S1PR1, 3, 4, and 5. Gilenya was the first S1PR agonist approved for clinical use for relapsing multiple sclerosis (MS).[69] S1P content appears to be of great significance for the homeostasis of the skin. Diminished S1P concentration is linked to increased endocytosis capacity of DC and

proliferation of keratinocytes, and, although not measured in the skin of patients with AD, reduced S1P level is found in skin lesions of atopic dogs.[70]

In terms of risk, findings in nonclinical toxicology studies were consistent with expectations based on the pharmacology of BMS-986166 and included on-target PD effects such as dose-dependent lymphocyte reduction in peripheral blood, increases/decreases in lymphoid cellularity in lymphoid organs, and suppression of the T-cell-dependent antibody response. Increases in trabecular bone were noted in the rat 6-month study, and testicular toxicity was noted in dogs in the 10-week and 9-month toxicity studies. All findings showed evidence of reversibility. For the purposes of monitoring the testicular finding, participants with history of significant testicular or epididymal disease will be excluded, and male sex hormones (follicle-stimulating hormone (FSH), luteinizing hormone (LH) and total testosterone) will be assessed at baseline and different time points throughout the treatment period and until study discharge.

Nonclinical studies have shown that BMS-986166 has a reduced risk for cardiovascular effects, macular edema, and pulmonary toxicity, compared with other members of the class.

Clinical safety of BMS-986166 was summarized in Section 3.2.1.5.

Based upon nonclinical toxicology findings and the mechanism of action of the compound (immunosuppression), this study incorporates appropriate assessments and risk-mitigation approaches (including careful consideration of appropriate exclusion criteria and monitoring of participants during and after dosing) in combination with conventional safety monitoring. These include assessment for latent tuberculosis (TB) infection (LTBI) and chronic viral infections, and ongoing clinical and laboratory monitoring to reduce the risk from infection, Pulmonary function tests (PFTs), optical coherence tomography (OCT) and close monitoring of vitals and ECGs. Frequent study visits are employed to enhance safety monitoring and reduce risk.

Possible CYP3A4-mediated DDI is anticipated with BMS-986166 as a victim drug when co-administered with CYP3A4 inhibitors or inducers. BMS-986166 did not inhibit any of the human UGTs and CYPs tested and did not induce human CYP1A2, CYP2B6, and CYP3A4. In addition, no inhibition of a panel of human drug transporters was observed for BMS-986166. The inhibition profile, together with the anticipated low efficacious concentration in vivo, suggests low DDI risk as a perpetrator drug.

In vivo studies to evaluate the developmental and reproductive effects of BMS-986166 have demonstrated that, like other SP1R1 modulators, BMS-986166 is a selective developmental toxicant in rats and rabbits, causing cardiac malformations at the lowest doses tested and embryo lethality at higher doses. Therefore, to ensure safety, the investigator will counsel WOCBP to use highly effective contraception, and pregnant women will not be enrolled in this study. It is not known whether BMS-986166 passes into human milk. Therefore, breastfeeding women will not be enrolled in this study.

The accumulated toxicology data and preclinical profile, as well as the Phase 1 clinical data for BMS-986166 suggest that the risks of S1PR1 class-related AEs such as pulmonary and macular edema have been largely mitigated, and the cardiovascular liabilities have been reduced, while

retaining marked peripheral lymphopenia. More detailed information about the known and expected benefits and risks and reasonably anticipated AEs (see Section 9.2.8) of BMS-986166 may be found in the IB.[38]

3.3.2 Branebrutinib

Assessments of benefit and risk rely on nonclinical data and on data from completed Phase 1 studies in healthy participants. The proposed 9 mg QD dosing regimen reflects implementation of appropriate safety margins (> 500× based on the AUC in rats and dogs at the NOAEL [20 mg/kg/day and 15 mg/kg/day in rats and dogs, respectively]) and is within the range of doses tested in the FIH study (Study IM014001).

The potential salutary effects of BTK inhibition by branebrutinib have been documented in pharmacology studies, demonstrating its potential benefit for disorders of immune activation (Section 3.2.2); and clinical data support the use of BTK inhibitors for the treatment of RA.[71] Because of the functional roles of BTK-expressing immunocytes (eg, mast cells, B-cells, and DC) in AD (Figure 3.1.2-1), inhibition of BTK may reduce AD disease activity.

In terms of risk, findings in nonclinical toxicology studies were consistent with expectations based on the pharmacology of branebrutinib and included on-target PD effects such as reductions in B-cell activity, suppression of KLH-specific IgM and IgG responses, and/or dose-related germinal center lymphoid depletion of minimal to moderate severity in the GALT.

Branebrutinib-related pancreatic toxicity was identified in oral Sprague-Dawley rat toxicity studies with up to 6 months of exposure. Findings related to branebrutinib were noted at all doses, and were generally islet-centric.[47] These pancreatic lesions are similar to those observed with other BTK inhibitors and represent an exacerbation of an age-related pancreatic finding specific to rats.[57] As such, these findings were considered non-adverse. The FDA has acknowledged that pancreatic lesions observed in rats treated with BTK inhibitors are unlikely to have relevance to the safety assessment for human participants treated with this drug class. Nonetheless, specific monitoring of pancreatic function, including assessments of, fasting glucose levels, were implemented in the Phase 1 studies to minimize unwanted risks to the healthy participants, and no branebrutinib-related elevations in these parameters were identified.

With the exception of an unrelated SAE that was consistent with the subject's medical history, AE in the FIH study (Study IM014001) were mild to moderate, reversible, and consistent with expectations based on nonclinical experience.

Based upon nonclinical toxicology findings and the mechanism of action of the compound (immunosuppression), this study incorporates appropriate assessments and risk-mitigation approaches (including careful consideration of appropriate exclusion criteria and monitoring of participants during and after dosing) in combination with conventional safety monitoring. These include assessment for LTBI and chronic viral infections, and ongoing clinical and laboratory monitoring to reduce the risk from infection. Frequent study visits are employed to enhance safety monitoring and reduce risk.

While blood BTK occupancy persisted longer (~50% at ~7 days and 30% at 10 days) after the cessation of multiple doses of branebrutinib as observed in the FIH study (14-day MAD), pharmacological inhibition of ex vivo lymphocyte stimulation started to wane within ~2 to 3 days after drug cessation. This is because signaling through BTK is very robust, and >95% inhibition in the whole blood is required to clearly inhibit lymphocyte function. Thus, 7 days after the last dose, the PD effect is considered to be significantly lower. Based on the biomarker data, and based on the fact that X-linked agammaglobulinemia (XLA) is essentially never noted in heterozygous females (BTK is a gene that escapes X-inactivation), it is anticipated the PD effects will wash out within 1 to 2 weeks after end of treatment.

The risk for DDIs with branebrutinib has been assessed in Study IM014013.[72] The potential for clinically relevant DDIs of branebrutinib with substrates of a number of enzymes and transporters (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and organic anion transporting polypeptide OATP1B1 and 1B3) is likely to be minimal based on the low projected therapeutic concentration (Cmax < 0.20 μM) and high serum protein binding. Branebrutinib may affect the PK of drugs that are sensitive substrates of CYP2C8 and P-gp as a weak inhibitor, based on the results of Study IM014013 and in vitro studies. Therefore, until more knowledge is gained, drugs that are sensitive substrates of CYP2C8 and P-gp (like digoxin) are restricted or excluded based on their therapeutic window and metabolism in this study. If such sensitive substrates must be used, therapeutic drug levels monitoring is recommended.

In vivo studies to evaluate the developmental and reproductive effects of branebrutinib have shown developmental toxicity in rabbits (at an exposure multiple of 53× relative to the dose of 9 mg proposed for this study) that were associated with maternal and developmental toxicity.[47] At the NOAEL of 40 mg/kg/day, the safety margin was 16× compared with the human AUC at 10 mg MAD. Branebrutinib was not associated with maternal or developmental toxicity in pregnant rats at exposure multiples up to 437× (versus human AUC at 10 mg MAD). To ensure safety, the study will require WOCBP to use highly effective contraception, and pregnant women will not be enrolled in this study. It is not known whether branebrutinib passes into human milk. Therefore, breastfeeding women will also not be enrolled in this study. The DDI study with oral contraceptives (Study IM014023) demonstrated lack of PK interaction,[73] which ensures efficacy of hormonal contraception co-administered with branebrutinib.

Ibrutinib, an irreversible inhibitor of BTK used for the first line treatment of chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL), has been shown in randomized trials to increase the risk for incident atrial fibrillation as compared to alternate treatments.[74] Atrial fibrillation (AF) and atrial flutter (range, 6 to 9%) have occurred in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation.[75] Although the mechanism is not fully elucidated, recent in vitro and in vivo nonclinical experiments strongly suggest that ibrutinib-mediated AF results from off-target kinase inhibition -- particularly that of C-terminal SRC-kinase,[76] though on-target mechanisms cannot yet be ruled out.[77] Because newer BTK inhibitors are more specific to the Tec kinase family than ibrutinib, they may not carry this mechanistic liability[78] though clinical confirmation is currently lacking.

In clinical trials with branebrutinb, no adverse events of atrial fibrillation have been reported. Patients with any prior history of atrial fibrillation or atrial flutter will be excluded from participation in this clinical trial. Cardiac monitoring with ECG assessments predose and at 1, 2, 4, and 6 hours post dose will be obtained in addition to hourly monitoring of the HR and blood pressure on Day 1. Standard 12-lead ECG will be collected and reviewed with every subsequent visit.

In sum, the potential benefits and risks of branebrutinib for patients with moderate or severe AD support its investigation in this protocol.

More detailed information about the known and expected benefits and risks and reasonably anticipated adverse events (AEs) of branebrutinib may be found in the IB.

3.3.3 COVID-19-associated Risks

3.3.3.1 BMS-986166

[redacted]

3.3.3.2 Branebrutinib

Risk from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is linked to the immune response following exposure. The immune system must control viral replication and cytopathology,[79] while avoiding the exaggerated inflammation associated with severe COVID-19.[80] It is reasonable to hypothesize that BTK function may influence both these aspects of the response to SARS-CoV-2. BTK is central to activation, proliferation, and survival responses downstream of the B cell antigen receptor and other receptors on B cells and key myeloid cell types. Details of BTK signaling are summarized in Section 3.2 of this protocol, Section 2 of the IB, and references therein. Notably, however, signaling through BTK depends both on the latter's kinase activity, and on its "scaffolding" activity (ie, physical association with other proteins).[43,81,82]

Insights into the effect of deficiency in both BTK activities can be gained by observing COVID-19 outcomes in patients with XLA, a genetic immunodeficiency characterized by profound reductions in B cell counts and serum immunoglobulins caused by null mutations in BTK. XLA patients demonstrate high susceptibility to bacterial and some viral infections that is largely ameliorated by administration of intravenous immunoglobulin and prophylactic antibiotics.[83] Published cases

of COVID-19 in XLA patients reveal disease courses ranging from mild disease[84] to nonlethal pneumonia[85,86,87]. While these reports are anecdotal, they do demonstrate that lifelong deficiency of BTK kinase and scaffolding activities does not preclude recovery from COVID-19. Moreover, susceptibility to COVID-19 in rheumatology patients treated with branebrutinib is plausibly lower than that of XLA patients because the former have: (i) intact BTK protein despite inhibition of kinase activity, (ii) fully-developed adaptive immunity with a lifetime of intact pretreatment BTK function, and (iii) normal B cell counts. A published description of 5 COVID-19 cases in Waldenstrom's macroglobulinemia patients chronically treated with full-dose ibrutinib demonstrated a mild infection course without need for hospitalization; a sixth patient chronically treated with low-dose ibrutinib had a more severe course but showed improvement temporally linked with increased dosage.[88] A cohort of 19 severely affected COVID-19 patients without prior indication for BTK inhibitor therapy, who were treated acutely and experimentally with acalabrutinib, demonstrated reduced inflammatory measures, and outcomes no worse than expected given their disease severity. [89] Thus, publicly disclosed COVID-19 experiences in patients with XLA or receiving BTK inhibitors do not indicate increased risk of adverse COVID-19 outcomes associated with pharmacologic BTK inhibition. Furthermore, professional rheumatology organizations have not advocated prophylactic withdrawal of any class of rheumatologic treatment including immunosuppressants and Janus kinase (JAK) inhibitors.[90,91] Indeed, elevated disease activity in RA and systemic lupus erythematosus (SLE) is associated with greater susceptibility to serious infections in general[92,93] while treatment with biologic or targeted disease-modifying antirheumatic drugs (DMARDs) may be associated with reduced risk of COVID-19-associated hospitalization.[94]

Branebrutinib offers the potential for better disease control with acceptable safety, as discussed in Section 3.2 of this protocol and in the IB. This, together with the currently available insight regarding BTK and COVID-19, supports the continued clinical evaluation of branebrutinib despite the pandemic. Individual investigators and each potential participant together should decide the appropriateness of study participation depending on the medical particulars of each participant, and the local COVID-19 situation. Because the understanding of COVID-19 risk and disease mechanisms is rapidly evolving, the Sponsor will monitor for emerging knowledge that might affect the risk-benefit profile of this study.

3.3.3.3 COVID-19-related Mitigations

[redacted]

3.3.3.4 Vaccination Against SARS-CoV-2

[redacted]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of BMS-986166 and of branebrutinib, each versus placebo at Week 16 in patients with moderate-to-severe AD.	• Mean percentage change from baseline in EASI score at Week 16
Secondary	
• To further evaluate the efficacy of BMS-986166 and of branebrutinib, each versus placebo at Week 16 in patients with moderate-to-severe AD.	• Proportion of participants exhibiting a vIGA-AD score of 0 (cleared) or 1 (almost cleared) AND a ≥ 2 point reduction from baseline at Week 16 • Proportions of participants exhibiting a $\geq$ 50% (EASI-50) reduction from baseline in EASI score at Week 16 • Proportion of participants exhibiting a $\geq$ 4-point improvement from baseline in Pruritus NRS at Week 16. • Mean percentage change from baseline in Pruritus NRS score at 16 weeks • Mean change from baseline in percentage of affected BSA at Week 16

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To assess the safety and tolerability of BMS-986166 and of branebrutinib in patients with moderate-to-severe AD.	• Incidence and severity of all AE, and SAE • Incidence and severity of clinically significant changes in vital signs, ECG, OCT, PFT, and/or safety laboratory tests
Tertiary/Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: AD = atopic dermatitis; AE = adverse event; ALC = absolute lymphocyte count; AUC(0-T) = area under concentration-time curve from time zero to the time of the last quantifiable concentration; AUC(TAU) = area under concentration-time curve within a dosing interval; BSA = body surface area; BTK = Bruton Tyrosine Kinase; Cmax = maximum concentration; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; FEV1 = forced expiratory volume in 1 second; IgE = immunoglobulin E; NRS = numerical rating scale; OCT = optical coherence tomography; PD = pharmacodynamic; PFT = pulmonary function test; PK = Pharmacokinetics; POEM = Patient Oriented Eczema Measure; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; vIGA-AD = Validated Investigator Global Assessment Scale for Atopic Dermatitis

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 2, multicenter randomized, double-blind, placebo-controlled, 5 parallel-group, study of BMS-986166 or branebrutinib to evaluate the efficacy and safety of 3 dose levels of BMS-986166 and a single dose level of branebrutinib in participants with moderate-to-severe AD who are intolerant of treatment, or inadequately treated and are candidates for systemic therapy. The overall study design is outlined in Figure 5.1-1.

The study consists of:

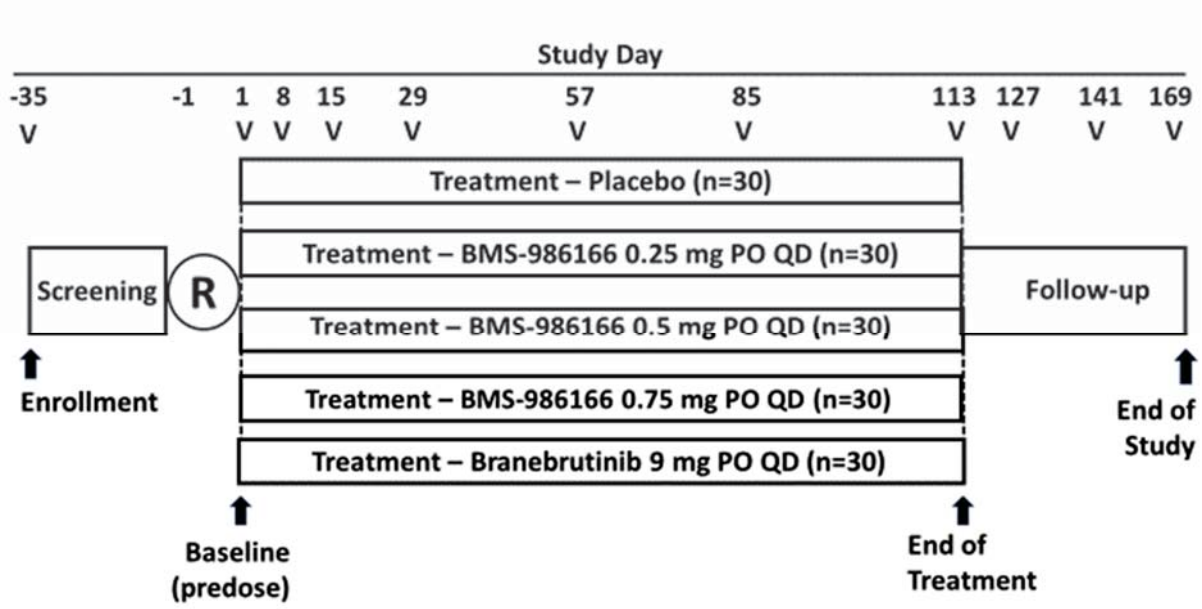
- A Screening Phase of up to 35 days, during which participants will be confirmed to have moderate-to-severe AD, and meet the other entry criteria for the study (Section 6);
- A Treatment Phase of approximately 16 weeks during which participants will be assessed for clinical responses to either placebo, BMS-986166, or branebrutinib;
- A Follow-up Phase of approximately 8 weeks.

Total duration of participation in the study will be approximately 29 weeks, although follow-up maybe extended until ALC recovers to the pre-specified threshold (Section 5.1.3).

White blood cell (WBC) counts and lymphocyte counts will be monitored centrally (and will not be provided to the site) to prevent potential unblinding of the investigator.

An external independent DMC will be empaneled to review safety on a periodic and as-needed basis.

Figure 5.1-1: Study Design Schematic



Abbreviations: n = number; PO = taken orally; QD = once daily; R = randomization; V = visits
Study day visits will be ± 3 days, except for the Day 7 visit (± 1 days).

Physical examinations, vital sign measurements, 12-lead ECG, OCT, PFT, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be monitored for adverse events throughout the study.

Blood samples will be collected for PK and PD analysis as described in Sections 9.5 and 9.8, respectively.

5.1.1 Screening Period Days -35 to -1

Eligibility will be based on specified inclusion and exclusion criteria (Sections 6.1 and 6.2), medical history, disease activity, and safety assessments. Screening and randomization must be completed within 35 days of signing the ICF. Participants who experience an AD flare defined as doubling of the EASI score between Screening and Baseline or worsening that requires administration of prohibited medications within 3 weeks of randomization should be discontinued from the study.

Participants that experience an AD flare prior to randomization should be discontinued from the study.

5.1.2 Treatment Period, Days 1-113

On Day 1, eligible participants will be randomly allocated to receive one of: placebo, BMS-986166 0.25 mg PO QD, BMS-986166 0.5 mg PO QD, BMS-986166 0.75 mg PO QD, or branebrutinib 9 mg PO QD for 16 weeks. Randomization will be in a 1:1:1:1:1 ratio. Blinded treatment assignment will be managed by Interactive Response Technology (IRT).

Participants will visit the clinic 7 times (including baseline) during the treatment period. Safety and efficacy will be assessed at each of these visits. This visit density is intended to allow monitoring of sufficiently high resolution to detect infections, excessively low leukocyte counts, inefficacy and/or flares, and other problems in a timely fashion; with on the other hand, participant burdens and risk of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) exposure associated with clinic visits. This frequency reflects customary practice in the field as reflected in other published studies.[31]

Participants may receive topical rescue therapy for intolerable symptoms up to Week 4 as described in Section 7.7.2. After Week 4, participants receiving rescue treatments will be considered treatment failures for categorical endpoints, those who require systemic rescue therapy will be immediately discontinued from study treatment.

5.1.3 Follow-up Period, Days 114-169

Follow-up after dosing cessation is planned for approximately 60 days (5x T-HALF for BMS-986166), with visits on Days 127, 141 and 169; participants will be followed for disease activity, safety, and washout of PD effects. If applicable, participants will be followed until absolute neutrophil count (ANC) > 1500/μL and ALC > 1000/μL, demonstrating sufficient washout of PD effects to permit discharge from the study.

5.1.4 Data Monitoring Committee

To ensure the safety of study participants, an external independent DMC consisting of 2 experienced dermatologists, an infectious disease clinician, and a statistician will be established for ongoing evaluation of safety assessments, AEs, and laboratory measurements. An independent reporting statistician not involved in the conduct of the study will be designated to provide the DMC with essential safety data unblinded to treatment during the study, if required.

The DMC will conduct at regular, pre-specified intervals and on an ad hoc basis if warranted, safety review meetings throughout the study to ensure that the benefit and risks of study participation remain acceptable. Ad hoc meetings may be initiated by the DMC or by the Sponsor based on emerging new safety information.

Blinded suspected, unexpected serious adverse reactions (SUSARs) will be sent to the DMC members on an ongoing basis. SAEs will be sent to the DMC on a monthly basis or on an ongoing basis as requested by the DMC.

The DMC will review safety data, including, but not limited to, SAEs and adverse events of interest (AEIs). At the request of the DMC, designated personnel will provide further information, including select efficacy data as needed for the medical assessment for a specific case.

The DMC may also consider external data from other BMS-986166 or branebrutinib studies that may be initiated in future, or from novel scientific information that may be generated on related compounds.

The DMC will act in an advisory capacity to BMS and will monitor participant safety data for the study. The BMS study team has primary responsibility for design and conduct of the study.

Based on the DMC's assessment, recommendations of protocol modifications or other actions may occur. In addition, hold of enrollment, pending more detailed assessment may be requested by the DMC.

Details of the DMC responsibilities and procedures will be specified in the DMC Charter.

5.2 Number of Participants

Approximately 150 participants will be randomized 1:1:1:1:1 into 5 parallel treatment groups.

5.3 End of Study Definition

The start of the study is defined as the date that the first participant is screened. End of study is defined as the last contact with the last participant (either last visit at which the last endpoint data is collected or last contact which could be a phone call). Study completion is defined as the final date on which data for the study was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, 5 parallel-group study to evaluate the efficacy and safety of 3 dose levels of BMS-986166 and a single dose level of branebrutinib in participants with moderate-to-severe AD who are intolerant of treatment, or inadequately treated and are candidates for systemic therapy (ie, not adequately controlled by a stable regimen [≥ 4 weeks] of topical corticosteroids, calcineurin inhibitors or biologics, or not eligible for topical therapy due to side effects or safety risks).

Two mechanistically distinct compounds will be simultaneously tested for the first time in this AD population. This is being done for the following reasons:

- It is more efficient than 2 separate studies since a single control group is used for both compounds – reducing the number of participants with burdensome AD symptoms who must be treated with placebo.
- While not a formal head-to-head comparison, this design best supports the main purpose of this study to evaluate provisional efficacy of two different mechanisms in AD – enabling Sponsor decision to advance one or both to Phase 2b/3 evaluation.
    - The effects of both compounds on clinical endpoints can be evaluated at the same sites simultaneously, and against the same placebo population. The latter point is of special interest given the small size of this study, and the well-known variability in placebo responses in AD – ranging from ~10% to >30% EASI reduction in Phase 2 studies.[30,103,104,105]
    - The effects of the 2 compounds on complex exploratory biomarkers (eg, messenger ribonucleic acid [mRNA] profiling of skin biopsies) can be measured at the same sites, over the same time interval, and in the same experimental batch runs – maximizing comparability.
- Each compound has extensive PK-PD characterization, both in nonclinical experiments and in Phase 1 studies, and both mechanisms are extensively described in the literature. Together, this

allows appropriate safety monitoring, general study conduct, and data interpretation to occur despite the added complexity of investigating 2 compounds simultaneously.

A parallel group design is being employed because (1) the time course of treatment is relatively long (~16 weeks), (2) BMS-986166 has a T-HALF (~12 days), and (3) IP-related changes in disease activity of a complex immunologic phenomenon like AD do not occur or "wash out" over usefully predictable times. These factors obviate crossover designs.

Five treatment groups will be evaluated: 1 for placebo, 1 for the favored dose of branebrutinib (Section 5.5.2), and 3 dose levels for the most promising doses of BMS-986166 (Section 5.5.1).

Sixteen weeks' treatment duration will be employed because it provides sufficient time for each mechanism to act, allows time for BMS-986166 to reach steady state, and provides a reasonable observation time to observe AEs. Study treatment durations of 12 to 16 weeks are customary in this field (eg, in the dupilumab and upadacitinib Phase 2 programs).[41,106] The Follow-up phase lasts approximately 60 days to allow 5 mean half-lives of BMS-986166 to pass after the final dose before participants are discharged from the study, for safety monitoring. This also allows sufficient time for branebrutinib receptor occupancy to decay to baseline.[47] Acceptable washout of BMS-986166 PD effects (ALC counts) will also be explicitly assessed before participants are discharged from the study.

5.5 Justification for Dose

5.5.1 BMS-986166

The BMS-986166 doses to be evaluated in this study (0.25 mg, 0.5 mg, and 0.75 mg) are based on their safety, tolerability, PK, and PD findings from FIH studies, as well as on nonclinical evaluations as detailed in Section 3.2.1.

The model predictions for participants receiving the 0.5 mg dose of BMS-986166, with average exposures, will typically exhibit reduction in nadir ALC greater than 75% of baseline ALC values and a 2-beat/minute net decrease in HR versus placebo. Translation of exposure-response analyses using ALC, and its relationship to efficacy in preclinical models lends confidence to the efficacy hypothesis at similar exposures yielding similar PD effects in humans.

Safety – In study IM018003, multiple oral doses of BMS-986166 up to 1.5 mg QD for 28 days were safe and generally well tolerated in healthy participants. The most frequently occurring AEs during BMS-986166 administration were lymphopenia (N=15; 62.5%) which is consistent with the pharmacology of the drug; contact dermatitis (N=8; 33.3%), associated with ECG electrode contact sites and increased blood creatine phosphokinase (N=7; 29.2%), assessed by the investigator as unrelated to study drug, were of equal frequency in the placebo and BMS-986166 cohorts; and headache (N=5; 20.8%). Safety results were similarly low and reversible between the 0.25 and 0.75 mg PO QD groups. The no-observed-adverse-effect level (NOAEL) in pivotal nonclinical toxicity studies yield adequate safety margins relative to the projected steady-state exposures at 0.75 mg PO QD.

PK – In the multiple ascending dose (MAD) study IM018003, healthy participants received BMS-986166 solution formulation at dose levels of 0.25, 0.75, and 1.5 mg PO QD for 28 days. Increases in whole blood maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) over the dosing interval (AUC[TAU]) were approximately dose proportional within the dose levels tested. The mean half-life (T-HALF) at Day 28 ranged from 276 to 321 hours across the dose range tested, indicating that BMS-986166 was slowly eliminated from the body. Consequently, as expected, accumulation after 28 days of dosing (near steady-state) was approximately 14-fold.

PD – Key PD biomarkers in Study IM018003 were peripheral blood absolute lymphocyte counts (ALC) and heart rate. Lymphocyte count, is a PD endpoint that roughly reflects efficacy endpoints – based on clinical results with preceding S1P receptor modulators such that exposure associated with a lymphocyte reduction below approximately 1,000 lymphocytes/μL are also associated with satisfactory efficacy in MS.[107] In a real-world examination of ALC responses to fingolimod in MS patients, typical percent reductions from baseline ALC of approximately 65% - 90% were noted.[108]

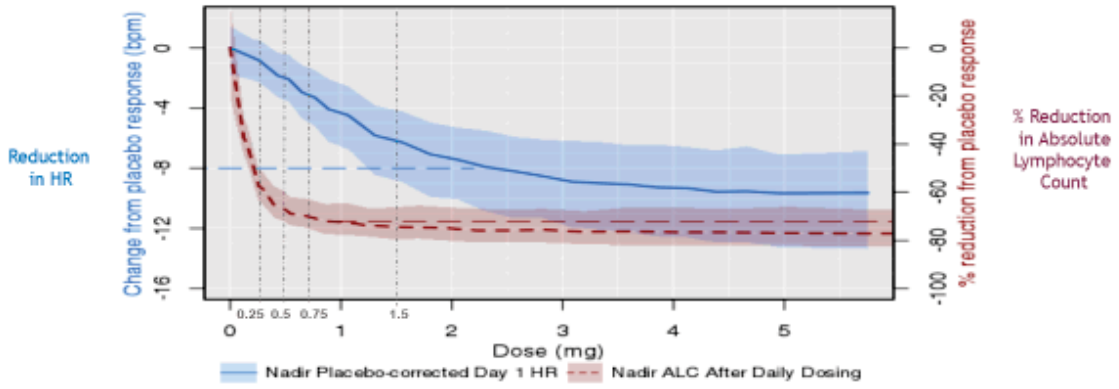
In Study IM018003, predictable, dose-dependent lymphocyte reductions reaching median nadirs (ie, largest percent reduction) of 53.7% (range: 31.7% to 55.9%), 75.9% (range: 63.3% to 85.8%), and 81.9% (range: 37.9% to 92.2%) occurred at the 0.25 mg, 0.75 mg, and 1.5 mg dose levels, respectively, by Day 28 of dosing.[38] In the 0.75 mg group 37.5% and 12.5% of patients experienced Grade 2 and 3 reduction of lymphocytes respectively without clinically meaningful infection implications.

In the same study, continuous Holter monitoring revealed roughly dose-dependent reductions in median time-matched nadir heart rates. These were of the order of 8 to 9 absolute beats/minute at the highest dose (1.5 mg) and reached maximum effect by 48 hours. At the 0.25 mg and 0.75 mg dose levels, placebo-controlled reductions in median time-matched nadir heart rates were always below 4 beats/minute. By 12-lead ECG, there were no discernible differences in heart rate from placebo at the end of the study (Clinical Study Report IM018003).

Based on the results from the FIH studies, a comprehensive population exposure-response and safety model was developed for both BMS-986166 and BMS-986166-P to guide the dose selection for Phase 2 clinical studies using model predictions and to optimize the benefit-risk balance. Simulations were conducted using various dosing scenarios to predict the effects of BMS-986166 and BMS-986166-P on PD (ALC) and safety (HR) parameters. This modeling of the relationships between dose, exposure, PD, and measures of lymphocyte and heart rate reduction, predicted that a 0.5 mg PO QD dose would lead to median nadir ALC greater than 75% of baseline and a 2-beat/minute net decrease in HR versus placebo (Figure 5.5.1-1). Hence, 0.5 mg dose is selected for evaluation in this study. To address the possibility of suboptimal tissue penetration or drug concentration disequilibrium between plasma and tissue, the 0.75 mg dose level is also selected to evaluate safety and efficacy at PD intensity levels best-suited for monotherapy. [redacted]

[redacted]

Figure 5.5.1-1: Model-predicted Reductions in Heart Rate and Lymphocyte Count by Dose



The shaded areas represent the 90% confidence intervals around the median lines. The dashed horizontal line at -8 bpm represents a drop of 8 bpm relative to placebo. The dashed horizontal line at -70 % represents a drop of 70% in ALC. The three vertical dotted lines represent the 0.25 mg, 0.5 mg, and 0.75 mg doses being investigated in this study.

Abbreviations: ALC = absolute lymphocyte; bpm = beats per minute; HR = heart rate
Source: BMS data on file.

Thus, the selected doses of 0.25 mg, 0.5 mg, and 0.75 mg of BMS-986166 are predicted to provide optimal evaluation of efficacy and safety for this proof-of-concept study.

5.5.2 Branebrutinib

The selection of the branebrutinib dose and regimen (9 mg, QD) to be assessed in the current study was based on findings in the FIH and nonclinical studies as detailed in Section 3.2.2.

Safety: The drug was well-tolerated at all dose levels, and most AEs observed were similar in participants receiving placebo and active treatment. The most common AEs included headache and upper respiratory tract infection. Based on the AUC in rats and dogs at the NOAEL after chronic daily administration (rat, 6 months; dog, 9 months), the safety multiple in humans after multiple doses of 10 mg is > 500×.[12]

PK: In the MAD panels of the FIH study (Study IM014001), healthy participants received branebrutinib solution QD for 14 days at 4 dose levels (0.3, 1, 3, and 10 mg). Increases in Cmax and AUC[TAU] were approximately dose proportional within the dose levels tested. T-HALF was shorter than 2 hours across the dose range tested, indicating that branebrutinib was rapidly eliminated from the body. Consequently, no accumulation was observed at steady state after multiple daily dosing.

PD: Biomarkers evaluated in Study IM014001 were BTK occupancy by branebrutinib (enzyme occupancy [EO]), inhibition of ex-vivo stimulated cluster of differentiation CD69 expression, and plasma CXC motif chemokine ligand 13 (CXCL13) levels.

Doses yielding high (≥ 95%) BTK occupancy are thought necessary for optimal clinical efficacy because only at such doses did (1) in vivo pharmacologic studies of experimental autoimmunity (eg, murine collagen-induced arthritis) show maximum efficacy, and (2) deep tissue (eg, spleen) EO rapidly match peripheral blood EO.

The maximum occupancy reached ≥ 99% at branebrutinib doses of 1 mg and above (100%; maximum occupancy at doses ≥ 3 mg); however, maximum occupancy was achieved faster and maintained longer at 3 mg and 10 mg doses (solution formulation). Furthermore, a high and sustained (~100%) BTK occupancy was achieved with the 10 mg dose over the dosing interval. The variability of the effect was also lower for the higher dose of 10 mg. A similar result was obtained for CD69 inhibition, for which the largest median inhibition was observed at the branebrutinib 10 mg dose. The highest inhibition of plasma levels of CXCL13 was also obtained at the 10 mg dose level. Considering the higher variability and expression of BTK in patients with immune mediated disorders[4], the 10 mg dose with the solution formulation is expected to more stably and completely inhibit BTK[47] -- for optimal chronic treatment of a larger proportion of patients. Moreover, based on the nonclinical branebrutinib exposure in rats and dogs at the NOAEL after chronic daily administration (rat, 6 months; dog, 9 months), the safety multiple in humans after multiple doses of 10 mg is > 500×.[12]

Relationship of 9 mg capsule dose to the 10 mg solution dose in Study IM014001:

The comparison of exposure between the branebrutinib 10 mg solution formulation from Study IM014001 and the branebrutinib 9 mg capsule formulation (3 × 3 mg) from Day 1 Cycle 2 in Study IM014023, a Phase 1 study of the effect of branebrutinib on the PK of combined oral contraceptives, demonstrated comparable exposure for Cmax and AUC(TAU) with only slight delay in time to maximum concentration (Tmax) for capsule formulation. Thus, the use of 3 × 3 mg capsules of branebrutinib is expected to be equivalent to the 10 mg solution formulation in terms of exposure, safety, and PD effects.

In summary, the dose to evaluate PD response with optimal safety and best potential to detect an efficacy signal was chosen to be 9 mg branebrutinib administered as 3 × 3 mg capsules.

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Understanding of, and willingness to participate in the study after completing all informed consent procedures – demonstrated by a signed ICF

b) Willingness and ability to complete all study-specific procedures and visits

2) Type of Participant and Target Disease Characteristics

a) Chronic AD diagnosed according to the Eichenfield modification of Hanifin's and Rajka's (E-HR) criteria[109] at Screening (Appendix 5)

b) Disease duration of at least 24 months since diagnosis by any criteria

c) EASI score ≥ 12 at Screening visit and ≥ 16 at Baseline visit

d) vIGA-AD ≥ 3 at Screening and Baseline visits

e) ≥ 10% BSA affected by AD at Screening and Baseline visits

f) Documented history of inadequate control of AD by a stable regimen (≥ 4 weeks) of topical corticosteroids, calcineurin inhibitors or biologics, within 6 months of randomization, or inappropriateness of therapy due to side effects or safety risks leading to prior discontinuation.

- Inadequate response is defined as either or both of:
- Failure to achieve and maintain a disease activity state comparable to vIGA-AD 0 = clear to 2 = mild, despite treatment with a daily regimen of topical corticosteroids (TCS) of medium to higher potency (± topical calcineurin inhibitors [TCI] as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information, whichever was shorter, or
- Necessity of systemic therapy to control disease.

g) Application of fixed doses of an additive-free, basic bland emollient twice-daily for ≥ 7 days before baseline visit and for the duration of the study participant to the guidance in Section 7.7.3.

h) Participants must have documentation of positive Varicella Zoster virus (VZV) IgG antibody status or complete VZV vaccination at least 90 days prior to randomization.

3) Age and Reproductive Status

Investigators shall counsel women of child bearing potential (WOCBP), and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants

i) Females aged 18 (or local age of majority) to 65, inclusive.

ii) Women of non-childbearing potential (WONCBP) are exempt from contraceptive requirements. WONCBP must have documented proof that they are not of childbearing potential.

iii) Women of childbearing potential (WOCBP) must have a negative, highly sensitive pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG, or as required by local regulations) within 24 hours prior to the start of study treatment.

(1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

iv) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities.

v) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

vi) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF.

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

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

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, as described in Appendix 4 during the intervention period and for at least 3 months after the last dose of study intervention, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

b) Male Participants

i) Males, ages 18 (or local age of majority) to 65, inclusive.

ii) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below.

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

iv) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom during the intervention period and for at least 3 months after the last dose of study intervention.

v) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the study intervention period and for at least 3 months after the last dose of the male participant's study intervention.

vi) Male participants must refrain from donating sperm during the intervention period and for at least 3 months after the last dose of study intervention.

vii) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

6.2 Exclusion Criteria

1) Medical Conditions

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

b) Pregnancy, lactation, or plans for either during the study or the post-study prohibition period (see Inclusion Criteria for prohibition period duration).

c) Clinically relevant cardiovascular conditions, including history or presence of:

i) Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, sick sinus syndrome, Class III/IV heart failure (Appendix 6)

ii) Prolonged QTcF interval (QTcF > 450 msec males, > 470 msec females), or at additional risk for QT prolongation (eg, hypokalemia, hypomagnesemia, congenital long-QT syndrome)

iii) Any prior history of atrial fibrillation or flutter

iv) Treatment with Class Ia or Class III anti-arrhythmic drugs or treatment with 2 or more agents in combination known to prolong PR interval

v) Patients with other pre-existing stable cardiac conditions who have not been cleared for the study by an appropriate cardiac evaluation by a cardiologist

d) Clinically relevant pulmonary conditions, including:

i) Unstable asthma or chronic obstructive pulmonary disease (COPD) (eg, acute episodes of exacerbation [nocturnal episodes, sudden episodes triggered by unidentifiable factors] despite a stable regimen of relevant medications); prior episode(s) of life-threatening asthma or COPD; or asthma or COPD that requires systemic glucocorticoid or biologic treatment, or inhaled budesonide or equivalent at > 1200 µg/day or fluticasone propionate at > 880 µg/day along with another anti-asthma/COPD drug such as a long-acting beta-agonist.

ii) Severe untreated sleep apnea

iii) Forced expiratory volume (FEV1) or forced vital capacity (FVC) < 70% of predicted values at screening

e) Cancer or history of cancer or lymphoproliferative disease (other than adequately treated cutaneous basal cell or squamous cell carcinoma with no evidence of recurrence within the previous 5 years), including pre-lymphoma (pseudolymphoma of the orbit and small intestine, lymphomatoid granulomatosis, angioimmunoblastic lymphadenopathy, and lymphoid interstitial pneumonitis)

f) History of diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c > 8%, or diabetic patients with significant co-morbid conditions such as retinopathy or nephropathy

g) Participants with a history of retinopathy, uveitis or other clinically significant ocular disease

h) Participants with any history of testicular or epididymal disease/disorder except uncomplicated epididymitis successfully treated with antibiotics.

i) Current or recent (within 3 months before randomization clinically significant) gastrointestinal disease, including gastrointestinal surgery, that could impact the absorption of study treatment

j) Any major surgery within the last 30 days before the first dose of study treatment, or any surgery planned during the course of the study.

k) History of any serious condition induced by drug allergy or other hypersensitivity (such as anaphylaxis or hepatotoxicity).

l) Participants with non-AD concomitant illness (eg, asthma) that, in the opinion of the investigator, is likely to require systemic corticosteroid or biologic therapy during the study

2) Infection Risk-related Criteria

a) Any of the following TB criteria:

i) History of active TB prior to screening visit, regardless of completion of adequate treatment

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

iii) Any imaging of the chest (eg, chest x-ray, chest CT scan) obtained during the screening period, or anytime within 6 months prior to screening with documentation, showing evidence of current active or old pulmonary TB

iv) LTBI defined by QuantiFERON-TB Gold testing at screening, in the absence of clinical manifestations

Note 1: Participant may be eligible if (i) there are no current signs or symptoms of active TB and (ii) participant has received adequate documented treatment for LTBI within 1 year of screening.

Note 2: An indeterminate QuantiFERON-TB Gold test may be repeated once during screening. If the repeat test is positive or indeterminate, the participant is excluded.

b) Hepatitis C, Hepatitis B, or HIV infection as demonstrated, by a positive blood screen for HCV antibody and confirmed by positive reflex HCV RNA test, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or HIV-1 and -2 antibody.

i) Participants who have been vaccinated for hepatitis B (hepatitis B surface antibody [HbsAb]-positive) are not excluded.

ii) Indeterminate tests require negative reflex testing results, or they are exclusionary.

iii) HCV history and documented 24-week sustained virologic response are permitted.

c) History of congenital or acquired immunodeficiency

d) Participants with any acute or chronic bacterial, fungal (except history of tinea pedis or ongoing onychomycosis will not be exclusionary) or viral infection, as well as any febrile illness within 14 days of screening

e) Known active infection, or any major episode of infection requiring hospitalization or treatment with parenteral (IM or IV) antimicrobial agents (eg, antibiotics, antiviral, antifungal, or antiparasitic agents) within 2 weeks of the screening visit, and/or completion of oral antimicrobial agents within 2 weeks of randomization, and/or recurrence prior to randomization.

f) Previous history of recurrent herpes zoster (more than 1 episode), disseminated herpes simplex before randomization or a history of disseminated/complicated herpes zoster infection (multidermatomal involvement, ophthalmic zoster, eczema herpeticum, central nervous system involvement, or postherpetic neuralgia)

g) History of atypical/opportunistic infection (eg, pneumocystis, cytomegalovirus, invasive fungal infections, atypical mycobacteria, etc.).

h) Presence of the following COVID-19-related exclusion criteria

i) Symptoms of COVID-19 at screening or randomization

ii) COVID-19 (either suspected or confirmed) within 12 weeks of screening, at screening, and/or Day 1.

iii) Known or suspected current sequelae of any sort following any prior episode of COVID-19.

iv) COVID-19 vaccination within 14 days of screening or participant has plans to receive a vaccination during his/her participation in the study.

3) AD-related Criteria

a) High likelihood - based on participant history, and investigator judgement – of requiring rescue therapy in < 4 weeks prior to randomization (see Section 7.7.2)

b) Evidence of acute flare between the Screening and Baseline/ Randomization (eg, doubling of the EASI score between Screening and Baseline, or worsening that requires administration of prohibited medications).

c) Skin lesion(s) and/or pruritus due to conditions other than AD that would interfere with the study specified assessments.

4) Prior/Concomitant Therapy

a) Treatment with anticoagulant or antiplatelet therapies, including aspirin for cardioprotection, within 2 weeks prior to randomization or during the study.

b) AD-related prescription or over-the-counter skin barrier treatments (eg, Cerave, Epicerum, etc.) therapy within 2 weeks prior to randomization

c) Any bleach baths within 2 weeks prior to randomization

d) Monoamine oxidase inhibitors (eg, selegiline, phenelzine) within 2 weeks prior to randomization

e) Use of strong or moderate inhibitors or inducers of CYP2C8 or CYP3A4 within the longer of 5 PK half-lives or 14 days prior to randomization (inhibitors), or within 3 weeks prior to randomization (inducers).

   i) Please refer to Table 7.7.1-1 for examples.

   ii) Sponsor's Medical Monitor should be consulted for any uncertainties regarding CYP2C8 or CYP3A4 modulators.

f) Phosphodiestersase-4 (PDE4) inhibitors within 3 weeks prior to randomization.

g) Use of phototherapy (ie, UVB, UVA) within 4 weeks prior to randomization.

h) Leukotriene inhibitor treatment within 4 weeks prior to randomization.

i) Diquafosol or rebamipide therapy within 4 weeks prior to randomization.

j) Systemic corticosteroid treatment within 4 weeks prior to randomization.

k) Systemic immunosuppressive drugs (CsA, MMF, AZA, MTX) or oral preparations of herbal immunomodulatory medications within 8 weeks prior to randomization.

l) Exposure to JAK inhibitors such as tofacitinib, baricitinib, filgotinib, or upadacitinib within 8 weeks prior to randomization.

m) Intravenous (IV) immunoglobulin within 8 weeks prior to randomization or during the study.

n) Allergen immunotherapy within 4 months of randomization.

o) Biologics depending on the type:

   i) Cell-depleting agents, including rituximab: within 6 months, or until the targeted population (eg, CD19+ lymphocyte counts for rituximab) returns to normal, whichever is longer

   ii) Biologics such as tocilizumab and anakinra within 8 weeks prior to randomization

   iii) Other biologics: within the longer of 5 half-lives (if known) or 6 months of randomization (eg. dupilumab)

p) Prior exposure to BTK inhibitors such as ibrutinib, acalabrutinib, or experimental drugs (eg, BMS-986166 or branebrutinib, tirabrutinib, vecabrutinib, zanibrutinib, ARQ-531, GDC-0853, or others) at any time.

q) Prior exposure to S1PR modulators (eg, fingolimod, etrasimod, ozanimod, etc.) at any time.

r) Use of any immunomodulator or investigational drug not listed above within the longer of 5 PK half-lives, 5 PD half-lives, or 6 months of randomization.

5) Laboratory Test and Procedural Findings

a) The following test findings at Screening or Baseline

i) WBC count < 3000/μL or > 14,000/μL

ii) ANC < the lower of: lower limit of normal (LLN) or 1500/μL

iii) ALC < 1000/μL

iv) Platelet count < 100,000/μL

v) Serum creatinine > 2 mg/dL

vi) Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[110]:

$eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black] -- where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κor 1, and max indicates the maximum of Scr/κ or 1.

vii) AST or ALT >1.5x ULN

viii) Total bilirubin > 2 mg/dL (34 μmol/L)

ix) Hemoglobin <10 g/dL

x) ECG: HR < 55 bpm; PR ≥ 210 msec; QRS ≥ 120 msec; QTcF >450 msec males, > 470 msec females, or any clinically significant heart conduction abnormality (eg, left bundle branch block, atrial fibrillation).

xi) Abnormality on posteroanterior + lateral chest radiograph, taken during the Screening period that is relevant to safe conduct of this study.

xii) Abnormality on optical coherence tomography (OCT) testing suggestive of macular or choroidal pathology beyond that expected for a healthy person of the participant's age.

xiii) Heart rate < 55 bpm or > 95 bpm at rest

xiv) Blood pressure > Grade 1 hypertension (> 159 mmHg systolic and > 99 mmHg diastolic) according to the 2018 European Society of Cardiology/European Society of Hypertension guidelines for the management of arterial hypertension[111]

xv) Any other clinically significant laboratory or procedure abnormalities that, in the opinion of the investigator, might pose unacceptable risk to the participant during the study.

6) Other Exclusion Criteria

a) Use of a tanning booth/parlor or significant change in sun exposure within 4 weeks of the Screening visit.

b) Onset of a new exercise routine or major change to a previous exercise routine within 2 weeks prior to randomization.

c) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances and participant to local law a person who has been imprisoned after enrollment may be permitted to continue as a participant. Strict conditions apply and Bristol Myers Squibb approval is required.)

d) Employment by the Sponsor, clinical research organizations, or study site.

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

f) Recent (within 6 months of study drug administration) drug or alcohol abuse as defined in DSM-5, Diagnostic Criteria for Drug and Alcohol Abuse (Appendix 7)

g) Inability to comply with restrictions as listed in Section 6.3 and prohibited/restricted treatments in Section 7.7.1.

h) Inability to tolerate oral medication.

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

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

6.3 Lifestyle Restrictions

Lifestyle restrictions are listed below.

6.3.1 Meals and Dietary Restrictions

With the exception of the 8-hour fasting requirement prior to blood sample collection for safety and PK testing on Day 1 and Day 85, no meal or dietary restrictions are required for this study. A light meal/snack may be provided after the 2-hour PK sample and/or ECG collection insofar as to not interfere with obtaining either.

However, participants are advised to abstain from excessive consumption of quinine (tonic water), grapefruit and Seville oranges.

St. John's wort and herbal medications are not allowed.

6.3.2 Caffeine, Alcohol, and Tobacco

With the exception of prohibited alcohol abuse as defined by the diagnostic criteria for Drug and Alcohol Abuse defined in the DSM-5 (Appendix 7) within six months prior to randomization, there are no restrictions on caffeine, alcohol, or tobacco use for this study. However, participants who use tobacco or alcohol should be counseled for potential contraindications with non-study treatments as appropriate, and continued study participation should be based on investigator judgment.

6.3.3 Activity

The use of contraceptives during sexual activity is mandatory as stated in Section 6.1.

Use of tanning beds is prohibited during the study.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been randomized / has not been treated) due to an issue that is transient. If re-enrolled, the participant must be re-consented.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted one time (in addition to any parameters that require a confirmatory value).The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

7 TREATMENT

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

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

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

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

Table 7-1: Study Treatments for IM018005

Product Description / Class and Dosage Form	Potency	IP	Blinded or Open Label	Packaging	Storage Conditions (per label)
BMS-986166-04 capsule	0.25 mg	IP	Blinded	Bottle	Refer to the label on the container
Branebrutinib capsule (BMS-986195-01)	3 mg	IP	Blinded	Bottle	Refer to the label on the container
Placebo capsule	NA	IP	Blinded	Bottle	Refer to the label on the container

Abbreviations: IP = investigational product; NA = not applicable

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows.

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s) / Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-986166	0.25 mg / 0.25 mg	QD	Oral
BMS-986166	0.25 mg / 0.50 mg	QD	Oral
BMS-986166	0.25 mg / 0.75 mg	QD	Oral
Branebrutinib	3 mg / 9 mg	QD	Oral
Placebo	NA	QD	Oral

Abbreviations: NA = not applicable; QD = once daily

Participants will be randomized to one of the following dose levels of BMS-986166 or branebrutinib or placebo in blinded fashion:

- BMS-986166 0.25 mg PO QD
- BMS-986166 0.50 mg PO QD
- BMS-986166 0.75 mg PO QD
- Branebrutinib 9 mg PO QD
- Placebo PO QD

- The first dose of double-blind study medication (BMS-986166 or branebrutinib or placebo) will be taken in the morning on Day 1 after fasting for at least 8 hours.
- Study medication should be taken at approximately the same time each day.
- Participants will take 3 capsules each day, one from each of 3 distinct bottle.

The actual IP taken by each participant is summarized in Table 7.1-2.

Table 7.1-2: Investigational Product: as Dispensed to Participants

Treatment Group	Double-blind Kit	Bottle A	Bottle B	Bottle C
Placebo	Each kit contains Bottle A, Bottle B, Bottle C	Placebo capsule	Placebo capsule	Placebo capsule
`166 0.25 mg QD		`166 capsule, 0.25 mg	Placebo capsule	Placebo capsule
`166 0.5 mg QD		`166 capsule, 0.25 mg	`166 capsule, 0.25 mg	Placebo capsule
`166 0.75 mg QD		`166 capsule, 0.25 mg	`166 capsule, 0.25 mg	`166 capsule, 0.25 mg
BRA 9 mg QD		BRA capsule, 3 mg	BRA capsule, 3 mg	BRA capsule, 3 mg

Abbreviations: ‘166 = BMS-986166-04; BRA = branebrutinib; QD = daily
Note: all capsules are identical (size 0).

In the morning on Day 1, after fasting for at least 8 hours, each participant will receive an oral dose of BMS-986166 or branebrutinib or placebo, each consisting of 3 capsules. At the time of

dosing, 240 mL of water will be administered to the participant along with his/her dose of study drug. The time of dose administration will be called "0" hour. A light meal/snack may be provided after the 2-hour PK sample and/or ECG collection insofar as to not interfere with obtaining either.

Storage of investigational product will be according to the label on the container and/or packaging.

Restrictions related to food and fluid intake are described in Section 6.3.

7.2 Method of Treatment Assignment

After the participant's initial eligibility is established and informed consent has been obtained, the participant must be entered into the study via the IRT to obtain a participant number. Specific instructions for using the IRT will be provided to the investigational site in a separate document. The investigator or designee will register the participant for screening by following the screening procedures established by BMS.

Once it is determined that the participant meets the eligibility criteria following screening, participant will be centrally randomized through the IRT.

The study will not allow participant replacement due to an AE.

7.3 Blinding

This is a randomized double-blinded study. Access to treatment codes will be restricted from all participants, and site and BMS personnel prior to database lock, with exceptions as specified below.

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 participant in which knowledge of the investigational product is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

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

For this study, the method of unblinding for emergency purposes is through the IRT system. In case of an emergency, the investigator has unrestricted access to randomization information via IRT and can break the blind through the IRT system without prior approval from the Sponsor.

After the unblinding, the investigator shall notify the Medical Monitor and/or Study Director. The method of unblinding for emergency purposes is described in the IRT Manual. Participant and

unblinded treatment information and the reason for the blind being broken must be recorded on the appropriate study status page of the electronic case report form (eCRF).

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

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

Designated staff of Bristol Myers Squibb Company may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol Myers Squibb Company (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

7.4 Dosage Modification

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

A Pharmacy Manual will not be provided for studies with oral dose formulations.

Dose reductions or dose escalations are not permitted. All dose modification rules apply to all arms given the blinded nature of this study.

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.5.1 Retained Samples for Bioavailability / Bioequivalence / Biocomparability

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability (Section 2). Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of an amendment, except where necessary to eliminate an immediate hazard(s) to study participants.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to or during the study (up through Study Day 149) are described below. Medications taken within 4 weeks prior to Screening must be recorded on the eCRF.

1) Use of Class Ia and class III antiarrhythmic agents.
2) Table 7.7.1-1 presents prohibited and/or restricted potential medications.

Table 7.7.1-1: Prohibited and Restricted Medications

Type of Medication	Examples (not exhaustive)	Restriction	Required Washout
Allergen immunotherapy	various intradermal or sublingual	Prohibited during the study	4 months prior to randomization
Anticoagulants or antiplatelet agents	aspirin, clopidogrel, ticlopidine, warfarin, heparin, apixaban, etc.	Prohibited during the study	2 weeks or effective post-discontinuation PD duration (whichever is longer) prior to randomization
Antihistamines - except fexofenadine	Diphenhydramine, loratadine	Stable dose during the screening period; consistent use through the treatment period	Not applicable
Biologics	Belimumab, dupilumab, or omalizumab	Prohibited during the study	6 months prior to randomization
	Abatacept	Prohibited during the study	6 months prior to randomization
	Other biologics, including tocilizumab, anakinra	Prohibited during the study	8 weeks prior to screening

Table 7.7.1-1: Prohibited and Restricted Medications

Type of Medication	Examples (not exhaustive)	Restriction	Required Washout
	Intravenous Immunoglobulin	Prohibited during the study	8 weeks prior to screening
Bronchodilators -inhaled	Albuterol, salmeterol, ipratropium bromide	Stable dose during screening and through treatment period	Not applicable
BTK inhibitors	Marketed drugs, eg, ibrutinib, acalabrutinib Experimental drugs, eg, tirabrutinib, vecabrutinib, zanibrutinib, ARQ-531, GDC-0853, and any others	Prohibited lifetime use	Not applicable
Calcineurin-inhibitor -Topical	cyclosporine, tacrolimus	Prohibited during the study	4 weeks prior to randomization
Corticosteroid -Inhaled, oral non-absorbable or modified-release	Budesonide, fluticasone	Must follow stable regimen throughout study; cannot be used on as-needed basis	Not applicable
Corticosteroid -Systemic	IM, IA, intrabursal, IV Prednisone, dexamethasone	Prohibited during the study	4 weeks prior to randomization
Corticosteroid -Topical	Fluocinolone, hydrocortisone	As rescue therapy until Week 4 as detailed in Section 7.7.2	3 weeks prior to randomization
CYP2C8 and CYP3A4 -Strong or moderate inhibitors	clopidogrel, gemfibrozil, clarithromycin, itraconazole	Prohibited during the study	5 PK half-lives or 14 days of randomization
CYP2C8 and CYP3A4 -Strong or moderate inducers	rifampin, phenytoin	Prohibited during the study	3 weeks of the randomization
CYP2C8 or P-gp Sensitive substrates with narrow therapeutic indices	Repaglinide, dabigatran, fexofenadine	Prohibited during the study (digoxin allowed under limited/urgent circumstances; see below)	5 PK half-lives or 14 days of randomization
Immunization against agents other than influenza or SARS-CoV-2	Live vaccines	Prohibited during the study	90 days before and 60 days after EOT
	Nonlive vaccines unassociated with influenza or SARS-CoV-2		30 days before and 60 days after EOT

Table 7.7.1-1: Prohibited and Restricted Medications

Type of Medication	Examples (not exhaustive)	Restriction	Required Washout
Immunization for influenza or SARS-CoV-2	Live vaccines	Prohibited during the study	90 days before and 60 days after EOT
	Nonlive vaccines for influenza or SARS-CoV-2		14 days prior to screening and 60 days after EOT
Immunosuppressants -systemic or oral preparations of herbal immunomodulatory medications	Mycophenolate-mofetil, azathioprine, methotrexate	Prohibited during the study	8 weeks prior to randomization
JAK inhibitors	Tofacitinib, baricitinib, filgotinib, and upadacitinib	Prohibited during the study	8 weeks prior to randomization
Leukotriene inhibitors	montelukast	Prohibited during the study	4 weeks prior to randomization
Monoamine Oxidase Inhibitors	Selegiline, phenelzine	Prohibited during the study	2 weeks prior to randomization
Narcotic analgesics	Oxycodone and, hydrocodone	Prohibited during the study	Not applicable
Non-narcotic analgesics	Acetaminophen	Brief courses for up to 7 days allowed	Not applicable
Phosphodiesterase Inhibitor	Apremilast, crisaborole	Prohibited during the study	3 weeks prior to randomization
Phototherapy	UVB, UVA	Prohibited during the study	4 weeks prior to randomization
S1P Receptor Modulators	Fingolimod, ozanimod, siponimod, etrasimod	Prohibited lifetime use	Not applicable
Treatments to be restricted or suspended during the study	rosiglitazone	Dose up to 4 mg can be used, monitor glucose closely	Not applicable
	torasemide	Dose up to 10 mg can be used	Not applicable
	digoxin	For acute use only, exclude at baseline; limit highest dose and monitor trough concentrations; stop treatment with IP during treatment with digoxin and for 3 days afterwards	Not applicable
Treatments -Other	Diquafosol, rebamipide	Prohibited during the study	4 weeks prior to randomization

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

The investigator should contact and confirm agreement with the BMS medical monitor (and acknowledgement from the contract research organization medical monitor) prior to the administration of any concomitant medications, excepting those needed for urgent/emergent treatment for which there is insufficient time for such contact.

7.7.2 Rescue Therapy

Participants having intolerable symptoms within the first 4 weeks of treatment may use the below topical agents (according to their respective label instructions) as rescue therapy up until Week 4 according to the investigator's judgement.

- Fluocinolone acetonide 0.025%
- Hydrocortisone butyrate 0.1%
- Mometasone furoate 0.1%
- Triamcinolone acetonide 0.1%

Participants requiring and completing ≤ 7 days of topical rescue therapy within the first 4 weeks of IP treatment initiation, will remain eligible to be counted as responders for categorical efficacy endpoints; their numerical endpoints will also be counted as if they did not receive rescue therapy.

Participants either (1) requiring topical rescue therapy after 4 weeks of IP treatment, or for more than 7 days, or (2) requiring systemic corticosteroid/immunosuppression or phototherapy will discontinue from study treatment and be considered treatment failures for categorical endpoints.

Participants who discontinue study treatment are to remain in the study and complete all study visits and assessments unless they withdraw consent (Section 8.2).

Statistical handling of data from participants requiring rescue medication appears in Section 10.3.1.

7.7.3 Use of Concomitant Emollient

Application of fixed doses of an additive-free, basic bland emollient twice-daily for ≥ 7 days before baseline visit and for the duration of the study is required.

Note: On study visit days, showering or bathing is permitted prior to attending the study visit, but participants must not moisturize or apply emollient. The additive-free, basic bland emollient is allowed after the visit.

7.8 Treatment After the End of the Study

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

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Asthma or COPD that requires systemic glucocorticoid or biologic treatment, or inhaled budesonide or equivalent at >1200 µg/day or fluticasone propionate at > 880 µg/day along with another anti-asthma/COPD drug such as a long-acting beta-agonist.
- Systemic or photo-based rescue therapy for AD (Section 7.7.2),
- Replication-competent (live) vaccine
- Grade 4 lymphopenia (ALC < 200) with repeat testing within 7 days(according to the Common Toxicity Criteria for Adverse Events [CTCAE] version 5.0)
- Elevation of ALT or AST > 5x ULN or concurrent elevations of ALT or AST > 3x ULN and bilirubin > 2x ULN
- Decline in PFT values (FEV1 and/or FVC) below 30% of the baseline values
- Diagnosis of macular edema, retinal or choroidal disease or syndrome
- Grade 2 or higher cardiac or bone marrow adverse events (with exception of ALC) according to the CTCAE version 5.0.
- Grade 3 for other system adverse events (according to the CTCAE version 5.0)
- Missed dose of ≥ 3 consecutive days or overall compliance < 85% over a period of > 30 days starting from study Day 1.

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

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy.

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

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

8.1.1 Post Study Treatment Study Follow-up

In this study, efficacy as measured by EASI is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 2 until death or the conclusion of the study.

If a patient withdraws before completion, every effort should be made to complete the assessments of the Follow-up Visits.

8.2 Discontinuation from the Study

Participants 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants 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 participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

9.1 Efficacy Assessments

Efficacy assessments completed by the investigator include vIGA-AD, Eczema Area and Severity Index (EASI), and % Body Surface Area (BSA) worksheet. Every effort should be made to ensure that the same assessor conducts the assessments at all study visits for a given participant.

9.1.1 Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD)

The vIGA-AD is a static 5-point assessment intended to assess the global severities of key acute clinical signs of AD, including erythema, induration/papulation, and oozing/crusting (lichenification excluded).[112] The rating of cleared (0), almost cleared (1), mild (2), moderate (3), and severe (4) will be assessed at each scheduled visit, and at unscheduled clinic visits, if applicable. Refer to Appendix 8.

The vIGA-AD will be collected prior to the EASI.

9.1.2 Eczema Area and Severity Index (EASI)

The EASI is a validated, composite scoring system assessed by the investigator based on the extent of each of the 4 body regions (head and neck, upper limbs, lower limbs, and trunk) affected with AD and the intensity of each of 4 key signs of AD (erythema, induration/papulation, excoriation, and lichenification) and is based on a 4-point scale of 0 (absent), 1 (mild), 2 (moderate), and 3 (severe).[113] For each of the 4 body regions, the mean intensity of inflamed lesions for each of the 4 signs is recorded. Xerosis, scaling, urticaria, or post-inflammatory pigmentation changes are not included. The total EASI score ranges from 0 to 72. The EASI will be collected at each scheduled and unscheduled clinic visit, if applicable. Further details of the evaluation and calculation of the EASI score are provided in Appendix 9.

9.1.3 Body Surface Area (BSA)

A widely used method of measuring BSA involvement by AD, is the rule of nines in which for each section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], genitals [1%]) and will be reported as a percentage of all major body sections combined.[114,115] Participants will undergo this assessment at each scheduled and unscheduled clinic visit, if applicable. Refer to Appendix 10.

9.1.4 Pruritus and Sleep Quality Numerical Rating Scale (NRS)

Participants will complete a daily diary recording the intensity of their pruritus and the average quality of sleep they experienced during the preceding 24 hours. The intensity of pruritus will be assessed using a validated 11-point NRS, ranging from 0 (“no itching”) to 10 (“the worst itching imaginable”). The quality of sleep will be assessed using a validated 11-point NRS ranging from 0 (“the best possible sleep”) to 10 (“the worst possible sleep) provided in Appendix 11.[116,117]

9.1.5 Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item, easy-to-use, self-administered, assessment of the participants’ perception of the impact of their skin disease on different aspects of their Quality of Life (QOL) over the previous week. The DLQI score ranges from 0 (no effect on the participant’s life) to 30 (extremely large effect on the participant’s life). For each item, the scale is rated as follows: 0 =’not at all’/’not relevant’; 1=’a little’; 2=’a lot’; 3=’very much’/’yes’ in question 7, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL.[118] The DLQI will be assessed at every scheduled and unscheduled clinic visit, if applicable. Refer to Appendix 12.

9.1.6 Patient Oriented Eczema Measure (POEM)

The POEM is a validated tool used for monitoring atopic eczema severity. It is a 7-item questionnaire completed by the subject to assess the severity of eczema over the last week and evaluates itch, sleep disturbance, skin bleeding, skin weeping or oozing, skin cracking, skin flaking, and skin dryness. Each item has the following response options: 0 = No Days, 1 = 1-2 Days, 2 = 3-4 Days, 3 = 5-6 Days and 4 = Every Day. A total score is calculated by summing each item and results in a score ranging from 0-28. The subject will complete the questionnaire onsite at study visits. Refer to Appendix 13.

9.1.7 Patient Global Impression of Change (PGI-C)

The PGI-C is a global rating anchor scale and has been used across different therapeutic categories to interpret the scores from participant-reported outcome measurements. The PGI-C will be used in this study to confirm the threshold for meaningful change on other patient reported outcomes instruments in the target patient population. Participants will be asked the following question as per the schedule of assessments: "Compared to the beginning of the study, before you started the study treatment, which of the following best describes the skin symptoms of your atopic dermatitis today?" The response choices will be as follows: much improved, moderately improved, a little improved, the same, a little worse, moderately worse, or much worse. Refer to Appendix 14.

9.1.8 Patient Global Impression of Severity (PGI-S)

The PGI-S is a global rating anchor scale and has been used across different therapeutic categories to interpret the scores from participant-reported outcome measurements. The PGI-S will be used in this clinical trial to confirm the threshold for meaningful change on other PRO instruments in the target population. The PGI-S is not subject to recall error and can be also used to assess change from baseline data. Participants will be asked the following question as per the schedule of assessments, "Which of the following best describes the severity of the skin symptoms of your atopic dermatitis over the past 7 days?" The response choices will be as follows: none, mild, moderate, severe, or very severe. Refer to Appendix 15.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

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

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 participant to discontinue before completing the study.

Contacts for SAE reporting specified in Appendix 3

Adverse events of interest (AEIs) are described in Section 9.2.8.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Appendix 1 in the Investigator's Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting.

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

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of interest (as defined in Section 9) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for 3 months after study product administration, the investigator must immediately notify the BMS Medical Monitor/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 3.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

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

If any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and at least for 3 months, after study product administration, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an informed consent form for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant 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).

Clinically significant changes, in the judgment of the investigator, in laboratory parameters (abnormalities) will be recorded as AEs. During the treatment period, all total WBC and WBC differential results will be blinded. Reductions in ALC levels is a known PD effect of BMS-986166. If any of the following results are observed, the investigator will be notified and asked to repeat the laboratory tests within approximately 7 days:

- Absolute lymphocyte count [ALC] < 200 cells/µL
- Absolute neutrophil count [ANC] < 1000 cells/µL
- Total WBC > 20,000 cells/µL

If the repeat values also exceed these limits, the investigator will be informed that the patient's results for the abnormal parameter have fallen below the acceptable threshold.

If ANC or total WBC counts are confirmed below the acceptable limits, the Medical Monitor will contact the treating investigator to request close monitoring for risk of serious infection and appropriate follow-up, at the discretion of the investigator.

If the ALC is confirmed < 200 cells/µL, the investigator will discontinue investigational drug and then consult with the Medical Monitor. Laboratory testing will be repeated weekly until ALC is > 500 cells/µL.

If participants have elevations in ALT and/or AST ≥ 3x the upper limit of normal (ULN), a retest should be performed as soon as possible but not later than 4 days after the original test. If the abnormality is confirmed, twice-weekly testing should occur until ALT and AST are < 3x ULN. If the ALT and/or AST stabilizes at a level > 3x ULN, the Medical Monitor may agree to less frequent testing. Other liver-related laboratory testing, including international normalized ratio (INR), alkaline phosphatase (AP), gamma-glutamyl transferase (GGT), hepatitis serologies, and other tests as deemed necessary by the investigator should be performed to better understand the observation.

The investigator should establish causality. In addition, the confirmed elevation > 3x ULN is an AEI (see Section 9.2.8) and should be reported by the investigator. At any time, if any of the following occur and there are no apparent alternative causes for the finding, the investigational drug must be permanently discontinued:

- ALT or AST > 8x ULN or
- ALT or AST > 5x ULN with confirmation, within 2 weeks or
- ALT or AST > 3x ULN and (total bilirubin > 2x ULN or INR > 1.5) or
- ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

The investigator should establish causality. After discontinuation due to elevation of ALT or AST > 5x ULN or concurrent elevations of ALT or AST > 3x ULN and bilirubin > 2x ULN, further liver function evaluation should be performed (for example, coagulation panel and alkaline phosphatase) in consultation with the Medical Monitor.

9.2.7 Potential Drug Induced Liver Injury (DILI)

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 Section 9 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

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

9.2.8 Monitoring of Participants with Adverse Events of Interest (AEIs)

Adverse events of interest (AEIs) are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. AEIs may be serious or nonserious. Such events may require further investigation to better characterize and understand them in addition to the conventional safety monitoring employed in the study. In the branebrutinib clinical development program, infection AEs have been identified as potential AEIs; however, there has been no definitive assessment on the causal relationship between these events and treatment with branebrutinib. Therefore, additional information about infection AEs may be collected on the eCRF in order to better characterize and understand them.

Potential AEs of interest that may be a consequence of S1PR1 modulation will therefore be monitored in the IM018005 study. These AEs include:

- **Bradycardia and heart conduction abnormalities:**

  Dose-related transient, reversible bradycardia and first-degree atrioventricular block were reported primarily as first dose effects in fingolimod studies. The HR reduction observed with S1PR1 agonists is an expected effect of S1PR modulation and appears to be conducted through the same pathway as vagus nerve stimulation. In addition, these negative chronotropic effects of S1PR1 agonists appear to attenuate over time secondary to S1PR desensitization and internalization on cardiac myocytes.[119] Because of its biased ligand properties, both nonclinical and clinical data suggest that this effect is less with BMS-986166 (Section 3.2 and IB).

  Nevertheless, ECG assessment predose and at 1, 2, 4, and 6 hours post-dose will be obtained; in addition to hourly monitoring of the HR and blood pressure on Day 1. Standard 12-lead ECG will be collected and reviewed with every subsequent visit.

  Clinicians should be particularly mindful of participants who have a low HR at baseline (spontaneously or through drug-induced ß-receptor blockade), prior to administration of the investigational drug. Atropine IV is recommended as the first-line treatment of bradycardia, up to a maximum daily dose of 3 mg. Furthermore, the common guidelines for treatment of bradycardia (eg, Advanced Cardiac Life Support [ACLS] guidelines) should be followed as appropriate.

- **Pulmonary effects:**

  An initial sharp decrease followed by a slow progressive decline over time in FEV1 was observed in fingolimod clinical studies. Nonclinical toxicity studies however with BMS-986166 have not revealed the potential for pulmonary toxicity at doses considerably higher than the pharmacologically active dose. PFTs including FEV1, FVC, and diffusion capacity of carbon monoxide (DLCO), will be measured in all participants. Every participant whose PFTs are abnormal will be followed until such time as resolution is confirmed or no further improvement is expected by the investigator.

  Any condition that might affect the outcome of pulmonary function testing including infection, respiratory symptoms, occupational exposures (including asbestos) and cigarette smoking needs to be collected before PFT testing and transcribed to the PFTs eCRF page. If participants experience a decline in PFT values (FEV1 and/or FVC) below 30% of the baseline values, treatment should be discontinued.

  If a participant discontinues due to a respiratory AE, the investigator should ensure that the patient has adequate evaluations as clinically indicated by a pulmonologist for the AE. Further evaluations will be conducted until such time as resolution is confirmed or no further improvement is expected by the investigator (based on a follow-up period of not less than 3 months).

- **Hepatotoxicity:**

  Fingolimod caused frequent, reversible liver enzyme elevations greater than 3-fold above the ULN in up to 12% of patients; this was a significant cause of cessation of therapy. In this study, clinical blood chemistry analyses to assess liver function tests (LFTs) will be performed. Every patient whose LFTs are abnormal will be followed until values return to baseline.

  Refer to Section 9.2.6 and Section 9.2.7 for instructions regarding hepatotoxicity.

- **Macular edema:**

  Instances of serious macular edema were reported in fingolimod renal transplant studies, and a 0.8% incidence was reported as an SAE in fingolimod (1.25 mg dose) MS clinical studies. Nonclinical studies with BMS-986166 have not revealed eye-related toxicities. In this study, visual acuity (VA) testing and OCT will be performed in all participants at screening and the end of study visits or early termination. In addition, participants will be questioned about visual signs or symptoms at each study visit and instructed to inform the investigator if they develop symptoms between visits. For participants with visual symptoms suggestive of macular edema, OCT and ophthalmologic examination, including visual acuity testing and dilated ophthalmoscopy, will also be performed. Every participant whose ophthalmic evaluations reveal abnormalities will be followed until values return to baseline.

  Study drug must be discontinued in any participant who has a diagnosis of macular edema. Participants with a diagnosis of macular edema must be followed up monthly or more frequently if needed based on the ophthalmologist's judgment. Further ophthalmological evaluations will be conducted until such time as resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow-up period of not less than 3 months). If the participant does not show definite signs of improvement on examination 6 to 8 weeks after discontinuation of investigational drug, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated.

- **Opportunistic or serious infections:**

  TB, serious bacterial infections, systemic fungal infections, viral infections such as herpes infections (including herpes zoster and disseminated herpes simplex), and protozoal infections should be reported as AEIs and treated accordingly.

  Malignancies

  Malignancies such as melanoma, basal cell carcinoma, breast cancer, lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma), and seminoma have also been reported for the class of S1P receptor modulators. Malignancy should be reported as AEIs and referred accordingly to the appropriate specialist.

  Progressive multifocal leukoencephalopathy (PML)

  PML is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that typically occurs in patients who are immunocompromised and may lead to death or

severe disability. JCV infection resulting in PML has been observed in patients treated with immunomodulatory therapies for MS and has been associated with some risk factors (eg, polytherapy with immunosuppressants, severely immunocompromised patients). Typical symptoms associated with PML vary, progress over days to weeks, and include progressive weakness on 1 side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

Investigators should be vigilant for clinical symptoms or other findings that may be suggestive of PML. If PML is suspected, a neurologist consultation should be obtained and magnetic resonance imaging (MRI) should be requested and treatment should be discontinued.

Posterior reversible encephalopathy syndrome (PRES)

PRES is a syndrome characterized by sudden onset of severe headache, confusion, seizures, and visual loss. If a participant develops any unexpected neurological or psychiatric symptoms/signs (eg, cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider an MRI. If PRES is suspected, treatment should be discontinued.

9.2.9 Other Safety Considerations

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

9.3 Overdose

For this study, any dose of BMS-986166 or branebrutinib greater than 2 daily doses of study treatment within a 24-hour time period will be considered an overdose. See Section 9 for AE assessment and reporting procedures regarding suspected overdose and intentional overdose.

Based on the IB, there has been no clinical experience nor known specific antidote for overdose with either BMS-986166 or branebrutinib.[38,47]

In the event of an overdose, the investigator should:

1) Contact the Medical Monitor immediately.
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities.
3) Obtain a plasma sample for PK analysis within 4 hours of the overdose 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 participant.

9.4 Safety

An external, independent DMC will be empaneled to review safety on a prescheduled and ad-hoc basis, in addition to contemporaneous safety monitoring by the study team. Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

9.4.1 Physical Examinations

A complete physical examination will include general appearance, vital signs, eyes, ears, nose, mouth, throat, neck, respiratory, cardiovascular, respiratory, gastrointestinal/abdomen, lymphatic, musculoskeletal, skin, psychiatric, and neurologic examinations.

A targeted physical examination will include any organ system associated with an AE, or a laboratory abnormality. Refer to the Schedule of Activities (Section 2).The examination includes examination of the abdomen, conjunctival mucosae, heart, lungs, lymph nodes, oral mucosa, skin, and any sites deemed necessary by the investigators based on symptoms or other findings.

9.4.2 Vital signs

Refer to the Schedule of Activities (Section 2).

9.4.3 Electrocardiograms

12-lead ECG will be performed at the visits indicated in the Schedule of Activities (Section 2). The participant will remain supine for 5 to 10 minutes prior to the ECG and must have lab work done after the tracing so that the ECG results remain as accurate as possible. The ECG results will be read by the primary study investigator or a designee.

9.4.4 TB Screening and Chest Imaging

A participant must not have active signs or symptoms of TB, as judged by the investigator, to be eligible for the study.

In addition to a complete physical examination and medical history to evaluate exposure to TB, all participants will have a screening interferon-gamma release assay (IGRA; eg, QuantiFERON®-TB Gold) performed centrally. If unable to obtain central laboratory results, an IGRA test could be obtained locally, after consultation with the BMS Medical Monitor. A participant with an indeterminate IGRA test result must be retested for confirmation. If the second result is again indeterminate, the participant will be excluded from the study. If the second result is positive, the participant should be considered as having LTBI provided there are no signs or symptoms of active TB. If the second result is negative, the participant may be eligible provided no other exclusion criterion for TB is met. A chest x-ray is also required during Screening.

9.4.5 Pulmonary Function Tests

Pulmonary findings in animals and humans are associated with full-agonist S1PR1 modulators such as fingolimod.[120,121] It is hypothesized that the differentiated biased-ligand properties of BMS-986166 (Section 3.2.1.1) obviates this phenomenon and its downstream consequences such as pulmonary effects and macular edema in animals and humans; this hypothesis is supported by observations in nonclinical models.[38]

- In both Studies IM018001[122] and IM018003,[123] there was no apparent effect of BMS-986166 on pulmonary function including FVC, FEV1, or DLCO. Participants underwent frequent safety assessments while in the clinic and during an extended follow-up period to monitor for AEs. Decline in PFT values (FEV1 and/or FVC) below 30% of the baseline values during treatment in this study (IM018005) will result in discontinuation from further study drug administration.

To monitor the potential pulmonary effects of BMS-986166, FEV1, FVC, and DLCO measurements will be performed as indicated the Schedule of Activities (Section 2).These tests will be performed at a qualified pulmonary function laboratory or respiratory department. Please refer to the American Thoracic Society/European Respiratory Society guidelines for standardization of spirometry and single breath determination of carbon monoxide uptake in the lung.[124,125,126]

9.4.6 Neurological Safety

Preclinical toxicity data in conjunction with large systemic exposure (AUC-based) margins suggest a low safety concern for likely neurological effects in human participants.

Consistent with the nonclinical results, comprehensive neurological examination and nerve conduction velocity results for participants in Study IM018001[101] or IM018003[102] demonstrated no concerning treatment-emergent neurological findings following dosing with BMS-986166.

Specific monitoring for neurologic toxicity, beyond standard safety measures, is not planned in Study IM018005.

9.4.7 Ophthalmological Examination

Full-agonist S1PR1 modulators such as fingolimod are associated with potential macular edema.[127] Accordingly VA and OCT will be performed at scheduled times as indicated in the Schedule of Activities (Section 2). Diagnosis of macular edema, retinal or choroidal disease, or syndrome during treatment will result in discontinuation from further study drug administration.

9.4.8 Male Sex Hormones

For the purposes of monitoring the preclinical testicular finding, participants with history of significant testicular or epididymal disease will be excluded, and male sex hormones (follicle-stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone) will be assessed at baseline and selected time points throughout the treatment period and until study discharge.[38]

9.4.9 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

A central laboratory will perform the analyses and will provide reference ranges for these tests. WBC counts and lymphocyte counts will be monitored centrally and will not be provided to the site to prevent potential unblinding of the investigator.

Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Coagulation Panel	
Prothrombin time/International normalized ratio (PT/INR)- screening only	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) Uric acid Fasting glucose Cholesterol & Lipid Panel Testosterone	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine phosphokinase eGFR calculation Hemoglobin A1c Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)
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	
Screening Serology	
Serum for hepatitis C antibody, hepatitis B surface antigen, hepatitis B core antibody, HIV-1 and -2 antibody (screening only)	
Other Analyses	
Test for drugs of abuse (urine or serum), (screening and predose on Day 1)	
Pregnancy test (WOCBP only).	
Follicle stimulating hormone (FSH) (screening only for select women only)	
QuantiFERON-TB Gold test (or equivalent if not available; screening only)	
SARS-CoV-2 serology test	
SARS-CoV-2: RT-PCR Test or Antigen test	

9.5 Pharmacokinetics

Pharmacokinetics of BMS-986166 and its major metabolites (BMS-986166-P) will be derived from blood concentration. Pharmacokinetics of branebrutinib will be derived from plasma concentration. Blood (BMS-986166 and its major metabolite [BMS-986166-P]) and plasma (branebrutinib) samples will be analyzed by validated assays. Samples collected from participants who receive placebo will not be analyzed. In addition, blood and plasma samples will be archived for potential additional metabolites analysis, if the need arises and to the extent possible. Detailed instructions for PK blood collection, labeling, processing, storage, and shipping will be provided to the sites.The pharmacokinetic parameters to be assessed include:

Cmax	Maximum observed blood concentration for BMS-986166 and its major metabolite BMS-986166-P Maximum observed plasma concentration for branebrutinib
Tmax	Time of maximum observed blood or plasma concentration
AUC(0-T)	Area under the blood or plasma concentration-time curve from time zero to time of last measured concentration wherever applicable
Ctrough	Trough observed blood or plasma concentration wherever applicable
AUC(TAU)	Area under the concentration-time curve in one dosing interval wherever applicable

Individual participant pharmacokinetic parameter values will be derived by non-compartmental methods by a validated pharmacokinetic analysis program. Actual times will be used for the analyses.

9.5.1 Sampling Schedule

The sampling schedule for the assessment of PK is provided in Table 9.5.1-1. Predose samples must be drawn before the dose on visit days, and after a fast of at least 8 hours for the Day 1and Day 85 visits. As described in Section 2, Schedule of Activities, the timing of other procedures at a given visit can be adjusted so that PK sampling can be performed at the scheduled time. If possible, PK samples should be collected from participants who discontinue treatment due to an AE. Further details of blood collection and processing will be provided to sites.

Table 9.5.1-1: Pharmacokinetic Sampling Schedule for All Participants (IM018005)

Study Day of Sample Collection	Event	Time Relative to BMS-986166 or Branebrutinib Dose (hr:min)	BMS-986166 + BMS-986166-P Blood Sample	Branebrutinib Plasma Sample
Day 1 (Week 0) (Randomization)[a]	Predose	0:00	X	X
		0:30	X	X
		1:00	X	X
		2:00	X	X
		4:00	X	X
		6:00	X	X
		12:00[b]	X	
Day 29 (Week 4)	Predose	0:00	X	
Day 57 (Week 8)	Predose	0:00	X	
Day 85 (Week 12)[a]	Predose	0:00	X	X
		0:30	X	X
		1:00	X	X
		2:00	X	X
		4:00	X	X
		6:00	X	X
		12:00[b]	X	
Day 113 (Week 16)	Post Dose	24:00	X	

Abbreviations: hr = hour; min = minute

[a] Participant is required to fast for 8 hours. A light meal/snack may be provided after the 2-hour PK collection insofar as to not interfere with obtaining PK sample.

[b] Samples collected from consenting participants at selected sites and will be analyzed for BMS-986166 and BMS-986166-P only.

It is expected that every effort will be made to collect PK samples at the times indicated.

At selected sites, participants will be asked to complete an additional blood draw 12 hours post-dose on Days 1 and 85. They will be required to sign a separate ICF before collection of the samples. All samples should be collected using the time point labels provided, even if they are outside of the scheduled sampling time. Actual sample times must be recorded. If samples cannot be taken within the specified time, then every effort should be made to take a sample as soon as possible.

9.6 Pharmacodynamics

Pharmacodynamic blood sampling should be performed at the nominal time(s) specified in this clinical protocol. All actual PD blood sample collection times will be recorded in the source

documents and eCRF. Explanation should be provided in the source documents and eCRF for missed or mishandled samples and for samples collected outside the following time windows (applicable to all parts of the study, as appropriate).

Exploratory analyses may not be conducted in all cohorts or at all timepoints in each cohort. The exact analyses and time points for each cohort will be communicated to the clinical site prospectively. For some exploratory analyses, samples will be collected and banked. Select banked samples may be analyzed based on emerging PD and/or PK data.

The sampling schedule for all biomarkers, including PD biomarkers, is outlined in Table 9.8-1. All samples will be collected predose.

9.6.1 Blood Collection for Immunocyte Profiling

Blood samples will be collected and measured by flow cytometry or other methods for quantitating immune cell populations including, but not limited to Th1, Th2, Th17, Tem, Tcm, Temra, B-cells subsets, basophils, eosinophils, and DCs by panels comprised of appropriate surface markers.

On days when IP is administered, samples will be collected prior to dosing.

9.6.2 Blood Collection for Plasma Cytokines

Blood samples will be collected to explore the in vivo effects of BMS-986166 and branebrutinib on cytokines and other circulating proteins. Cytokines measured may include, but not limited to TSLP, IFN-γ, IL-1α, IL-1β, IL-6, IL-17A, IL-17F, IL-31, IL-33, TNF-α, CRP, CXCL10, and CXCL13.

On days when IP is administered samples will be collected prior to dosing.

9.6.3 Blood Collection for Gene Expression

Blood samples will be collected to explore the effects of BMS-986166 and branebrutinib on gene expression from total cells in whole blood or from purified cell types. Samples will be collected and mRNA isolated for assessment of expression levels of genes encoding proteins including, but not limited to TSLP, IFN-γ, IL-1α, IL-1β, IL-6, IL-17A, IL-17F, IL-31, IL-33, TNF-α, CRP, CXCL10, CXCL13, and Th, B-cell, pDC, and eosinophil associated genes. Whole blood RNA will be analyzed pending efficacy results and may not be assessed for all time points and treatment arms.

On days when IP is administered samples will be collected prior to dosing.

9.7 Pharmacogenomics

Whole-genome sequencing or single-nucleotide polymorphism (SNP) analysis of DNA may be performed to determine if there is a genetic basis associated with the response to BMS-986166 and/or branebrutinib. Variants examined will include, but are not limited to, genes with known relevance to small-molecule drug distribution and metabolism, and to AD pathogenesis such as filaggrin (FLG), human leukocyte antigen analyses, and mutations/SNPs in disease relevant pathways such as genes involved in type I IFN signaling and the JAK/ signal transducer and activator of transcription pathway. Epigenetic analyses of DNA may also be performed.

9.7.1 ADME Sampling

A 6-mL whole blood sample will be drawn at baseline (Day 1, as indicated in Section 2 Schedule of Activities and Table 9.8-1) for potential analysis of DNA variants in ADME-related genes (see Appendix 16 which contains the lists of ADME-related genes from http://pharmaadme.org, analyses will likely include these genes but may not be limited to them). Further details of blood collection and processing will be provided to the site in the procedure manual.

9.8 Biomarkers

The objectives of the biomarker work are to confirm target engagement for BMS-986166 (S1PR) and branebrutinib (BTK), and to understand the biological consequences of blocking these pathways in AD participants. [redacted] Samples may also be used to build or improve assays related to the above questions. The biomarker approaches for this study are discussed in the following subsections in greater detail, and will focus on leukocyte counts and inflammatory signaling molecules in blood (eg, Th2 cells and eosinophils in whole blood, RAST, Serum IgE, and cytokines), gene expression analysis in blood and tissue, pathologic analyses of skin biopsies (eg, histology, lymphocyte and neutrophil infiltration, eosinophils, mast cells), and proteomic/gene expression analyses of skin tape stripping samples. Where possible, blood and tissue samples will be collected at multiple timepoints to facilitate longitudinal analyses.

The collection of the stratum corneum, the uppermost layer of the epidermis, by tape-stripping offers the advantage of obtaining skin samples in a simple and noninvasive manner. This technique has been used to determine different skin biomarkers such as interleukin (IL)-1 cytokines, enzymes, lipids, and filaggrin degradation products. Details on the use of tape stripping procedures in AD patients as well as the downstream biomarker analyses[128,129,130,131] will be provided in the Study Laboratory Manual.

Measurements may also include, but are not limited to, assessments of SARS-CoV-2 serologic status. Serum will be collected at baseline and end of study for optional measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 IgM and/or IgG and/or IgA). Further details of sample collection and processing for blood, serum, and skin biopsies will be provided to the site in the Study Laboratory Manual.

Table 9.8-1: Biomarker Sampling Schedule All Participants (IM018005)

Study Day of Sample Collection	Serum Biomarkers[a]	Whole Blood for BTK Occupancy	Whole Blood Total BTK pBTK	Whole Blood DNA	Whole Blood Epigenetic Analyses[b]	Whole Blood RNA (PAXgene)[c]	Flow Cytometry	Skin Tape Stripping	Skin Biopsy (optional)	SARS-CoV-2 Serology
Day 1	X	X	X	X	X	X	X	X	X	X
Day 8	X	X	X			X				
Day 29	X	X	X		X	X	X	X		
Day 85	X	X	X			X				
Day 113 / EOT	X	X	X		X	X	X	X	X	
Follow Up - Day 127	X	X	X		X	X	X			
Follow Up - Day 169	X	X	X		X	X	X			X
Study Withdrawal										X

Abbreviations: BTK = Bruton Tyrosine Kinase; DNA = deoxyribonucleic acid; EOT = end of treatment: RNA = ribonucleic acid

[a] Serum analyses on Day 8 and Day 85 will be performed if deemed necessary based on efficacy and other biomarker results.

[b] Epigenetic samples will be stored for later analysis.

[c] Whole blood for all RNAseq (RNA sequencing) time points will be stored, and analyses will be performed if warranted based on efficacy and other biomarker results.

9.8.1 Pathway Engagement Assays

As one of the primary biological roles of S1P signaling is regulation of tissue/blood leukocyte trafficking.[132] S1P target and pathway engagement will be assessed by absolute lymphocyte count (ALC) in blood and tissue assessments of lymphocyte infiltration in AD lesions.

Blood and tissue analyses of other immune cell populations will be assessed in parallel to determine if any effects seen are global or specific to subsets of leukocytes.

Branebrutinib target engagement will be assessed by a mass-spectrometric based BTK occupancy assay and measurement of total BTK in whole blood.

9.8.2 Additional Exploratory Biomarkers

As current scientific literature and internal BMS research suggests that BTK and S1P signaling may impact many overlapping, complementary immunological processes and immune cell types, exploratory analyses will be performed with the goal of producing the same data outputs whenever possible. This approach will maximize the translational value of the dataset, ensuring that this study will advance understanding of the field regardless of the efficacy seen in this study, and thus provide value to the AD patient community.

Cellular analyses will include, but may not be limited to, skin and blood analysis of Th2 cells and other T-cells subsets, B-cells, eosinophils, basophils, mast cells, neutrophils, myeloid cells, and innate lymphoid cells. A combination of techniques including gene expression analyses, ELISA or other protein measurements for serum IgE and cytokines, proteomic/gene expression analyses of skin tape stripping samples, autoantibodies, and clinical chemistry tests such as RAST and serum surrogates of mast cell activation will be used to build a comprehensive picture of the response of AD participants to BTK and S1P inhibition. Genetic analyses will include, but are not limited to mutations in the Filaggrin gene (FLG), with FLG potentially informing on disease mechanisms relevant to pediatric vs. adult AD in particular.[24,133]

Skin punch biopsies will be optional but strongly encouraged, with a minimum goal of 12 biopsies per group, since they are critical to a full understanding of response to these therapies in AD participants. Looking to future studies, having as many skin samples as possible will also allow for greater understanding of which tissue measures may have viable blood/serum surrogates and what can only be assessed accurately from biopsies. Immune cell trafficking, expected to be one of the major phenomena affected by BMS-986166, is expected to fall into the category of those requiring tissue assessment. Skin punch biopsies will be taken at baseline and at end of treatment, and either frozen, placed in formalin, or sent into an equivalent process as appropriate for the experimental end use of the material (ie, separate processing for RNA extraction). Details for the biopsy procedures will be provided in the Study Laboratory Manual.

Extra serum, plasma and whole blood for DNA and RNA will be taken to explore pathways impacted by branebrutinib and BMS-986166 and pathophysiological aspects of AD. RNA may be analyzed by any common technique, including RNA sequencing, to enable broad or directed profiling of gene expression.

Biomarker samples will be collected in the appropriate collection tubes or devices at the times indicated in Table 9.8-1.

Allowed windows of biomarker assessments will be detailed in the lab manual.

Biomarker samples will be shipped to a central and contracted laboratories for the analytical assessments for the measurement of the following exploratory biomarkers:

- Target engagement assay, mass-spectrometric BTK occupancy assay (branebrutinib), or ALC (BMS-986166)
- Pathway engagement: ALC / assessment of immune cell infiltrate in AD skin lesions (BMS-986166)
- Immune cell counts from whole blood
- Leukocyte profiling from whole blood
- Eosinophil and basophil profiling from whole blood
- Serum cytokines, inflammatory markers, and soluble proteins
- Clinical chemistry measures of mast cell activity in serum (eg, serum histamine)
- Extra serum (explore pathway, disease and drug effects)
- Extra plasma (explore pathway, disease and drug effects)
- RNA from whole blood
- DNA from whole blood
- RNA and cytokine analyses
- Skin tape stripping samples for proteomic / gene expression analyses
- Skin biopsy (optional)
- Pathologic analyses of skin and immune cell populations in punch biopsies (optional)
- Gene expression and cytokine analyses in skin biopsies (optional)

Details for collection, processing, storing, and shipping these samples will be provided in the Study Laboratory Manual.

9.8.3 Additional Research Collection

This protocol will include sample collection and/or residual sample storage for additional research (AR).

For All US sites:

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

For non-US Sites

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right participants. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

- Prospective samples of serum, whole blood, and plasma will be collected at selected time points (see Table 9.8.3-1)
- Residual samples of all types from all test collections (see Table 9.8.3-2) will also be retained for additional research purposes

Samples kept for future research will be stored at the BMS Biorepository in New Jersey, USA or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be participant to the recipient's agreement to establish similar storage procedures.

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

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 9.8.3-1: Prospective Additional Research Sampling Schedule

Study Day	Time (Event) Hour	Time (Relative To Dosing) Hour: Min	Blood Sample	Serum Sample	Plasma Sample
Day 1	0 (predose)	00:00	X	X	X
Day 8	0 (predose)	00:00	X	X	X
Day 15	0 (predose)	00:00	X	X	X
Day 29	0 (predose)	00:00	X	X	X
Day 57	0 (predose)	00:00	X	X	X
Day 85	0 (predose)	00:00	X	X	X
Day 113/EOT	0 (predose)		X	X	X
Day 127/Final Follow-up Visit	0		X	X	X
Day 169	0		X	X	X

Abbreviations: EOT = end of treatment: min = minute

Table 9.8.3-2: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
Plasma	All
Whole Blood	All
Serum	All
Skin Biopsy	All

9.9 Health Economics OR Medical Resource Utilization and Health Economics

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

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size calculation is driven by the power to compare mean percentage change from baseline in EASI score at Week 16 between BMS-986166 or branebrutinib versus placebo. Thirty participants per group will provide 84% power to detect a treatment difference (versus placebo) of 30 % at the type I error of $\alpha = 0.05$ (1-sided), assuming a common standard deviation of 43%. The assumed treatment difference of 30% is similar to the mean difference observed from historical data on approved drugs across different mechanism of actions. No adjustment will be made for multiplicity.

Assuming a 15% dropout rate (ie, the fraction of participants not completing Week 16 assessment), 25 participants per group will still provide 78% power to detect a treatment difference of 30%.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent
Randomized	All participants who are randomized to a treatment
Treated	All participants who take at least 1 dose of study treatment
modified Intent-To-Treat (mITT)	All participants who are randomized and received at least one dose of study treatment
Safety	All randomized participants who take at least 1 dose of double-blind study treatment. Participants will be included in the treatment group they were randomized to, except in the following cases: • If a participant received the same incorrect treatment throughout the study, then the participant will be analyzed based on the treatment received. • If a participant received study drug from more than one treatment group, and none of the administrations were consistent with the assigned randomized treatment group, then the participant will be analyzed based on the first non-placebo treatment received. • If a participant is randomized to placebo treatment and receives non-placebo treatment, then the participant will be analyzed based on the first non-placebo treatment received.
Pharmacokinetic	All participants who received any corresponding study drug and have any available concentration-time data
Biomarker	All participants that received any study treatment and have any available biomarker measurement

Safety analysis will be based on Safety population, participants will be analyzed as per actual treatment received. Efficacy analysis will be based on mITT population, participants will be analyzed as per randomized treatment.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will include a more technical and detailed description of the statistical analyses described in this section. This

section is a summary of planned statistical analyses of the most important endpoints including primary and secondary endpoints.

A description of the participant population will be included in a statistical output report, including subgroups of age, gender and race.

10.3.1 Efficacy Analyses

10.3.1.1 Primary Endpoint

The primary efficacy endpoint is mean percent change from baseline in EASI score at Week 16.

A mixed effect model will be fit with treatment, visit and treatment-by visit interaction as the fixed effects and measurements within each participant as the repeated measurements. Adjusted mean % change (LSMEAN) and unadjusted mean % change with corresponding 95% CI per treatment group will be provided. The difference in adjusted means and corresponding 95% CIs will be provided for the difference between active treatment groups and placebo group at different visits (week 16 for primary endpoints). P-value will be provided for difference at Week 16.

10.3.1.2 Secondary Endpoint

The secondary efficacy endpoints are:

- Proportion of participants exhibiting a vIGA-AD score of 0 (cleared) or 1 (almost cleared) AND a ≥ 2 point reduction from Baseline at Week 16;
- Proportions of participants exhibiting a ≥ 50% (EASI-50) reduction from baseline in EASI score at Week 16
- Proportion of participants exhibiting a ≥ 4 point improvement from baseline in Pruritus NRS at Week 16.
- Mean percentage change from baseline in Pruritus NRS at Week 16
- Mean change from baseline in percentage of affected BSA at Week 16

For categorical (proportion) endpoints, the estimate and its corresponding 95% CI of each treatment group will be estimated using Clopper-Pearson method. The difference of the proportion between active treatments and the placebo will be estimated and their corresponding 95% CI will be calculated.

All participants discontinuing prematurely prior to Week 16, regardless of reason, will be counted as non-responders at subsequent visits.

For continuous (percent change from baseline and change from baseline) endpoints, the similar mixed effect model (as used in Section 10.3.1.1) will be fit with treatment, visit, and treatment-by visit interaction as the fixed effects and measurements within each participant as the repeated measurements. The baseline value will be added into the model as a covariate if necessary, for change from baseline endpoints. Adjusted mean % change (LSMEAN) and unadjusted mean % change with corresponding 95% CI per treatment group will be provided. The difference in adjusted means and corresponding 95% CIs will be provided for the difference between active treatment groups and placebo group at specific visits (eg, week 16 for secondary endpoints).

For participants requiring topical rescue therapy after the first 4 weeks of treatment or for more than 7 days, efficacy assessment after administration of rescue therapy will be considered as missing for continuous endpoints and considered as non-responder for categorical endpoints.

10.3.2 Safety Analyses

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

10.3.3 Other Analyses

PK, PD/biomarker and additionally efficacy exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and PD analyses will be presented separately from the main clinical study report.

10.3.4 Interim Analyses

When approximately 50% of the participants reached Week 16 or discontinued, an interim analysis (IA) for safety and efficacy will be performed to accelerate internal decision making. The safety analysis will focus on incidence and severity of AE, and SAE. The efficacy analysis will focus on percent change from baseline in EASI score and proportion of participants with ≥ 4 point improvement from baseline in Pruritus NRS at Week 16. The probability of treatment difference greater than certain value will be calculated using a Bayesian method. The interim analysis will be performed by individuals or vendor independent of the study team. The study team will remain blinded during interim analysis. The interim analysis results will be reviewed by an unblinded sponsor team to facilitate internal decision making related to the development of this asset. This unblinded sponsor team will not be involved in the study conduct.

The Statistical Analysis Plan will further describe the planned interim analyses.

11 REFERENCES

1 Sacotte R, Silverberg JI. Epidemiology of adult atopic dermatitis. Clin Dermatol. 2018;36(5):595-605.

2 Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR; International Study of Asthma and Allergies in Childhood (ISAAC) Phase One and Three Study Groups. Is eczema really on the increase worldwide? J Allergy Clin Immunol 2008;121(4):947–54.

3 Kang K, Polster AM, Nedorost ST, et al. Atopic dermatitis. In: Dermatology, Bolognia JL, Jorizzo JL, Rapini RP, et al (Eds), Mosby, New York 2003. p.199.

4 Mortz CG, Andersen KE, Dellgren C, Barington T, Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. Allergy. 2015;70(7):836-45.

5 Sandström MH, Faergemann J. Prognosis and prognostic factors in adult patients with atopic dermatitis: a long-term follow-up questionnaire study. Br J Dermatol. 2004;150(1):103-10.

6 Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. J Invest Dermatol. 2019;139(3):583-590.

7 Eckert L, Gupta S, Amand C, et. al. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: An analysis using the National Health and Wellness Survey. J Am Acad Dermatol. 2017;77(2):274-279.

8 Chandra RK, Lin D, Tan B, et al. Chronic rhinosinusitis in the setting of other chronic inflammatory diseases. Am J Otolaryngol 2011; 32(5): 388–91.

9 Mallol J, Crane J, Mutius E von, et. al. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global synthesis. Allergol Immunopathol (Madr) 2013;41(2):73–85.

10 Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: A practice parameter update 2012. J Allergy Clin Immunol. 2013;131(2):295-9.

11 Adamson AS. The Economics Burden of Atopic Dermatitis. Adv Exp Med Biol. 2017;1027:79-92.

12 Kelleher M, Dunn-Galvin A, Hourihane J O'B, et. al. Skin barrier dysfunction measured by transepidermal water loss at 2 days and 2 months predates and predicts atopic dermatitis at 1 year. J Allergy Clin Immunol. 2015;135(4):930-5.

13 Flohr C, England K, Radulovic S, et. al. Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. Br J Dermatol. 2010;163(6):1333-6.

[14] Gupta J, Grube E, Ericksen MB, et. al. Intrinsically defective skin barrier function in children with atopic dermatitis correlates with disease severity. J Allergy Clin Immunol. 2008;121(3):725-730.

[15] Boguniewicz M, Leung DYM. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. Immunol Rev. 2011;242(1):233-46.

[16] Akdis C A, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/ American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. J Allergy Clin Immunol 2006;118(1):152-169.

[17] Novak N, T. Bieber. Allergic and nonallergic forms of atopic diseases. J Allergy Clin Immunol. 2003; 112(2):252-262.

[18] Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis--part I: clinical and pathologic concepts. J Allergy Clin Immunol. 2011;127(5):1110-8.

[19] Guttman-Yassky E, Dhingra N, Leung DY. New era of biologic therapeutics in atopic dermatitis. Expert Opin Biol Ther. 2013;13(4):549-61.

[20] Kabashima K. New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity. J Dermatol Sci. 2013;70(1):3-11.

[21] Holmes J, Fairclough LC, Todd I. Atopic dermatitis and autoimmunity: the occurrence of autoantibodies and their association with disease severity. Arch Dermatol Res. 2019; 311(3):141-162; 2020;312(5):393.

[22] Alexander H, Patton T, Jabbar-Lopez ZK, et. al. Novel systemic therapies in atopic dermatitis: what do we need to fulfil the promise of a treatment revolution?. F1000Res. 2019;8:F1000 Faculty Rev-132.

[23] Muraro A, Lemanske RF Jr, Hellings PW, et al. Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2016;137(5):1347-58.

[24] Czarnowicki T, He H, Krueger J, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol. 2019;143(1):1-11.

[25] FDA. Medical Review, Dupilumab BLA 761055Orig1s000. 2016.

[26] Simpson E, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Eng J Med 2016;375(24):2335-48.

[27] Guttman-Yassky E, Nograles K, Krueger J. Contrasting pathogenesis of atopic dermatitis and psoriasis--part II: immune cell subsets and therapeutic concepts. J Allergy Clin Immunol. 2011;127(6):1420-32.

[28] Weidinger S, Beck L, Bieber T, et. al. Atopic dermatitis. Nat Rev Dis Primers. 2018;4(1):1.

[29] Ariëns L, Bakker D, van der Schaft J, Garritsen FM, Thijs JL, de Bruin-Weller MS. Dupilumab in atopic dermatitis: rationale, latest evidence and place in therapy. Ther Adv Chronic Dis. 2018;9(9):159-170.

[30] Kabashima K, Matsumura T, Komazaki H, et. al. Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus. N Engl J Med. 2020;383(2):141-150.

[31] Ruzicka T, Hanifin JM, Furue M, et al. Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis. N Engl J Med. 2017;376(9):826-835.

[32] Hla T. Physiological and pathological actions of sphingosine 1-phosphate Semin Cell Dev Biol 2004;15(5):513-20.

[33] Stepanovska B, Huwiler A. Targeting the S1P receptor signaling pathways as a promising approach for treatment of autoimmune and inflammatory diseases. Pharmacol Res. 2020;154:104170.

[34] Herzinger T, Kleuser B, Schäfer-Korting M, et. al. Sphingosine-1-phosphate signaling and the skin. Am J Clin Dermatol. 2007;8(6):329-36; 2008;9(4):277.

[35] Allende ML, Sipe LM, Tuymetova G, et. al. Sphingosine-1-phosphate phosphatase 1 regulates keratinocyte differentiation and epidermal homeostasis. J Biol Chem. 2013;288(25):18381-91.

[36] Jeon S, Song J, Lee D, et al. Inhibition of sphingosine 1-phosphate lyase activates human keratinocyte differentiation and attenuates psoriasis in mice. J Lipid Res. 2020;61(1):20-32.

[37] ADVISE. https://clinicaltrials.gov/ct2/show/NCT04162769

[38] S1P Receptor Modulator BMS-986166 Investigator's Brochure, Version 03. Bristol-Myers Squibb Company, 2021. Document Control No. 930097755.

[39] Gooderham MJ, Forman SB, Bissonnette R, et al. Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2 Randomized Clinical Trial JAMA Dermatol. 2019;155(12):1371-1379.

[40] Simpson E et al. Poster presented at: 28th EADV Congress; October 9-13, 2019; Madrid, Spain.

[41] Guttman-Yassky E, Thaçi D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020;145(3):877-884.

[42] Smith CI, Baskin B, Humire-Greiff P, et al. Expression of Bruton's agammaglobulinemia tyrosine kinase gene, BTK, is selectively down-regulated in T lymphocytes and plasma cells. J Immunol 1994;152(2):557-65.

[43] Middendorp S, Dingjan GM, Maas A, et al. Function of Bruton's tyrosine kinase during B cell development is partially independent of its catalytic activity. J Immunol 2003;171(11):5988-96.

[44] Chang BY, Huang MM, Francesco M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 ameliorates autoimmune arthritis by inhibition of multiple effector cells. Arthritis Res Ther 2011;13(4):R115.

[45] Di Paolo JA, Huang T, Balazs M, et al. Specific Btk inhibition suppresses B cell- and myeloid cell-mediated arthritis. Nat Chem Biol 2011;7(1):41-50.

[46] Xu D, Kim Y, Postelnek J, et al. RN486, a selective Bruton's tyrosine kinase inhibitor, abrogates immune hypersensitivity responses and arthritis in rodents. J Pharmacol Exp Ther 2012;341(1):90-103.

[47] Branebrutinib BMS-986195 Investigator's Brochure, Version 06. Bristol-Myers Squibb Company, 2020. Document Control No. 930097752.

[48] Szilveszter KP, Németh T, Mócsai A. Tyrosine Kinases in Autoimmune and Inflammatory Skin Diseases. Front Immunol. 2019;10:1862.

[49] Rankovic Z, Brust TF, Bohn LM. Biased agonism: An emerging paradigm in GPCR drug discovery. Bioorg Med Chem Lett. 2016;26(2):241-250.

[50] Evaluation of S1PR1 Modulator BMS-986166 in an Animal Model of Atopic Dermatitis. Study IM00331. Bristol-Myers Squibb Company; 2021. Document Control No. 930163082.

[51] Wedman PA, Aladhami A, Chumanevich AP, et. al. Mast cells and sphingosine-1-phosphate underlie prelesional remodeling in a mouse model of eczema. Allergy. 2018;73(2):405-415.

[52] Yoon SB, Lee CH, Kim HY, et al. A novel sphingosylphosphorylcholine and sphingosine-1-phosphate receptor 1 antagonist, KRO-105714, for alleviating atopic dermatitis. J Inflamm (Lond). 2020;17:20.

[53] BMS-986166: 6-Month Oral Gavage Toxicity Study in Rats, with an 8-week Recovery Period (Study DN17005). Bristol-Myers Squibb Company; 2018. Document Control No. 930127381.

[54] BMS-986166: 9-Month Oral Toxicity Study in Beagle Dogs, with a 12-week Post-Dose Recovery Period (Study DN16259). Bristol-Myers Squibb Company; 2018 Document Control No. 930131924.

[55] Nonclinical evaluation of the pharmacokinetics and metabolism of BMS-986166. Bristol-Myers Squibb Company; 2016. Document Control No. 930101208.

[56] In vitro characterization of absorption, distribution, metabolism, and elimination properties of BMS-986166. Bristol-Myers Squibb Company, 2015. Document Control No. 930086619.

[57] BMS-986195: Characterization of the irreversible BTK inhibitor BMS-986195 in biochemical and human immune cell assays (Study IM00086). Bristol-Myers Squibb Company; 2016. Document Control No. 930096590.

[58] BMS-986195: In vivo pre-clinical pharmacology of the irreversible BTK inhibitor BMS-986195 in mice (Study IM00085). Bristol-Myers Squibb Company; 2016. Document Control No. 930096587.

[59] BMS-986195: 6-month oral toxicity study in rats, with a 5-week recovery period (Study DN16062). Bristol-Myers Squibb Company; 2017. Document Control No. 930116391.

[60] Erickson RI, Schutt LK, Tarrant JM, et al. Bruton's Tyrosine Kinase Small Molecule Inhibitors Induce a Distinct Pancreatic Toxicity in Rats. J Pharmacol Exp Ther 2017;360(1):226-238.

[61] BMT-136986: Two-week exploratory toxicity study in rats (Study DN15006). Bristol-Myers Squibb Company; 2015. Document Control No. 930096737.

[62] BMS-986195: One-month Oral Toxicity Study in Rats with a Two-week Post-dose Recovery (Study DM15036). Bristol-Myers Squibb Company; 2016. Document Control No. 930097403.

[63] BMS-986195: One-month Oral Toxicity Study in Rats (Study DM16005). Bristol-Myers Squibb Company; 2016. Document Control No. 930103158.

[64] BMS-986195: 9-month oral toxicity study in beagle dogs with a 4-week recovery period (Study DN16030). Bristol-Myers Squibb Company; 2017. Document Control No. 930116257.

[65] Randomized, placebo-controlled, single and multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and nonrandomized, bioavailability (BA) study of BMS-986195 in healthy subjects (Clinical Protocol IM014001). Bristol-Myers Squibb Research and Development; 2016. Document Control No. 930093934.

[66] Liu, FT, Goodarzi, H, Chen, H. IgE, mast cells, and eosinophils in atopic dermatitis. Clin Rev Allerg Immunol 2011;41(3):298-310.

[67] Sidbury R, Davis DM, Cohen DE, et.al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014: 71(2):327-49.

[68] Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. J Allergy Clin Immunol. 2014;133(2):429–38.

[69] Gilenya (fingolimod) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2019.

[70] Bäumer W, Rossbach K, Mischke R, et. al. Decreased concentration and enhanced metabolism of sphingosine-1-phosphate in lesional skin of dogs with atopic dermatitis: disturbed sphingosine-1-phosphate homeostasis in atopic dermatitis. J Invest Dermatol. 2011;131(1):266–8.

[71] Cohen S, Tuckwell K, Katsumoto TR, et al. Fenebrutinib versus Placebo or Adalimumab in Rheumatoid Arthritis: A Randomized, Double-Blind, Phase II Trial (ANDES Study). Arthritis Rheumatol. 2020;10.1002/art.41275.

[72] Effects of concomitant administration of BMS-986195 on the single-dose pharmacokinetics of methotrexate and probe substrates for cytochrome P450 1a2, 2c8, 2c9, 2cl9, 3a4, organic anion transporter polypeptide 1b1 and P-glycoprotein in healthy participants (Study IM014013); Clinical Study Report. Bristol-Myers Squibb; 2018. Document Control No. 930126532.

[73] The effect of BMS-986195 on the pharmacokinetics of a combined oral contraceptive (Ethinyl Estradiol/Norethindrone) in healthy female subjects (Study IM014023). Bristol-Myers Squibb Company; 2018. Document Control No. 930152299.

[74] Leong DP, Caron F, Hillis C, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. Blood. 2016; 128(1):138–140.

[75] Imbruvica (ibrutinib) [product monograph]. Toronto, Ontario, Canada: Janssen Inc; December 2020.

[76] Xiao L, Salem JE, Clauss S, et al. Ibrutinib-mediated atrial fibrillation attributable to Inhibition of C-Terminal Src Kinase. Circulation. 2020;142(25):2443-2455.

[77] McMullen JR, Boey EJ, Ooi JY, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood. 2014;124(25):3829-30.

[78] Shafaattalab S, Lin E, Christidi E, et al. Ibrutinib displays atrial-specific toxicity in human stem cell-derived cardiomyocytes. Stem Cell Reports. 2019;12(5):996-1006.

[79] Poland GA, Ovsyannikova IG, Kennedy RB. SARS-CoV-2 immunity: review and applications to Phase 3 vaccine candidates. Lancet 2020;396(10262):1595-606.

[80] Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. NEJM 2020;383(25):2451-60.

[81] Buggy JJ, Elias L. Bruton tyrosine kinase (BTK) and its role in B-cell malignancy. Int Rev Immunol 2012;31(2):119-32.

[82] Roman-Garcia S, Merino-Cortes SV, Gardeta SR, et al. Distinct roles for Bruton's tyrosine kinase in B cell immune synapse formation. Front Immunol 2018;9:2027.

[83] El-Sayed ZA, Abramova I, Aldave JC, et al. X-linked agammaglobulinemia (XLA):Phenotype, diagnosis, and therapeutic challenges around the world. World Allergy Organ J 2019;12(3):100018.

[84] Quinti I, Lougaris V, Milito C, et al. A possible role for B cells in COVID-19? Lesson from patients with agammaglobulinemia. J Allergy Clin Immunol 2020;146(1):211-3.e4.

[85] Buckland MS, Galloway JB, Fhogartaigh CN, et al. Treatment of COVID-19 with remdesivir in the absence of humoral immunity: a case report. Nat Commun 2020;11(1):6385.

[86] Mira E, Yarce OA, Ortega C, et al. Rapid recovery of a SARS-CoV-2-infected X-linked agammaglobulinemia patient after infusion of COVID-19 convalescent plasma. J Allergy Clin Immunol Pract 2020;8(8):2793-5.

[87] Soresina A, Moratto D, Chiarini M, et al. Two X-linked agammaglobulinemia patients develop pneumonia as COVID-19 manifestation but recover. Pediatr Allergy Immunol 2020;31(5):565-9.

[88] Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. Blood 2020;135(21):1912-5.

[89] Roschewski M, Lionakis MS, Sharman JP, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. Sci Immunol 2020;5(48):eabd0110.

[90] Mikuls TR, Johnson SR, Fraenkel L, et al. American College of Rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic: Version 3. Arthritis Rheumatol 2021;73(2):e1-12.

[91] Schulze-Koops H, Krüger K, Hoyer BF, et al. Updated recommendations of the German Society for Rheumatology for the care of patients with inflammatory rheumatic diseases in times of SARS-CoV-2 methodology, key messages and justifying information. Rheumatology 2021;60(5):2128-33.

[92] Au K, Reed G, Curtis JR, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70(5):785-91.

[93] Pimentel-Quiroz VR, Ugarte-Gil MF, Harvey GB, et al. Factors predictive of serious infections over time in systemic lupus erythematosus patients: data from a multi-ethnic, multi-national, Latin American lupus cohort. Lupus 2019;28(9):1101-10.

[94] Hyrich KL, Machado PM. Rheumatic disease and COVID-19: epidemiology and outcomes. Nat Rev Rheumatol 2021;17(2):71-2.

[95] Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med. 2020;26(8):1205-1211.

[96] Li H, Wang S, Zhong F, et al. Age-dependent risks of incidence and mortality of COVID-19 in Hubei Province and other parts of China. Front Med (Lausanne). 2020;7:190.

[97] Liu Y, Mao B, Liang S, et al. Association between age and clinical characteristics and outcomes of COVID-19. Eur Respir J. 2020;55(5):2001112.

[98] Comirnaty. Summary of Product Characteristics. BioNTech Manufacturing GmbH; 2021.

[99] COVID-19 Vaccine Moderna. Summary of Product Characteristics. Moderna Biotech Spain, S.L.; 2021.

[100] Vaxzevria. Summary of Product Characteristics. AstraZeneca AB; 2021.

[101] COVID-19 Vaccine Janssen. Summary of Product Characteristics. Janssen-Cilag International NV; 2021.

[102] Pfaar O, Klimek L, Hamelmann E, et al. COVID-19 vaccination of patients with allergies and type-2 inflammation with concurrent antibody therapy (biologicals)- A Position Paper of the German Society of Allergology and Clinical Immunology (DGAKI) and the German Society for Applied Allergology (AeDA). Allergol Select 2021 5 140-7.

[103] Hamilton JD, Suárez-Fariñas M, Dhingra N. et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol. 2014;134(6):1293-1300.

[104] Tofte SJ, Papp K., Sadick N, et al. Efficacy and safety of dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults: A pooled analysis of two phase 2 clinical trials. J Am Assoc Nurse Pract. 2018;30(9):529-541.

[105] Simpson EL, Imafuki S., Poulin Y, et. al. A Phase 2 Randomized Trial of Apremilast in Patients with Atopic Dermatitis. J Invest Dermatol. 2019;139(5):1063-1072.

[106] Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371(2):130-9.

[107] Lee J-Y, Wang Y. Use of a biomarker in exposure-response analysis to support dose selection for fingolimod. CPT Pharmacometrics Syst Pharmacol. 2013;2(8):e67.

[108] Kaufmann M, Haase R, Proschmann U, et. al. Real World Lab Data: Patterns of Lymphocyte Counts in Fingolimod Treated Patients. Front Immunol. 2018;9:2669.

[109] Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338-51.

[110] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12; 2011;155(6):408.

[111] Williams B, Mancia G, Spiering W, et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2018;36(12):2284-2309.

[112] Simpson E, Bissonnette R, Eichenfield LF, et al. "The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): The development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis." J. Am. Acad Dermol 2020; 83(3);839-846.

[113] Hanifin JM, Thurston M, Omoto M, et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol 2001; 10(1):11-8.

[114] Charman CR, Venn AJ, Williams HC. Measurement of body surface area involvement in atopic eczema: an impossible task?. Br J Dermatol. 1999;140(1): 109-11.

[115] Severity scoring of atopic dermatitis: the SCORAD Index. Consensus report of the European Task Force on Atopic Dermatitis. Dermatology 1993;186(1):23-31.

[116] Martin S, Chandran A, Zografos L, et. al. Evaluation of the impact of fibromyalgia on patients' sleep and the content validity of two sleep scales. Health Qual Life Outcomes 2009;7:64.

[117] Reich A, Heisig M, Phan NQ, et. al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. Acta Derm Venereol 2012;92(5):497-501.

[118] Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19(3):210–6.

[119] Kovarik JM, Slade A, Riviere GJ, et. al. The ability of atropine to prevent and reverse the negative chronotropic effect of fingolimod in healthy subjects. Br J Clin Pharmacol. 2008;66(2):199-206.

[120] Oo ML, Thangada S, Wu MT, et al. Immunosuppressive and antiangiogenic sphingosine-1-phosphate receptor-1agonist induce ubiquitinylation and proteasomal degradation of the receptor. J Biol Chem 2007; 282(12):9082-9.

[121] Miron VE, Schubart A and Antel JP. Central nervous system-directed effects of FTY720 (fingolimod). J Neuro Sci 2008;274(1-2):13-7.

[122] A Randomized, Double-blinded, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BMS-986166 in Healthy Subjects. Clinical Study Report Addendum to Study IM018001. Bristol-Myers Squibb; 2021. Document Control No. 930158432.

[123] A Randomized, Double Blind, Placebo-controlled, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BMS-986166 in Healthy Subjects. Clinical Study Report Addendum to Study IM018003. Bristol-Myers Squibb; 2021. Document Control No. 930158483.

[124] Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005;26(4):720-35.

[125] Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J 2005;26(1):153-61.

[126] Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319-38.

[127] Mandal P, Gupta A, Fusi-Rubiano W et al. Fingolimod: therapeutic mechanisms and ocular adverse effects. Eye (Lond) 2017; 31(2):232-240.

[128] Olesen CM, Pavel AB, Wu J, et. al. Tape-strips provide a minimally invasive approach to track therapeutic response to topical corticosteroids in atopic dermatitis patients. J Allergy Clin Immunol Pract. 2020; S2213-2198(20)30869-2.

[129] He H, Bissonnette R, Wu J, et. al. Tape strips detect distinct immune and barrier profiles in atopic dermatitis and psoriasis. J Allergy Clin Immunol. 2020; S0091-6749(20)30824-1.

[130] Pavel AB, Renert-Yuval Y, Wu J, et. al. Tape strips from early-onset pediatric atopic dermatitis highlight disease abnormalities in nonlesional skin. Allergy. 2020.

[131] Guttman-Yassky E, Diaz A, Pavel AB, et. al. Use of Tape Strips to Detect Immune and Barrier Abnormalities in the Skin of Children With Early-Onset Atopic Dermatitis. JAMA Dermatol. 2019 Oct 9;155(12):1358-70.

[132] Matloubian M, Lo CG, Cinamon G, et. al. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature. 2004; 427(6972):355-60.

[133] Rasheed Z, Zedan K, Saif GB, et. al. Markers of atopic dermatitis, allergic rhinitis and bronchial asthma in pediatric patients: correlation with filaggrin, eosinophil major basic protein and immunoglobulin E. Clin Mol Allergy 2018;16:23.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AD	atopic dermatitis
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AEI	adverse event of interest
AF	atrial fibrillation
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	additional research
AST	aspartate aminotransferase
AT	aminotransferase
AUC	area under the concentration-time curve
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
AV	atrioventricular
AZA	azathioprine
BCR	B-cell receptor
BCRP	breast cancer resistance protein
BMS	Bristol Myers Squibb
bpm	beats per minute
BRA	Branebrutinib
BSA	body surface area
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval

Term	Definition
Cmax, CMAX	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRF	Case Report Form, paper or electronic
CRP	C-reactive protein
CTCAE	Common Toxicity Criteria for Adverse Events
Ctrough	Trough observed plasma concentration
CXCL13	chemokine ligand 13,
CXR	chest X-ray
CYP	cytochrome p-450
DC	dendritic cell
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DLCO	Diffusion capacity of carbon monoxide
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EC50	half maximal effective concentration
ECG	electrocardiogram
eCRF	electronic Case Report Form
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EHT	electronic health record
EMR	electronic medical record
EO	enzyme occupancy
EOS	end of study
EOT	end of treatment

Term	Definition
ERK	extracellular signal-related kinase
FDA	Food and Drug Administration
FEV	forced expiratory volume
FIH	first in human
FITC	fluorescein isothiocyanate
FLG	filaggrin
FSH	follicle stimulating hormone
FTY-720	fingolimod
FTY-P	fingolimod phosphate
FVC	forced vital capacity
GALT	gut associated lymphoid tissue
GLP	good laboratory practice
GTP	guanosine triphosphate
H / hr	hour
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's brochure
IC50	half maximal inhibitory concentration
IC	Immune complexes
ICF	Informed consent form
IDEC	inflammatory dendritic epidermal cell
ie	id est (that is)
IEC	Independent Ethics Committee
IFN	interferon
IGA	Investigators' Global Assessment

Term	Definition
IgA	Immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon gamma release assay
IL	interleukins
ILC2	type 2 innate lymphoid cell
ILC	innate lymphoid cell
IMP	Investigational Medicinal Products
INF	infinity
INR	International Normalized Ratio
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IU/L	International units per liter
IV	intravenous
JAK	Janus kinase
JCV	John Cunningham virus
KLH	keyhole limpet hemocyanin
LC	Langerhans cell
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LTBI	latent TB infection
MAD	multiple ascending dose
mg	milligram
min	minute
mL	milliliter

Term	Definition
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
MTD	maximum tolerated dose
MTX	methotrexate
µg	microgram
N	number of subjects or observations
NA	not applicable
NCV	nerve conduction velocity
ng	nanogram
NOAEL	no-observed-adverse-effect-level
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
NSVT	nonsustained ventricular tachycardia
NYHA	New York Heart Association
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OCT	optical coherence tomography
PA	posteroanterior
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PDE4	phosphodiesterase 4
PFT	pulmonary function test
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
P-gp	P-glycoprotein
PI	Principle investigator
PID	patient identification number
PK	pharmacokinetics

Term	Definition
PML	progressive multifocal leukoencephalopathy
PO	taken orally
POEM	Patient Oriented Eczema Measure
PPE	personal protective equipment
PRES	posterior reversible encephalopathy syndrome
PVC	premature ventricular contraction
PT	prothrombin time
QD	once daily
QOL	quality of life
QRS	Quick-Reaction Spare
QTc	QT interval corrected for heart rate
RA	rheumatoid arthritis
RAST	radioallergosorbent test
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAD	single ascending doses
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SNP	Single nucleotide polymorphisms
SUSAR	Serious Adverse Reactions
S1P	sphingosine-1-phosphate
S1P-1R	sphingosine-1-phosphate-1 receptor
TB	tuberculosis
TDAR	T-cell-dependent antibody response
TEAE	treatment-emergent adverse events
Th	helper T-cell
Th1	type 1 helper T-lymphocytes
Th2	type 2 helper T-lymphocytes
T-HALF	mean half-life
TK	toxicokinetics

Term	Definition
Tmax	time to maximum concentration
TNF	tumor necrosis factor
Trm	Resident memory T-cell
TSLP	thymic stromal lymphopoietin
UA	urinalysis
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
UV	ultraviolet
VA	visual acuity testing
vIGA-AD	Validated Investigator Global Assessment scale for Atopic Dermatitis
VZV	Varicella Zoster virus
W	week
WBC	white blood cell
WNOCBP	women **not** of childbearing potential
WOCBP	women of childbearing potential
XLA	X-linked agammaglobulinemia

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

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

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

- ICH guidelines,

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

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

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

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

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

SOURCE DOCUMENTS

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

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

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found in systems that may include, but are not limited to, electronic medical/health records (EMRs/EHTs), adverse event (AE) tracking/reporting, protocol required assessments, and/or drug accountability records).

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

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

STUDY INTERVENTION RECORDS

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

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

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

CASE REPORT FORMS

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

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

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

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

The completed CRF, 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 eCRFs, review and approval/signature is completed electronically through the BMS EDC tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records. Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

Certain CRF pages and/or electronic files may serve as the source documents.

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, or 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 interventions 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). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. 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 commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the 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.

STUDY AND SITE START AND CLOSURE

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

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

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases

in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

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

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

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

SCIENTIFIC PUBLICATIONS

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

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

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

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment 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 treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event 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 Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
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 participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs (see Section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or product information for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- **Assessment of Intensity**

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

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

Follow-up of AEs and SAEs

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

If an ongoing SAE changes in its intensity or relationship to study treatment 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 treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the electronic case report form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF) to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed facsimile transmission

SAE Email Address: worldwide.safety@BMS.com.

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

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. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgement in checking serum FSH levels.

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

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

End of Relevant Systemic Exposure

End of relevant systemic exposure is the timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed adverse effect level or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device • Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b,c] • Bilateral tubal occlusion.

- Vasectomized partner

Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

A vasectomy is a highly effective contraception method provided that the participant is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

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

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence.
- Periodic abstinence (including but not limited to calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

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

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 DIAGNOSTIC CRITERIA FOR ATOPIC DERMATITIS

BOX 1

Adapted from Journal of the American Academy of Dermatology, Volume 49, Eichenfield, LF, Hanifin JM, Luger TA, Stevens SR, Pride HB. Consensus conference on pediatric atopic dermatitis, pages 1088–1095, Copyright 2003, with permission from the American Academy of Dermatology.

Features to be considered in diagnosis of patients with atopic dermatitis

- **ESSENTIAL FEATURES**; must be present:
  - Pruritus
  - Eczema (acute, subacute, chronic):
    - Typical morphology and age-specific patterns*
    - Chronic or relapsing history

  Patterns include:
  1) facial, neck, and extensor involvement in infants and children;
  2) current or prior flexural lesions in any age group;
  3) sparing of groin and axillary regions.

- **IMPORTANT FEATURES**; seen in most cases, adding support to the diagnosis:
  - Early age of onset
  - Atopy
    - Personal and/or family history
    - IgE reactivity
  - Xerosis

- **ASSOCIATED FEATURES** ; these clinical associations help to suggest the diagnosis of AD but are too non-specific to be used for defining or detecting AD for research and epidemiologic studies:
  - Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
  - Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis
  - Ocular / periorbital changes
  - Other regional findings (e.g., perioral changes / periauricular lesions)
  - Perifollicular accentuation / lichenification / prurigo lesions

- **EXCLUSIONARY CONDITIONS;** it should be noted that a diagnosis of AD depends on excluding conditions such as:
    - scabies
    - seborrheic dermatitis
    - contact dermatitis (irritant or allergic)
    - ichthyoses
    - cutaneous T-cell lymphoma
    - psoriasis
    - photosensitivity dermatoses
    - immune deficiency diseases
    - erythroderma of other causes

APPENDIX 6 NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF CARDIOVASCULAR DISABILITY

CLASS	NYHA FUNCTIONAL CLASSIFICATION
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less-than-ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th ed, Little, Brown & Co, Boston 1994. p.253.

APPENDIX 7 DSM-5 DIAGNOSTIC CRITERIA FOR SUBSTANCE USE DISORDER

DSM-5 diagnostic criteria for substance use disorder are described below:

A problematic pattern of use leading to clinically significant impairment or distress is manifested by two or more of the following within a 12-month period:

1. Often taken in larger amounts or over a longer period than was intended.
2. A persistent desire or unsuccessful efforts to cut down or control use.
3. A great deal of time is spent in activities necessary to obtain, use, or recover from the substance's effects.
4. Craving or a strong desire or urge to use the substance.
5. Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by its effects.
7. Important social, occupational, or recreational activities are given up or reduced because of use.
8. Recurrent use in situations in which it is physically hazardous.
9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance.
11. Withdrawal.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013

APPENDIX 8 VALIDATED INVESTIGATOR GLOBAL ASSESSMENT SCALE FOR ATOPIC DERMATITIS (VIGA-AD™)

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

2. Excoriations should not be considered when assessing disease severity.

APPENDIX 9 ECZEMA AREA AND SEVERITY INDEX (EASI)

Eczema Area and Severity Index (EASI) case report form - age ≥8 years

Area of Involvement: Each body region has potentially 100% involvement. Score **0 to 6** based on the following table:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of **0 to 3**:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved area.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)

Scoring table:

Body region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification(0-3)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(+	+	+	)	X	X 0.1	
Trunk	(+	+	+	)	X	X 0.3	
Upper extremities	(+	+	+	)	X	X 0.2	
Lower extremities	(+	+	+	)	X	X 0.4	
The final EASI score is the sum of the 4 region scores:							_____ (0-72)

From Harmonising Outcome Measures for Eczema (HOME) (http://www.homeforeczema.org/documents/easi-case-report-form-for-age-8-years-and-over-v2.docx)

APPENDIX 10 BODY SURFACE AREA ESTIMATE WORKSHEET (SCORAD-A METHOD)

Estimate of the Total Body Surface Area (BSA) Affected by Atopic Dermatitis

SUBJECT ID: _____ DATE (dd/MMM/yyyy): _____/_____/_____

VISIT NO: _____

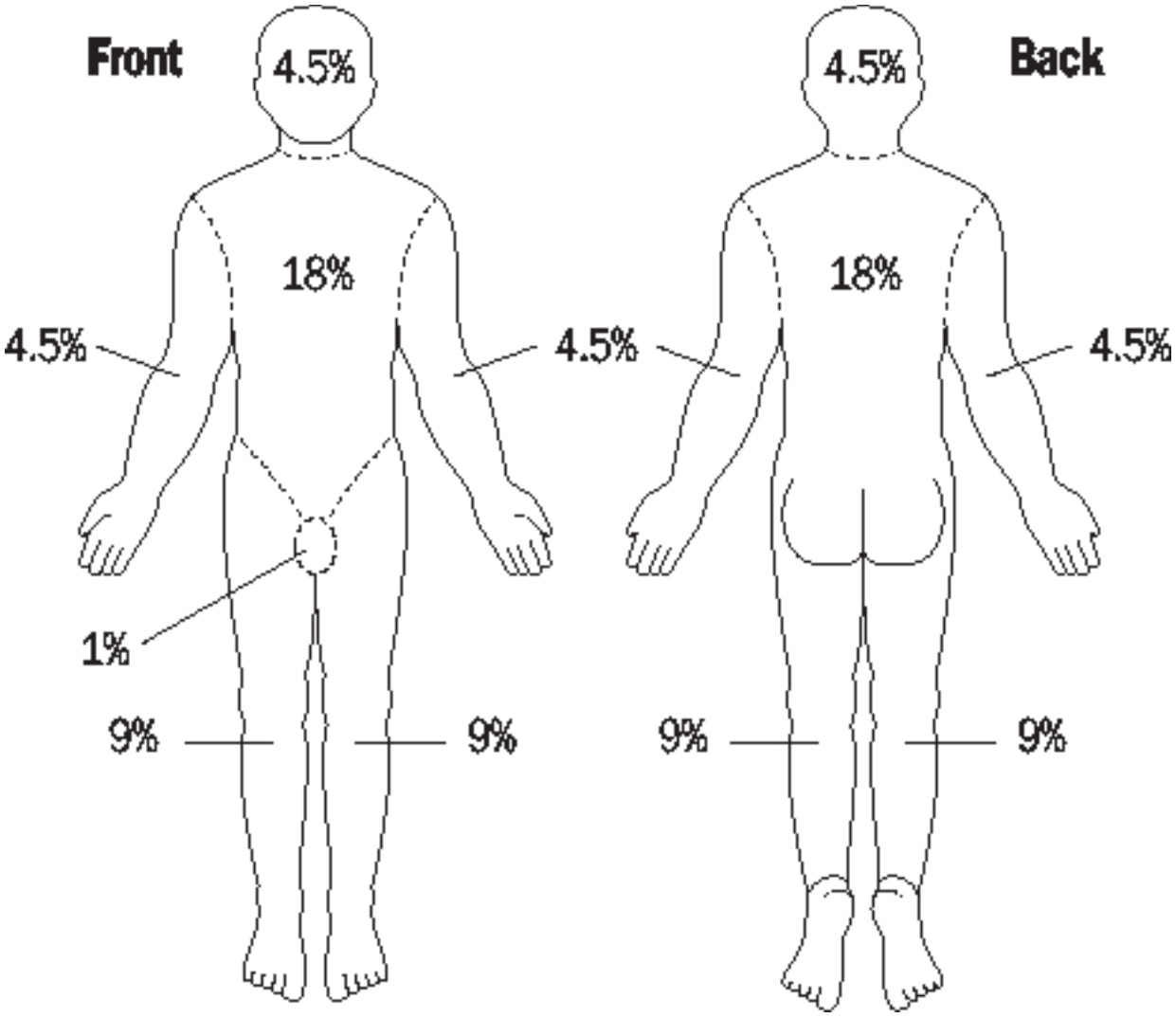
Investigator's Signature:_____

The extent of atopic dermatitis is assessed as % BSA. Please use the following table for the calculation of the total % BSA affected by atopic dermatitis.

Anatomic Structure	**% of Total BSA**
Anterior head	
Posterior head	
Anterior torso	
Posterior torso	
LEFT anterior arm	
RIGHT anterior arm	
LEFT posterior arm	
RIGHT posterior arm	
LEFT anterior leg	
RIGHT anterior leg	
LEFT posterior leg	
RIGHT posterior leg	
Genitalia/perineum	
Total BSA affected (%)	

✓ Please outline or shade the affected area(s) in the below diagrams.

Body Surface Area Estimate Work Sheet (Continued)



APPENDIX 11 PRURITUS AND SLEEP QUALITY NUMERICAL RATING SCALES (NRS)

Pruritus Rating Scale

Please select the number that best describes your itching during the past 24 hours. (Circle one number only.)

0	1	2	3	4	5	6	7	8	9	10
No itching										Worst itching imaginable

Sleep Quality Numerical Rating Scale

Please complete the following question upon awakening. Select the number that best describes the quality of your sleep during the past 24 hours. (Circle one number only.)

0	1	2	3	4	5	6	7	8	9	10
Best possible sleep										Worst possible sleep

APPENDIX 12 DERMATOLOGY LIFE QUALITY INDEX (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date: Score: ☐

Name: Diagnosis:

Address:

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

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

Please check you have answered EVERY question. Thank you.

APPENDIX 13 PATIENT ORIENTED ECZEMA MEASURE (POEM)

Patient-Oriented Eczema Measure

Please circle one response for each of the seven questions below. Young children should complete the questionnaire with the help of their parents. Please leave blank any questions you feel unable to answer.

1. **Over the last week, on how many days has your/your child's skin been itchy because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
2. **Over the last week, on how many nights has your/your child's sleep been disturbed because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
3. **Over the last week, on how many days has your/your child's skin been bleeding because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
4. **Over the last week, on how many days has your/your child's skin been weeping or oozing clear fluid because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
5. **Over the last week, on how many days has your/your child's skin been cracked because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
6. **Over the last week, on how many days has your/your child's skin been flaking off because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
7. **Over the last week, on how many days has your/your child's skin felt dry or rough because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day

Total Score (maximum 28) _____

APPENDIX 14 PATIENT GLOBAL IMPRESSION OF CHANGE (PGI-C)

Compared to the beginning of the study, before you started the study treatment, which of the following best describes the skin symptoms of your atopic dermatitis today?

- ☐ 1 Much improved
- ☐ 2 Moderately improved
- ☐ 3 A little improved
- ☐ 4 The same
- ☐ 5 A little worse
- ☐ 6 Moderately worse
- ☐ 7 Much worse

APPENDIX 15 PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

Which of the following best describes the severity of the skin symptoms of your atopic dermatitis over the past 7 days?

- ☐ 1 None
- ☐ 2 Mild
- ☐ 3 Moderate
- ☐ 4 Severe
- ☐ 5 Very Severe

APPENDIX 16 ADME GENE LIST (From HTTP://PHARMAADME.ORG)

Core ADME Gene List

Gene Symbol	Full Gene Name	Class
ABCB1	ATP-binding cassette, subfamily B (MDR/TAP), member 1	Transporter
ABCC2	ATP-binding cassette, subfamily C (CFTR/MRP), member 2	Transporter
ABCG2	ATP-binding cassette, subfamily G (WHITE), member 2	Transporter
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	Phase I
CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2	Phase I
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6	Phase I
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6	Phase I
CYP2C19	cytochrome P450, family 2, subfamily C, polypeptide 19	Phase I
CYP2C8	cytochrome P450, family 2, subfamily C, polypeptide 8	Phase I
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9	Phase I
CYP2D6	cytochrome P450, family 2, subfamily D, polypeptide 6	Phase I
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1	Phase I
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4	Phase I
CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5	Phase I
DPYD	dihydropyrimidine dehydrogenase	Phase I
GSTA1	glutathione S-transferase A1	Phase II
GSTM1	glutathione S-transferase M1	Phase II
GSTP1	glutathione S-transferase pi	Phase II
GSTT1	glutathione S-transferase theta 1	Phase II
NAT1	N-acetyltransferase 1 (arylamine N-acetyltransferase)	Phase II
NAT2	N-acetyltransferase 2 (arylamine N-acetyltransferase)	Phase II
SLC15A2	solute carrier family 15 (H+/peptide transporter), member 2	Transporter
SLC22A1	solute carrier family 22 (organic cation transporter), member 1	Transporter
SLC22A2	solute carrier family 22 (organic cation transporter), member 2	Transporter
SLC22A6	solute carrier family 22 (organic anion transporter), member 6	Transporter
SLCO1B1	solute carrier organic anion transporter family, member 1B1	Transporter
SLCO1B3	solute carrier organic anion transporter family, member 1B3	Transporter
SULT1A1	sulfotransferase family, cytosolic, 1 A, phenol-preferring, member 1	Phase II
TPMT	thiopurine S-methyltransferase,	Phase II
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	Phase II
UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15	Phase II
UGT2B17	UDP glucuronosyltransferase 2 family, polypeptide B17	Phase II
UGT2B7	UDP glucuronosyltransferase 2 family, polypeptide B7	Phase II

Extended ADME Gene List

Rank	Gene Symbol	Full Gene Name	Class
7	ABCB8	ATP-binding cassette, subfamily B (MDR/TAP), member 8	Transporter
7	ABCC12	ATP-binding cassette, subfamily C (CFTR/MRP), member 12	Transporter
7	ABCC3	ATP-binding cassette, subfamily C (CFTR/MRP), member 3	Transporter
7	ABCC4	ATP-binding cassette, subfamily C (CFTR/MRP), member 4	Transporter
7	AHR	aryl hydrocarbon receptor	Modifier
7	ALDH4A1	aldehyde dehydrogenase 4 family, member A1	Phase I
7	ALDH5A1	aldehyde dehydrogenase 5 family, member A1	Phase I
7	ALDH6A1	aldehyde dehydrogenase 6 family, member A1	Phase I
7	CES1	carboxylesterase 1 (monocyte/macrophage serine esterase 1)	Phase I
7	CES2	carboxylesterase 2 (intestine, liver)	Phase I
7	CYP7A1	cytochrome P450, family 7, subfamily A, polypeptide 1	Phase I
7	EPHX1	epoxide hydrolase 1, microsomal (xenobiotic)	Phase I
7	FMO3	flavin containing monooxygenase 3	Phase I
7	GSTA1	glutathione S-transferase A1	Phase II
7	GSTA2	glutathione S-transferase A2	Phase II
7	GSTA3	glutathione S-transferase A3	Phase II
7	GSTA4	glutathione S-transferase A4	Phase II
7	GSTA5	glutathione S-transferase A5	Phase II
7	GSTM2	glutathione S-transferase M2 (muscle), glutathione S-transferase M4	Phase II
7	GSTM3	glutathione S-transferase M3 (brain)	Phase II
7	GSTM4	glutathione S-transferase M4	Phase II
7	GSTO1	glutathione S-transferase omega 1, glutathione S-transferase omega 2	Phase II
7	GSTO2	glutathione S-transferase omega 2	Phase II
7	GSTT2	glutathione S-transferase theta 2	Phase II
7	SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	Transporter
7	SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1	Transporter
7	SLC22A11	solute carrier family 22 (organic anion/cation transporter), member 11	Transporter
7	SLC22A8	solute carrier family 22 (organic anion transporter), member 8	Transporter

Rank	Gene Symbol	Full Gene Name	Class
7	SLC7A5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	Transporter
7	SLCO1A2	solute carrier organic anion transporter family, member 1A2	Transporter
7	SLCO2B1	solute carrier organic anion transporter family, member 2B1	Transporter
7	SULT1A2	sulfotransferase family, cytosolic, 1 A, phenol-preferring, member 2	Phase II
7	SULT1A3	sulfotransferase family, cytosolic, 1 A, phenol-preferring, member 3	Phase II
7	SULT1B1	sulfotransferase family, cytosolic, 1B, member 1	Phase II
7	UGT1A3	UDP glucuronosyltransferase 1 family, polypeptide A3	Phase II
7	UGT1A6	UDP glucuronosyltransferase 1 family, polypeptide A6	Phase II
7	UGT1A7	UDP glucuronosyltransferase 1 family, polypeptide A7	Phase II
7	UGT1A8	UDP glucuronosyltransferase 1 family, polypeptide A8	Phase II
7	UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	Phase II
7	UGT2A1	UDP glucuronosyltransferase 2 family, polypeptide A1	Phase II
7	UGT2B11	UDP glucuronosyltransferase 2 family, polypeptide B11	Phase II
7	UGT2B28	UDP glucuronosyltransferase 2 family, polypeptide B28	Phase II
7	UGT2B4	UDP glucuronosyltransferase 2 family, polypeptide B4	Phase II
6	ABCA1	ATP-binding cassette, subfamily A (ABC1), member 1	Transporter
6	ABCA4	ATP-binding cassette, subfamily A (ABC1), member 4	Transporter
6	ABCB11	ATP-binding cassette, subfamily B (MDR/TAP), member 11	Transporter
6	ABCB4	ATP-binding cassette, subfamily B (MDR/TAP), member 4	Transporter
6	ABCB5	ATP-binding cassette, subfamily B (MDR/TAP), member 5	Transporter
6	ABCB6	ATP-binding cassette, subfamily B (MDR/TAP), member 6	Transporter
6	ABCB7	ATP-binding cassette, subfamily B (MDR/TAP), member 7	Transporter

Rank	Gene Symbol	Full Gene Name	Class
6	ABCC1	ATP-binding cassette, subfamily C (CFTR/MRP), member 1	Transporter
6	ABCC10	ATP-binding cassette, subfamily C (CFTR/MRP), member 10	Transporter
6	ABCC11	ATP-binding cassette, subfamily C (CFTR/MRP), member 11	Transporter
6	ABCC5	ATP-binding cassette, subfamily C (CFTR/MRP), member 5	Transporter
6	ABCC6	ATP-binding cassette, subfamily C (CFTR/MRP), member 6	Transporter
6	ABCC8	ATP-binding cassette, subfamily C (CFTR/MRP), member 8	Transporter
6	ABCC9	ATP-binding cassette, subfamily C (CFTR/MRP), member 9	Transporter
6	ABCG1	ATP-binding cassette, subfamily G (WHITE), member 1	Transporter
6	ADH1A	alcohol dehydrogenase 1 A (class I), alpha polypeptide	Phase I
6	ADH1B	alcohol dehydrogenase IB (class I), beta polypeptide	Phase I
6	ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	Phase I
6	ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide	Phase I
6	ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide, methionyl aminopeptidase 1	Phase I
6	ADH6	alcohol dehydrogenase 6 (class V)	Phase I
6	ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	Phase I
6	ALDH1A1	aldehyde dehydrogenase 1 family, member A1	Phase I
6	ALDH1A2	aldehyde dehydrogenase 1 family, member A2	Phase I
6	ALDH1A3	aldehyde dehydrogenase 1 family, member A3	Phase I
6	ALDH1B1	aldehyde dehydrogenase 1 family, member B1	Phase I
6	ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	Phase I
6	ALDH3A1	aldehyde dehydrogenase 3 family, memberA1	Phase I
6	ALDH3A2	aldehyde dehydrogenase 3 family, member A2	Phase I
6	ALDH3B1	aldehyde dehydrogenase 3 family, member B1	Phase I
6	ALDH3B2	aldehyde dehydrogenase 3 family, member B2	Phase I
6	ALDH7A1	aldehyde dehydrogenase 7 family, member A1	Phase I
6	ALDH8A1	aldehyde dehydrogenase 8 family, member A1	Phase I
6	ALDH9A1	aldehyde dehydrogenase 9 family, member A1	Phase I
6	AOX1	aldehyde oxidase 1	Phase I
6	ARNT	aryl hydrocarbon receptor nuclear translocator	Modifier
6	CBR1	carbonyl reductase 1	Phase I

Rank	Gene Symbol	Full Gene Name	Class
6	CBR3	carbonyl reductase 3	Phase I
6	CDA	cytidine deaminase	Modifier
6	CYB5R3	cytochrome b5 reductase 3	Phase I
6	CYP11A1	cytochrome P450, family 11, subfamily A, polypeptide 1	Phase I
6	CYP11B1	cytochrome P450, family 11, subfamily B, polypeptide 1	Phase I
6	CYP11B2	cytochrome P450, family 11, subfamily B, polypeptide 2	Phase I
6	CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1	Phase I
6	CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	Phase I
6	CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
6	CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
6	CYP21A2	cytochrome P450, family 21, subfamily A, polypeptide 2	Phase I
6	CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	Phase I
6	CYP26A1	cytochrome P450, family 26, subfamily A, polypeptide 1	Phase I
6	CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1	Phase I
6	CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	Phase I
6	CYP2A7	cytochrome P450, family 2, subfamily A, polypeptide 7	Phase I
6	CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18	Phase I
6	CYP2F1	cytochrome P450, family 2, subfamily F, polypeptide 1	Phase I
6	CYP2J2	cytochrome P450, family 2, subfamily J, polypeptide 2	Phase I
6	CYP39A1	cytochrome P450, family 39, subfamily A, polypeptide 1	Phase I
6	CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43	Phase I
6	CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7	Phase I
6	CYP4B1	cytochrome P450, family 4, subfamily B, polypeptide 1	Phase I

Rank	Gene Symbol	Full Gene Name	Class
6	CYP4F11	cytochrome P450, family 4, subfamily F, polypeptide 11	Phase I
6	CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	Phase I
6	EPHX2	epoxide hydrolase 2, cytoplasmic	Phase I
6	FMO1	flavin containing monooxygenase 1	Phase I
6	FMO2	flavin containing monooxygenase 2	Phase I
6	FMO4	flavin containing monooxygenase 4	Phase I
6	FMO5	flavin containing monooxygenase 5	Phase I
6	GPX2	glutathione peroxidase 2 (gastrointestinal)	Phase I
6	GPX3	glutathione peroxidase 3 (plasma)	Phase I
6	GPX7	glutathione peroxidase 7	Phase I
6	GSR	glutathione reductase	Phase I
6	GSTK1	glutathione S-transferase kappa 1	Phase II
6	GSTM5	glutathione S-transferase M5	Phase II
6	GSTZ1	glutathione transferase zeta 1 (maleylacetoacetate isomerase)	Phase II
6	NNMT	nicotinamide N-methyltransferase	Phase II
6	NR1I2	nuclear receptor subfamily 1, group I, member 2	Modifier
6	NR1I3	nuclear receptor subfamily 1, group I, member 3	Modifier
6	PNMT	phenylethanolamine N-methyltransferase	Phase II
6	PON1	paraoxonase 1	Phase I
6	PON2	paraoxonase 2	Phase I
6	PON3	paraoxonase 3	Phase I
6	POR	P450 (cytochrome) oxidoreductase	Modifier
6	PPARD	peroxisome proliferative activated receptor, delta	Modifier
6	PPARG	peroxisome proliferative activated receptor, gamma	Modifier
6	RXRA	retinoid X receptor, alpha	Modifier
6	SLC10A2	solute carrier family 10 (sodium/bile acid cotransporter family), member 2	Transporter
6	SLC13A1	solute carrier family 13 (sodium/sulfate symporters), member 1	Transporter
6	SLC13A2	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	Transporter
6	SLC13A3	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3	Transporter
6	SLC16A1	solute carrier family 16 (monocarboxylic acid Transporter), member 1	Transporter
6	SLC19A1	solute carrier family 19 (folate transporter), member 1	Transporter

Rank	Gene Symbol	Full Gene Name	Class
6	SLC22A10	solute carrier family 22 (organic anion/cation transporter), member 10	Transporter
6	SLC22A12	solute carrier family 22 (organic anion/cation transporter), member 12	Transporter
6	SLC22A13	solute carrier family 22 (organic cation transporter), member 13	Transporter
6	SLC22A14	solute carrier family 22 (organic cation transporter), member 14	Transporter
6	SLC22A15	solute carrier family 22 (organic cation transporter), member 15	Transporter
6	SLC22A16	solute carrier family 22 (organic cation transporter), member 16	Transporter
6	SLC22A17	solute carrier family 22 (organic cation transporter), member 17	Transporter
6	SLC22A18	solute carrier family 22 (organic cation transporter), member 18	Transporter
6	SLC22A18AS	solute carrier family 22 (organic cation transporter), member 18 antisense	Transporter
6	SLC22A3	solute carrier family 22 (extraneuronal monoamine transporter), member 3	Transporter
6	SLC22A4	solute carrier family 22 (organic cation transporter), member 4	Transporter
6	SLC22A5	solute carrier family 22 (organic cation transporter), member 5	Transporter
6	SLC22A7	solute carrier family 22 (organic anion transporter), member 7	Transporter
6	SLC22A9	solute carrier family 22 (organic anion/cation transporter), member 9	Transporter
6	SLC27A1	solute carrier family 27 (fatty acid transporter), member 1	Transporter
6	SLC28A1	solute carrier family 28 (sodium-coupled nucleoside transporter), member 1	Transporter
6	SLC28A2	solute carrier family 28 (sodium-coupled nucleoside transporter), member 2	Transporter
6	SLC28A3	solute carrier family 28 (sodium-coupled nucleoside transporter), member 3	Transporter
6	SLC29A1	solute carrier family 29 (nucleoside Transporter), member 1	Transporter
6	SLC29A2	solute carrier family 29 (nucleoside Transporter), member 2	Transporter
6	SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	Transporter
6	SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5	Transporter

Rank	Gene Symbol	Full Gene Name	Class
6	SLC5A6	solute carrier family 5 (sodium-dependent vitamin transporter)	Transporter
6	SLC6A6	solute carrier family 6 (neurotransmitter transporter, taurine), member 6	Transporter
6	SLC7A8	solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	Transporter
6	SLCO1C1	solute carrier organic anion transporter family, member 1C1	Transporter
6	SLCO2A1	solute carrier organic anion transporter family, member 2A1	Transporter
6	SLCO3A1	solute carrier organic anion transporter family, member 3A1	Transporter
6	SLCO4A1	solute carrier organic anion transporter family, member 4A1	Transporter
6	SLCO4C1	solute carrier organic anion transporter family, member 4C1	Transporter
6	SLCO5A1	solute carrier organic anion transporter family, member 5A1	Transporter
6	SLCO6A1	solute carrier organic anion transporter family, member 6A1	Transporter
6	SULT1C1	sulfotransferase family, cytosolic, 1C, member 1	Phase II
6	SULT1C2	sulfotransferase family, cytosolic, 1C, member 2	Phase II
6	SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	Phase II
6	SULT2A1	sulfotransferase family, cytosolic, 2 A, DHEA preferring, member 1	Phase II
6	SULT2B1	sulfotransferase family, cytosolic, 2B, member 1	Phase II
6	TAP1	transporter 1, ATP-binding cassette, subfamily B (MDR/TAP)	Transporter
6	UGT1A10	UDP glucuronosyltransferase 1 family, polypeptide A10	Phase II
6	UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4	Phase II
6	UGT1A5	UDP glucuronosyltransferase 1 family, polypeptide A5	Phase II
6	UGT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10	Phase II
5	ABCC13	ATP-binding cassette, subfamily C (CFTR/MRP), member 13	Transporter
5	ARSA	arylsulfatase A	Modifier
5	CAT	catalase	Modifier
5	CHST8	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8	Phase II

Rank	Gene Symbol	Full Gene Name	Class
5	CYP19A1	cytochrome P450, family 19, subfamily A, polypeptide 1	Phase I
5	CYP26C1	cytochrome P450, family 26, subfamily C, polypeptide 1	Phase I
5	CYP27B1	cytochrome P450, family 27, subfamily B, polypeptide 1	Phase I
5	CYP2R1	cytochrome P450, family 2, subfamily R, polypeptide 1	Phase I
5	CYP2S1	cytochrome P450, family 2, subfamily S, polypeptide 1	Phase I
5	CYP46A1	cytochrome P450, family 46, subfamily A, polypeptide 1	Phase I
5	CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11	Phase I
5	CYP4F12	cytochrome P450, family 4, subfamily F, polypeptide 12	Phase I
5	CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	Phase I
5	CYP4F3	cytochrome P450, family 4, subfamily F, polypeptide 3	Phase I
5	CYP4F8	cytochrome P450, family 4, subfamily F, polypeptide 8	Phase I
5	CYP4Z1	cytochrome P450, family 4, subfamily Z, polypeptide 1	Phase I
5	CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1	Phase I
5	CYP8B1	cytochrome P450, family 8, subfamily B, polypeptide 1	Phase I
5	DHRS13	dehydrogenase/reductase (SDR family) member 13	Phase I
5	DHRS2	dehydrogenase/reductase (SDR family) member 2	Phase I
5	GPX1	glutathione peroxidase 1	Phase I
5	GPX4	glutathione peroxidase 4 (phospholipid hydroperoxidase)	Phase I
5	GPX5	glutathione peroxidase 5 (epididymal androgen-related protein)	Phase I
5	GPX6	glutathione peroxidase 6 (olfactory)	Phase I
5	GSS	glutathione synthetase	Phase I
5	GSTCD	glutathione S-transferase, C-terminal domain containing	Phase II
5	HNF4A	hepatocyte nuclear factor 4, alpha	Modifier
5	HNMT	histamine N-methyltransferase	Phase II
5	HSD11B1	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
5	HSD17B11	hydroxysteroid (17-beta) dehydrogenase 11	Phase I

Rank	Gene Symbol	Full Gene Name	Class
5	HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14	Phase I
5	LOC731356	similar to dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
5	MGST1	microsomal glutathione S-transferase 1	Phase II
5	MGST2	microsomal glutathione S-transferase 2	Phase II
5	MGST3	microsomal glutathione S-transferase 3	Phase II
5	MPO	myeloperoxidase	Modifier
5	NOS1	nitric oxide synthase 1 (neuronal)	Phase I
5	NOS2A	nitric oxide synthase 2 A (inducible, hepatocytes)	Phase I
5	NOS3	nitric oxide synthase 3 (endothelial cell)	Phase I
5	PPARA	peroxisome proliferator-activated receptor alpha	Modifier
5	SERPINA7	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 7	Modifier
5	SLC7A7	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7	Transporter
5	SOD1	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	Modifier
5	SOD2	superoxide dismutase 2, mitochondrial	Modifier
5	SOD3	superoxide dismutase 3, extracellular precursor	Modifier
5	SULF1	sulfatase 1	Phase I
5	SULT4A1	sulfotransferase family 4 A, member 1	Phase II
5	TAP2	transporter 2, ATP-binding cassette, subfamily B (MDR/TAP)	Transporter
5	UGT8	UDP glycosyltransferase 8 (UDP-galactose ceramide galactosyltransferase)	Phase II
5	XDH	xanthine dehydrogenase	Phase I
4	ADHFE1	alcohol dehydrogenase, iron containing, 1	Phase I
4	CHST1	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1	Phase II
4	CHST10	carbohydrate sulfotransferase 10	Phase II
4	CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	Phase II
4	CHST12	carbohydrate (chondroitin 4) sulfotransferase 12	Phase II
4	CHST13	carbohydrate (chondroitin 4) sulfotransferase 13	Phase II
4	CHST2	carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2	Phase II
4	CHST3	carbohydrate (chondroitin 6) sulfotransferase 3	Phase II
4	CHST4	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 4	Phase II
4	CHST5	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 5	Phase II

Rank	Gene Symbol	Full Gene Name	Class
4	CHST6	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6	Phase II
4	CHST7	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7	Phase II
4	CHST9	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9	Phase II
4	CYP2D7P1	cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1	Phase I
4	DDO	D-aspartate oxidase	Phase I
4	DHRS1	dehydrogenase/reductase (SDR family) member 1	Phase I
4	DHRS12	dehydrogenase/reductase (SDR family) member 12	Phase I
4	DHRS3	dehydrogenase/reductase (SDR family) member 3	Phase I
4	DHRS4	dehydrogenase/reductase (SDR family) member 4	Phase I
4	DHRS4L1	dehydrogenase/reductase (SDR family) member 4 like 1	Phase I
4	DHRS4L2	dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
4	DHRS7	dehydrogenase/reductase (SDR family) member 7	Phase I
4	DHRS7B	dehydrogenase/reductase (SDR family) member 7B	Phase I
4	DHRS7C	dehydrogenase/reductase (SDR family) member 7C	Phase I
4	DHRS9	dehydrogenase/reductase (SDR family) member 9	Phase I
4	DHRSX	dehydrogenase/reductase (SDR family) X-linked	Phase I
4	DPEP1	dipeptidase 1 (renal)	Phase I
4	FMO6P	flavin containing monooxygenase 6	Phase I
4	HAGH	hydroxyacylglutathione hydrolase	Phase I
4	IAPP	islet amyloid polypeptide	Modifier
4	KCNJ11	potassium inwardly-rectifying channel, subfamily J, member 11	Modifier
4	LOC728667	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
4	LOC731931	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
4	MAT1A	methionine adenosyltransferase I, alpha	Modifier
4	METAP1	methionyl aminopeptidase 1	Phase I
4	PDE3A	phosphodiesterase 3A, cGMP-inhibited	Phase I
4	PDE3B	phosphodiesterase 3B, cGMP-inhibited	Phase I
4	PLGLB1	plasminogen-like B1	Phase I
3	ATP7A	ATPase, Cu++ transporting, alpha polypeptide (Menkes syndrome)	Modifier
3	ATP7B	ATPase, Cu++ transporting, beta polypeptide	Modifier
3	CFTR	cystic fibrosis transmembrane conductance regulator	Modifier